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REVIEW ARTICLE

IMMUNE AGING IN THE YOUNG: CONSEQUENCES OF HIV-INDUCED SENESCENCE IN CHILDREN

Emmanuel Ifeanyi Obeagu[1]*, Chukwuma J. Okafor[2]
[1]*Department of Biomedical and Laboratory Science, Africa University, Mutare, Zimbabwe.*
[2]*Department of Pathology and Biochemistry, State University of Zanzibar, Tanzania.*

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***Address for Correspondence:**
Dr. Emmanuel Ifeanyi Obeagu, Department of Biomedical and Laboratory Science, Africa University, Zimbabwe. Tel: +263-778025658
E-mail: *emmanuelobeagu@yahoo.com*

Abstract

The immune systems of children that are still developing are particularly susceptible to being affected by long-lasting infections like HIV. Children infected perinatally show indications of immune aging or immune senescence significantly sooner than their uninfected counterparts, even with the prompt start of combination antiretroviral therapy (cART). This rapid aging process is marked by persistent immune activation, thymic impairment, disrupted hematopoiesis, and the premature buildup of senescent and weary immune cells. These changes jeopardize immune function during a vital period of growth and development. At the heart of HIV-related senescence in children is the ongoing condition of systemic inflammation and immune imbalance, despite the presence of viral suppression. Thymic involution diminishes the production of naïve T-cells, whereas telomere shortening and increased levels of senescence markers like p16^INK4a and PD-1 indicate cellular tiredness. These immunological changes have significant clinical consequences, including heightened vulnerability to infections, insufficient vaccine efficacy, and premature development of non-AIDS-related comorbidities like cardiovascular and neurocognitive issues.

Keywords: Chronic inflammation, HIV, immune senescence, pediatric immunology, T-cell exhaustion.

INTRODUCTION

The Human Immunodeficiency Virus (HIV) continues to be a worldwide public health challenge; with pediatric cases constituting a major portion, especially in areas with elevated mother-to-child transmission levels[1,2]. Despite significant advancements in both prevention and treatment, around 1.5 million children worldwide are currently living with HIV, the majority of whom contracted the virus during birth. Although the prompt start of combination antiretroviral therapy (cART) has greatly enhanced survival rates and lowered the incidence of opportunistic infections, it has not fully restored immune function in infected children[3,4]. This has resulted in an increasing focus on the lasting immunological impacts of HIV in childhood, encompassing the concept of immune senescence. Immune senescence, traditionally linked to aging, denotes the progressive decline in immune function characterized by thymic involution, diminished T-cell repertoire diversity, chronic inflammation, and compromised immune surveillance. Interestingly, children infected with HIV display comparable signs of immune aging at an early age a phenomenon known as premature or accelerated immune senescence[5,6]. This unusual pathway arises even with the strong regenerative ability usually seen in the pediatric immune system, questioning the belief that early cART alone can effectively restore immune balance. Perinatally acquired HIV is distinctive because it affects the immune system during its most active developmental phase. Unlike adults, who show immune senescence following years of chronic infection and aging, children undergo these changes during their first ten years of life[7].

The thymus is essential to the pediatric immune response, as it produces naïve T cells required for recognizing antigens and forming immune memory[8]. HIV infection greatly affects thymic output, resulting in reduced generation of recent thymic emigrants and a disruption in T-cell populations. This dysfunction of the thymus, along with telomere shortening and heightened levels of senescence markers (like CD57 and p16^INK4a), leads to an altered immune repertoire that reflects the immunosenescence seen in older adults. These disturbances have significant effects on the immune capacity of children infected with HIV. The clinical ramifications of immune senescence caused by HIV in children are extensive and troubling[9,10]. Children affected are more prone to

repeated infections, exhibit weak responses to vaccines, and face a higher risk for early-onset non-AIDS comorbidities like cardiovascular issues, neurodevelopmental delays, and metabolic conditions. Moreover, immunosenescence could influence the effecttiveness of upcoming immunotherapeutic approaches and vaccines, highlighting the necessity for customized clinical management and extended follow-up[11-13]. While cART has significantly transformed pediatric HIV treatment, its capacity to reverse pre-existing immune senescence is still restricted. Research indicates that although cART can inhibit viral replication and somewhat improve $CD4^+$ T-cell levels, it fails to completely alleviate chronic inflammation or rebuild thymic function[14-16].

