



The Role of Monocytes and Macrophages in the Pathogenesis of Non-AIDS Defining Events: Mechanisms and Therapeutic Implications

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ABSTRACT

Monocytes and macrophages play a pivotal role in the pathogenesis of HIV infection, contributing not only to viral persistence but also to the development of non-AIDS-defining events (nADEs) in People Living with HIV (PLWH). These innate immune cells act as long-lived viral reservoirs, driving chronic inflammation through persistent immune activation, oxidative stress, and tissue-specific damage. HIV-infected monocytes infiltrate tissues, including the cardiovascular system, liver, kidneys, and central nervous system, where they differentiate into macrophages and release pro-inflammatory cytokines (e.g., TNF- α , IL-6), reactive oxygen species (ROS), and matrix metalloproteinases (MMPs). These mediators promote endothelial dysfunction, fibrosis, and organ damage, underpinning conditions such as atherosclerosis, neurocognitive disorders, and

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hepatorenal disorder. Emerging evidence highlights the role of macrophage polarization (M1/M2 imbalance) and epigenetic modifications in sustaining inflammation despite antiretroviral therapy (ART). Understanding these mechanisms provides critical insights for developing targeted therapies, including immunomodulators (e.g., IL-6 inhibitors), antioxidant agents, and reservoir-elimination strategies. This review synthesizes current knowledge on monocyte/macrophage-driven pathogenesis in HIV-associated nADEs. It explores plausible novel therapeutic approaches to mitigate chronic inflammation and improve clinical outcomes in PLWH.

Keywords: HIV; monocyte; macrophages; inflammation; immune activation; viral reservoirs; tissue-specific damage; non-AIDS-defining events; reservoir elimination.

1. INTRODUCTION

Human Immunodeficiency Virus (HIV) infection continues to pose a significant global health challenge, despite the remarkable success of ART in reducing AIDS-related morbidity and mortality. Individuals living with HIV now face an increased risk of certain chronic illnesses collectively referred to as non-AIDS defining events (nADEs), which are disproportionately common among PLWH (Deeks et al., 2013; Serrano-Villar et al., 2014). This spectrum includes cardiovascular disease, neurocognitive disorders, liver/kidney fibrosis, metabolic syndrome, and non-AIDS cancers, which can arise despite effective ART, contributing to morbidity and mortality in the post-ART era (Deeks et al., 2013).

These conditions occur in PLWH at a younger age than in the general population. They are driven mainly by chronic immune activation, inflammation, and immune dysregulation, in which monocytes and macrophages play a central role (Campbell et al., 2014; Joseph et al., 2022).

Monocytes and macrophages, integral members of the myeloid lineage, are HIV tropic and express HIV entry receptors, CD4 and CCR5 (Ancuta et al., 2008). These cells not only serve as targets for the infection and propagation of HIV but also contribute to the virus's persistence and disease progression over the long term (Campbell et al., 2014; Kruize & Kootstra, 2019). Following their differentiation from monocytes, HIV-infected macrophages migrate into tissues where they help spread the infection to nearly every tissue in the body, including the gut, testes, lung, gut-associated lymphoid tissue, brain, liver, urethra, and lymph nodes (Tso et al., 2018; Rose et al., 2016; Ganor et al., 2019). Additionally, macrophages reside in anatomical sanctuaries with restricted ART penetration, which benefits viral persistence even during therapy (Clayton et

al., 2018; Borkham-Kamphorst & Weiskirchen, 2016).

Human monocytes were first identified in 1880 when Paul Ehrlich and Ilya Metchnikoff recognized them based on their distinct morphological features (Teh et al., 2023; Gramegna et al., 2011). However, the development of flow cytometry in the 1970s enabled the creation of a specific antibody panel that classifies monocytes according to the degree of expression of specific surface proteins, namely the pattern recognition receptor CD14 and the Fc gamma III receptor CD16 (Kapellos et al., 2019). This parameter categorizes circulating monocytes into three key subpopulations: classical, non-classical, and intermediate. These subpopulations, which differ in abundance and primary functions, can be identified by their size, granularity, and expression of these specific surface markers (Ziegler-Heitbrock et al., 2010; Liberale et al., 2020).