The aim of this review is to explore the mechanisms underlying HIV-induced immune senescence in pediatric patients, to assess the consequences of this condition on their long-term health, and to evaluate current and emerging therapeutic strategies aimed at mitigating the effects of immune aging.

Mechanisms of HIV-induced immune senescence in children

HIV-driven immune senescence in children is a complex, multifactorial phenomenon influenced by persistent immune activation, immune cell fatigue, inflammatory responses, and thymic insufficiency. Unlike adults, who undergo immune senescence over decades, children with HIV face early aging of their immune system due to the ongoing and severe immunological stress from the virus. The factors behind this phenomenon are linked and mainly entail changes in immune cell types, signaling pathways, and the general inflammatory environment.

1. Chronic immune activation

A key mechanism of immune senescence caused by HIV is persistent immune activation. HIV infection causes ongoing activation of the immune system, even when effective ART is being administered. Ongoing viral replication, even at minimal levels, leads to constant antigenic stimulation, causing immune cells, especially T cells, to stay in an activated state. As time passes, this extended activation results in the increased expression of co-stimulatory molecules on immune cells, including CD28 and PD-1, along with the generation of pro-inflammatory cytokines. This overstimulation of the immune system hastens the aging of immune cells by depleting their capacity to multiply and react efficiently to new pathogens[17].

2. T-cell exhaustion and dysfunction

T-cell exhaustion is a hallmark of immune senescence in HIV-infected individuals. $CD4^+$ T-helper cells, crucial for coordinating immune responses, and $CD8^+$ cytotoxic T lymphocytes, which are responsible for directly killing infected cells, become functionally impaired in children with HIV. Persistent exposure to viral antigens causes these T cells to enter a state of dysfunction, marked by the expression of inhibitory receptors such as PD-1, Tim-3, and LAG-3. These receptors dampen T-cell activity, leading to a diminished ability to eliminate the virus and respond to other infections. The exhaustion of T cells is further compounded by a reduced proliferative capacity, which ultimately diminishes the immune system's ability to mount effective responses, accelerating immune system aging[18,19].

3. Dysregulated cytokine production

Chronic immune activation in HIV-infected children also results in dysregulated cytokine production, contributing significantly to immune senescence. HIV infection triggers the overproduction of pro-inflammatory cytokines, including TNF-α, interleukin-6 (IL-6), and interferon-gamma (IFN-γ). These cytokines are typically involved in immune defense but, when overproduced in the context of chronic HIV infection, contribute to an environment of systemic inflammation. This persistent inflammatory state leads to the activation of immune cells inappropriately, driving them towards senescence. Additionally, the imbalance between pro-inflammatory and anti-inflammatory cytokines accelerates tissue damage and further exacerbates immune dysfunction, perpetuating a cycle of immune aging[20-22].

4. Impaired thymic function

The thymus plays a critical role in the development of naïve T cells, which are essential for a functional adaptive immune response. In children with HIV, thymic function is often compromised, leading to a decreased ability to generate new T cells. HIV infection induces thymic atrophy, reducing the number of naïve T cells available to respond to novel pathogens. This impairment in thymic output is particularly concerning in pediatric patients, as it exacerbates immune senescence by limiting the capacity of the immune system to regenerate itself. Furthermore, the lack of a robust supply of naïve T cells hinders the immune system's ability to adapt to new challenges, leading to a reduced immune repertoire and an overall decline in the immune function[23-25].

5. Accumulation of senescent immune cells

One of the consequences of chronic immune activation and T-cell exhaustion is the accumulation of senescent immune cells, including both T cells and B cells, in the circulation. Senescent immune cells are characterized by reduced proliferative capacity, resistance to apoptosis (programmed cell death), and altered function. These cells often express markers such as CD57 and p16INK4a, which are indicative of cellular aging. In children with HIV, the accumulation of senescent immune cells not only impairs the immune response but also contributes to systemic inflammation and tissue damage. This accumulation, coupled with a diminished ability to generate new, functional immune cells, leads to the early onset of immune dysfunction and compromises the child's ability to combat infections[26-28].

6. Disruption of immune homeostasis

HIV infection alters the equilibrium among immune cell subsets, resulting in immune dysregulation. Specifically, the ratio of regulatory T cells (Tregs), which assist in sustaining immune tolerance and inhibit excessive inflammation, is frequently modified in individuals infected with HIV. Moreover, there is a growth of activated memory T cells that, while essential for enduring immunity, can lead to persistent

inflammation and immune malfunctions when excessive. The disparity among various T-cell subsets leads to a disturbance in immune balance, which further worsens the aging of the immune system. This altered immune condition hinders the body's ability to adequately react to new infections and environmental factors, increasing morbidity risk for children with HIV[29].

7. Impact on B-cell function and humoral immunity

Along with T-cell dysfunction, HIV impacts B-cell activity, which further exacerbates immune aging in pediatric patients. B cells are crucial for generating antibodies that defend the body against pathogens. In children with HIV, B-cell activation and maturation are compromised, resulting in reduced antibody responses. This impaired capacity to produce particular antibodies not only lessens the immune system's response to infections but also undermines the efficacy of vaccinations. The impairment of B cells, along with T-cell fatigue, weakens both humoral and cellular immune responses, resulting in an immune system that is less reactive and less flexible[30].

8. The role of chronic inflammation in accelerating immune senescence

Chronic inflammation is a central feature of HIV infection and plays a key role in accelerating immune senescence. The persistent activation of the immune system and the continuous presence of viral antigens drive a state of systemic inflammation, which directly contributes to the aging of immune cells. This inflammatory environment not only impairs immune cell function but also causes damage to various tissues and organs, increasing the risk of comorbidities such as cardiovascular disease, neurocognitive decline, and metabolic disorders. In pediatric HIV patients, chronic inflammation may also impact growth and development, further exacerbating the overall burden of the disease[31].

Consequences of immune senescence in pediatric HIV patients

Immune senescence in pediatric HIV patients represents a significant challenge to their overall health and well-being. The premature aging of the immune system in these children has profound consequences, extending beyond the immediate effects of HIV infection. The accelerated loss of immune function due to immune senescence predisposes these children to increased susceptibility to infections, a reduced ability to respond to vaccinations, the development of comorbidities typically associated with aging, and a diminished quality of life. These consequences highlight the urgent need for strategies to mitigate immune senescence and enhance the long-term health of children living with HIV[32].

1. Increased susceptibility to opportunistic infections

One of the most severe consequences of immune senescence in pediatric HIV patients is an increased susceptibility to opportunistic infections (OIs). Immune senescence impairs the body's ability to mount effective immune responses to pathogens, including bacteria, fungi, and viruses. The progressive exhaustion of T cells and the accumulation of senescent immune cells limit the ability to mount both cellular and humoral immune responses. This makes children with HIV more vulnerable to infections that would otherwise be controlled by a healthy immune system. Opportunistic infections such as tuberculosis, Pneumocystis jirovecii pneumonia, and fungal infections are particularly dangerous in immuno-compromised individuals and are associated with higher morbidity and mortality in HIV-infected children with immune senescence[33,34].