Classical monocytes, characterized by the expression profile CD14⁺⁺CD16⁻, constitute the majority (80–90%) of monocytes. They are the first responders to infections or tissue damage and primarily initiate immune responses through phagocytosis, antigen presentation, and the release of pro-inflammatory cytokines (Ziegler-Heitbrock et al., 2010; Potula et al., 2008).

Non-classical monocytes exhibit a CD14⁺CD16⁺⁺ expression pattern and are the least abundant (2-8%). They respond to viral infections, play a crucial role in antibody-dependent cellular cytotoxicity (ADCC), patrol the endothelial lining of blood vessels, and participate in tissue repair and regeneration. The intermediate subset, designated CD14⁺⁺CD16⁺, shows characteristics that bridge classical and non-classical monocytes (Tanwar et al., 2020). They possess enhanced capabilities for antigen presentation, aid in tissue repair and angiogenesis, and engage in resolving

inflammation, making them significant in various inflammatory diseases (Wong et al., 2011).

Macrophages are specialized, long-lived phagocytic cells of the innate immune system involved in recognizing, engulfing, and degrading cellular debris, pathogens, and other foreign substances. Until recently, they were thought to differentiate solely from monocytes, but newer findings have shed light on the complexities of their differentiation and immunological profiles. Macrophages can originate from two distinct sources: from classical monocytes, which migrate into tissues to differentiate into macrophages or dendritic cells (monocyte-derived macrophages [MDM]), and from self-renewing tissue-resident macrophages that arise from primitive embryonic precursors (Sattentau & Stevenson, 2016).

This article explores the mechanisms by which monocytes and macrophages contribute to the pathogenesis of HIV and the development of nADEs, with a focus on their roles as viral reservoirs, mediators of inflammation, and drivers of tissue damage.

2. HIV INFECTION OF MONOCYTES AND MACROPHAGES: KEY FACTORS IN THE PATHOGENESIS OF HIV

Monocytes and macrophages are significant targets for HIV-1 infection and play crucial roles in viral transmission, dissemination, and persistence. While monocytes can be infected by HIV-1, their susceptibility to the virus varies depending on their differentiation status. As monocytes differentiate into macrophages, they become more receptive to infection, acting as important reservoirs for the virus. These macrophages can productively replicate HIV-1 even in the presence of antiretroviral therapy (ART) (Parihar et al., 2010).

In contrast to CD4+ T cells, which are rapidly depleted during acute infections, HIV-infected monocytes and macrophages exhibit greater resistance to the cytopathic effects of the virus. This resilience allows them to harbor HIV for extended periods, contributing to viral persistence (Miguel et al., 2023). This, in turn, hinders efforts to achieve a cure and drives chronic immune activation and inflammation, leading to various consequences (Campbell et al., 2014).

The causes of chronic immune activation in HIV infection are complex and not yet completely

understood, encompassing both direct factors (such as the enduring presence of HIV RNA) and indirect triggers (microbial translocation and co-infections) (Mazzuti et al., 2022). But ultimately, the persistent antigenic stimulation leads to sustained elevations of pro-inflammatory cytokines, such as IL-6 and TNF- α , along with immune activation markers like CD38 and HLA-DR (Paiardini & Müller-Trutwin, 2013; Lederman et al., 2013). Monocytes, particularly the CD16+ intermediate and non-classical subsets, play a vital role in this inflammatory environment, exhibiting an activated phenotype characterized by increased expression of adhesion molecules, chemokine receptors, and toll-like receptors (TLRs), which enhances their migration into tissues and responsiveness to microbial products (Ancuta et al., 2008). The ongoing inflammation contributes to tissue damage and plays a role in the development of non-AIDS events (nADEs) (Burdo et al., 2011).

Moreover, HIV infection alters the functional properties of monocytes and macrophages, diminishing their ability to eliminate pathogens and regulate immune responses. For instance, HIV-infected macrophages demonstrate reduced phagocytosis and impaired antigen presentation capabilities, while monocytes exhibit downregulated MHC II expression. This downregulation inhibits the formation of MHC II-antigen complexes and diminishes the ability of monocytes to uptake antigens for processing and presentation to T cells (Nabatanzi et al., 2018). Such impairments contribute to immune exhaustion, increasing susceptibility to opportunistic infections (Kedzierska & Crowe, 2001). Additionally, HIV can induce a pro-fibrotic phenotype in macrophages, potentially leading to organ fibrosis and dysfunction in conditions such as liver cirrhosis and chronic kidney disease (Kaspar & Sterling, 2017).

In HIV infection, excessive production of reactive oxygen species (ROS) and impaired antioxidant defenses in macrophages and monocytes lead to oxidative stress, which exacerbates chronic inflammation, immune dysfunction, and organ-specific injury, even in individuals receiving antiretroviral therapy (ART) (Ivanov et al., 2016). Several mechanisms contribute to this issue.

One key mechanism is the upregulation of NADPH oxidase, a significant ROS-producing enzyme in macrophages, induced by HIV proteins such as tat and gp120. This results in the overproduction of superoxide and hydrogen

peroxide, which can damage lipids, proteins, and DNA. Additionally, HIV disrupts mitochondrial electron transport, causing an increase in mitochondrial ROS (Harshithkumar et al., 2024). It also depletes glutathione, the primary cellular antioxidant, by reducing the expression of glutamate-cysteine ligase in macrophages (Lin et al., 2023).

These mechanisms vary in intensity across different organs and contribute to the organ-specific damage observed in people living with HIV (PLWH), forming the basis for the development of non-AIDS-related events (nADEs).

3. ORGAN-SPECIFIC EFFECTS OF MONOCYTES AND MACROPHAGES IN HIV DISEASE: MECHANISMS OF TISSUE DAMAGE

3.1 Cardiovascular Disease (CVD)

HIV is the main contributing factor to CVD in PLWH, accounting for approximately a two-fold increase in the relative risk of this disease (Ancuta et al., 2008). CVD is the leading cause of death worldwide, and has atherosclerosis as the main underlying pathology (Jebari-Benslaiman et al., 2022).

Atherosclerosis is a condition in which plaque, made up of fat, cholesterol, and other substances, accumulates in the intima of arteries, causing them to narrow and stiffen. This process begins with damage to the endothelium, accompanied by the retention and modification of low-density lipoprotein (LDL) in the intima (Mundi et al., 2017). The recruitment of monocytes into the intima triggers an inflammatory state critical to the development of atherosclerosis. Monocytes recruited into the arterial wall differentiate into macrophages and foam cells, facilitating plaque formation (Subramanian et al., 2012).

Moreover, the increased elaboration of pro-inflammatory cytokines by HIV-infected monocytes and macrophages maintains a systemic inflammatory state, accelerating atherosclerosis and endothelial dysfunction (Deeks et al., 2013). Elevated levels of markers of macrophage activation, soluble CD163 and soluble CD14, are strongly associated with subclinical atherosclerosis and cardiovascular events in PLWH (Serrano-Villar et al., 2014).

Furthermore, the increased expression of adhesion molecules (ICAM-1, VCAM-1) and chemokine receptors (CCR2, CX3CR1) by HIV-infected monocytes enhances their adhesion to and infiltration into the vascular endothelium. This endothelial barrier disruption promotes vascular inflammation, exacerbates endothelial dysfunction, and vascular remodeling, thereby increasing cardiovascular risk (Hsue et al., 2012). Additionally, cytokines derived from macrophages (TNF- α , IL-6) and HIV proteins (Tat, Nef) directly activate endothelial cells, resulting in increased permeability that accelerates leukocyte recruitment (Ganor et al., 2019).