2. Impaired vaccine responses

Vaccination is one of the most effective preventive health strategies, especially for children. However, immune senescence in pediatric HIV patients significantly hampers their ability to respond to vaccines. The aging immune system's reduced capacity to generate a robust immune response to vaccines leaves these children more susceptible to vaccine-preventable diseases. For example, studies have shown that HIV-infected children with immune senescence have a diminished ability to produce adequate levels of antibodies following vaccination. This weakened immune response reduces the protective benefits of immunization, placing these children at increased risk for diseases such as influenza, pneumococcal infections, and hepatitis. As vaccination remains a cornerstone of pediatric health, this impaired response has significant public health implications[35,36].

3. Development of comorbidities typically seen in older adults

Immune senescence in pediatric HIV patients is also linked to the development of comorbidities typically associated with aging, such as cardiovascular disease, metabolic disorders, and neurocognitive decline. Chronic immune activation and inflammation, which are central to the process of immune senescence, can lead to endothelial dysfunction and the early onset of atherosclerosis. Children with HIV may experience accelerated cardiovascular aging, leading to an increased risk of heart disease later in life. Similarly, immune dysfunction and inflammation contribute to the development of metabolic disorders, including insulin resistance and obesity, which are often observed in HIV-infected children with immune senescence. Furthermore, neuroinflammation and impaired brain immune responses can lead to neurocognitive impairments, including deficits in learning, memory, and executive function[37].

4. Reduced immune system regeneration and adaptability

A key characteristic of immune senescence is a reduced ability of the immune system to regenerate and adapt to new threats. In pediatric HIV patients, thymic atrophy and impaired T-cell production severely limit the generation of new, naïve T-cells, which are essential for responding to novel infections. This loss of immune adaptability reduces the child's ability to respond to new pathogens, making them more vulnerable to emerging infections and less able to mount a robust immune defense. Additionally, the accumulation of exhausted immune cells, coupled with a diminished capacity to generate new immune cells, leaves the child with an immune system that is not only

less functional but also more rigid in its response to new challenges[38,39].

5. Long-term health and developmental impact

The effects of immune senescence extend beyond immediate health concerns to long-term developmental impacts. In addition to the physical toll of chronic infections and comorbidities, immune senescence may also hinder growth and development in HIV-infected children. Immune dysregulation, coupled with chronic inflammation, can impair the normal development of organs and systems, leading to growth retardation and delayed puberty. In some cases, children with HIV-induced immune senescence may experience stunted growth and lower height and weight percentiles compared to their peers. Additionally, the inability to mount proper immune responses may interfere with cognitive development, as neuroinflammation and immune dysfunction impact brain development and learning abilities[40].

6. Increased risk of cancer

The immunocompromised state caused by immune senescence in HIV-infected children can also increase the risk of malignancies, particularly cancers that are associated with immune dysfunction. HIV-infected individuals, including children, are at an elevated risk for developing certain cancers, such as Kaposi's sarcoma, non-Hodgkin lymphoma, and cervical cancer, due to their impaired immune surveillance. The diminished ability to eliminate cancerous cells or prevent the progression of latent viruses, such as human papillomavirus or Epstein-Barr virus, leads to an increased cancer burden in this population. As immune senescence accelerates the depletion of immune functions, HIV-infected children may face an even higher risk of developing malignancies as they grow older[41,42].

7. Psychological and social implications

The long-term consequences of immune senescence in pediatric HIV patients also have significant psychological and social implications. Children with HIV-induced immune senescence often experience heightened anxiety related to their health, as they face the challenges of chronic illness, frequent medical visits, and the potential for repeated infections. The visibility of chronic illness and frequent hospitalizations can also contribute to stigma and social isolation, further impacting the child's mental health. The psychosocial burden of growing up with HIV and an aging immune system can lead to feelings of depression, stress, and anxiety, which can affect the child's overall well-being and quality of life[43].

Therapeutic approaches to combat HIV-induced immune senescence

The premature aging of the immune system, or immune senescence, in pediatric HIV patients poses significant challenges in terms of disease management and long-term health. Immune senescence accelerates the risk of infections, immunologic dysfunction, and comorbidities, thereby necessitating therapeutic strategies to mitigate its effects. While current treatment primarily revolves around ART, several adjunctive approaches are being explored to address the underlying mechanisms of immune aging in children living with HIV. These strategies aim not only to control viral replication but also to rejuvenate the immune system and restore immune function[44,45].

1. Antiretroviral therapy (ART) optimization

ART remains the cornerstone of HIV treatment, helping to reduce viral load, improve immune function, and prevent the progression to acquired immunodeficiency syndrome (AIDS). While ART significantly improves outcomes, it does not completely reverse immune senescence, particularly in pediatric patients. The optimization of ART regimens to reduce inflammation and improve immune reconstitution is critical. Emerging therapies, such as long-acting injectable ART, may provide more stable viral suppression and reduce the burden of constant immune activation. ART regimens that minimize drug toxicity and inflammatory responses are being explored as ways to slow the process of immune senescence. Moreover, the combination of ART with drugs that target specific immune pathways, such as inhibitors of inflammatory cytokines or checkpoint inhibitors, might help mitigate immune dysfunction and reduce immune exhaustion. Personalized ART regimens tailored to the individual's immune status could also play a role in minimizing the long-term effects of HIV-induced immune senescence[46,47].

2. Immune modulation and immune checkpoint inhibitors

Immune checkpoint inhibitors are gaining attention as a potential therapeutic approach to reverse T-cell exhaustion, one of the key hallmarks of immune senescence in HIV patients. Checkpoints such as PD-1 (programmed cell death protein 1) and CTLA-4 (cytotoxic T-lymphocyte-associated protein 4) play a central role in regulating T-cell activation and tolerance. Chronic HIV infection leads to the overexpression of these inhibitory receptors, which limits the ability of immune cells to respond effectively to the virus and other pathogens. By blocking these checkpoints, immune checkpoint inhibitors can rejuvenate T-cell function, promote the activation of exhausted T cells, and restore immune system functionality. While immune checkpoint inhibitors have shown promise in cancer immunotherapy, their role in pediatric HIV treatment is still under investigation. Clinical trials are exploring whether these inhibitors can help reverse T-cell exhaustion and rejuvenate the immune system in HIV-infected children. This approach could reduce chronic inflammation, improve immune responses, and delay or prevent the onset of age-related comorbidities associated with immune senescence[48,49].

3. Thymic regeneration therapies

The thymus plays a vital role in the development of naïve T cells, which are crucial for an adaptive immune response. HIV infection, particularly in children, often results in thymic atrophy, which impairs the production of new T cells. This leads to a diminished ability to respond to infections and contributes to immune senescence. Strategies to regenerate thymic function and promote T-cell production are being explored as potential therapies. Thymic regeneration therapies, including the use of recombinant growth factors such

as interleukin-7 (IL-7) and stem cell-based approaches, aim to restore thymic output and enhance T-cell replenishment. Research into these therapies has demonstrated promising results in enhancing immune reconstitution in HIV-infected adults, and similar strategies may prove beneficial for children. By promoting the development of naïve T cells, thymic regeneration could improve immune responses, reduce the accumulation of exhausted immune cells, and help delay the onset of immune senescence[50].

4. Anti-inflammatory and immunomodulatory agents

Chronic inflammation plays a critical role in driving HIV-induced immune senescence. The persistent activation of the immune system and the overproduction of inflammatory cytokines such as TNF-α, IL-6, and IFN-γ contribute to immune exhaustion and tissue damage. Anti-inflammatory and immunomodulatory therapies that target these inflammatory pathways hold promise for reducing immune senescence. Medications such as Janus kinase (JAK) inhibitors, which target signaling pathways involved in cytokine production, and other anti-inflammatory drugs may help control the inflammatory environment and reduce immune system overactivation. Additionally, the use of corticosteroids or nonsteroidal anti-inflammatory drugs (NSAIDs) might provide short-term relief from inflammation, although their long-term use requires careful monitoring. Incorporating these agents into treatment regimens could improve immune function and reduce the harmful effects of chronic inflammation on immune cells[51,52].

5. Vaccination strategies and immune reconstitution

For HIV-infected children, the capacity to respond to vaccines is often compromised due to immune senescence. As immune function declines, the ability to generate a robust immune response to vaccination diminishes. However, there are ongoing efforts to enhance vaccine responses through immune boosting and reconstitution strategies. For example, the administration of immune modulators like IL-7 or the use of novel adjuvants may improve immune responses to vaccines. Furthermore, vaccination strategies aimed at boosting the immune response to HIV itself, such as therapeutic vaccines or broadly neutralizing antibodies, could help to control viral replication and reduce the chronic immune activation that drives immune senescence. Research is also exploring the development of vaccines that target the inflammatory pathways driving immune aging, potentially offering a dual benefit of enhancing immune function while reducing inflammation[53].

6. Stem cell therapy and gene editing

Stem cell-based therapies and gene editing represent cutting-edge approaches that may hold promise for combating HIV-induced immune senescence. Stem cell therapies aim to replenish the immune system by transplanting healthy hematopoietic stem cells, which can regenerate both T and B cells. This approach is still in the early stages of clinical research, but it has the potential to provide long-term immune reconstitution for children with HIV. Additionally, gene-editing technologies like CRISPR-Cas9 have the potential to correct genetic defects in immune cells or even create HIV-resistant immune cells by editing the CCR5 receptor (the primary co-receptor HIV uses to enter cells). These therapies could offer a revolutionary way to address both the viral load and the immune senescence caused by chronic HIV infection[54].

7. Lifestyle and nutritional interventions

While pharmaceutical interventions are crucial, lifestyle and nutritional strategies also play an important role in combating immune senescence. Nutritional deficiencies, particularly in vitamins and minerals that are critical for immune function, are common in HIV-infected children. Supplementation with nutrients such as vitamin D, zinc, and antioxidants may help modulate immune responses and reduce inflammation. Moreover, physical activity and stress reduction techniques, such as yoga or mindfulness, may help regulate immune function and reduce the adverse effects of chronic stress on immune health[55].

8. Psychological and social interventions

Psychosocial interventions are also crucial in managing the effects of immune senescence in HIV-infected children. Chronic illness and frequent medical treatments can lead to emotional and psychological stress, which exacerbates immune dysfunction. Psychological support, counseling, and social support networks can improve the mental well-being of children with HIV and help them cope with the challenges of living with the virus. By addressing the psychological burden, these interventions may also help to improve immune function indirectly[55].

CONCLUSIONS

Genetic information is pivotal in influencing the diagnosis, prognosis, and treatment of thalassemia. Developments in molecular diagnostics, such as PCR, MLPA, and next-generation sequencing, have facilitated accurate mutation identification, early carrier identification, and enhanced risk stratification. These advancements enhance tailored treatment approaches, ranging from improved transfusion protocols and iron chelation to hematopoietic stem cell transplants and new gene-centric therapies. Identifying genetic modifiers, like co-inherited α-thalassemia and polymorphisms that enhance fetal hemoglobin, provides insight for personalized patient care by forecasting disease severity and treatment response. New gene therapy techniques, such as lentiviral vector-mediated globin transfer and CRISPR/Cas9 gene editing, show potential for curative treatment, possibly altering long-term outcomes for those impacted. Incorporating genetic insights into clinical practice improves patient care while also guiding preventive measures and research focus.

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AUTHOR'S CONTRIBUTION

Obeagu EI: conceived the idea, writing the manuscript, literature survey. **Okafor CJ:** formal analysis, data processing. Final manuscript was checked and approved by both authors.

DATA AVAILABILITY

The empirical data used to support the study's conclusions are available upon request from the corresponding author.

CONFLICTS OF INTEREST

The authors declare no conflict of interest

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