In addition, HIV infection and ART disrupt lipid metabolism, leading to elevated levels of triglycerides and LDL cholesterol. Macrophages in PLWH accumulate lipids and exhibit impaired cholesterol efflux due to downregulation of ABCA1 and ABCG1 transporters (Clayton et al., 2018). These proteins are crucial ATP-binding cassette transporters in macrophages that facilitate cholesterol efflux and play a role in reverse cholesterol transport. Deficiency or downregulation of these transporters can lead to increased cholesterol accumulation in macrophages, contributing to foam cell formation and potentially accelerating atherosclerosis (Yvan-Charvet et al., 2007).

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Additionally, HIV-infected monocytes and macrophages produce increased levels of pro-

inflammatory cytokines, maintaining a systemic inflammatory state that accelerates atherosclerosis and endothelial dysfunction (Deeks et al., 2013). Elevated levels of markers for macrophage activation, such as soluble CD163 and soluble CD14, have a strong association with subclinical atherosclerosis and cardiovascular events in PLWH (Serrano-Villar et al., 2014).

Furthermore, the increased expression of adhesion molecules (like ICAM-1 and VCAM-1) and chemokine receptors (such as CCR2 and CX3CR1) on HIV-infected monocytes enhances their ability to adhere to and infiltrate the vascular endothelium. This disruption of the endothelial barrier promotes vascular inflammation, worsens endothelial dysfunction, and contributes to vascular remodeling, all of which increase cardiovascular risk (Hsue et al., 2012). Cytokines released from macrophages (like TNF- α and IL-6) and HIV proteins (such as Tat and Nef) directly activate endothelial cells, resulting in increased permeability and accelerated recruitment of leukocytes (Hsue et al., 2012).

Lastly, HIV infection and ART can disrupt lipid metabolism, leading to elevated levels of triglycerides and LDL cholesterol. In PLWH, macrophages accumulate lipids and demonstrate impaired cholesterol efflux, largely due to the downregulation of critical ATP-binding cassette transporters, ABCA1 and ABCG1 (Yvan-Charvet et al., 2007). These transporters play a vital role in cholesterol efflux and reverse cholesterol transport. Their deficiency or downregulation can lead to increased cholesterol accumulation in macrophages, promoting foam cell formation and potentially accelerating atherosclerosis (Yvan-Charvet et al., 2007).

3.2 Neurocognitive Disorders

HIV-associated neurocognitive disorders (HAND) refer to a range of neurological and cognitive impairments linked to HIV infection and AIDS. These disorders remain common despite ART and can affect up to 50% of PLWH. HAND ranges from mild cognitive deficits to severe dementia and can significantly impact daily functioning (Adhikary et al., 2025).

The blood-brain barrier (BBB) is compromised in HIV infection, allowing for the establishment of viral reservoirs in the brain. The HIV-1 envelope glycoprotein, gp120, plays a key role in damaging the integrity of the BBB by altering

tight junction proteins in human brain microvascular endothelial cells (Said & Venketaraman, 2025). However, the initial trigger for HAND is the movement of HIV-infected monocytes across the BBB into the central nervous system (CNS), where they differentiate into perivascular macrophages (León-Rivera et al., 2021).

Perivascular macrophages are long-lived, tissue-resident cells that occupy the spaces around blood vessels. They express CD14, CD16, and CD163, and, together with microglia, contain HIV even in individuals receiving ART, contributing to chronic low-level viral replication (Kruize & Kootstra, 2019). Additionally, HIV-infected monocytes secrete matrix metalloproteinases (MMP-9), which degrade tight junction proteins (such as claudin-5 and occludin), thereby increasing BBB permeability. Similar to the pathogenesis of cardiovascular disease, the increased expression of adhesion molecules and chemokine receptors (such as CCR2 and CX3CR1) in HIV-infected monocytes enables their adhesion to and crossing of the BBB. Activated astrocytes and endothelial cells produce chemokines like CCL2, also known as monocyte chemoattractant protein-1 (MCP-1), which help recruit monocytes into the CNS (Hernandez et al., 2024).

The degradation of tight junctions, the apoptosis of endothelial cells, and the consequent BBB leakage allow plasma proteins (e.g., fibrinogen) and peripheral immune cells to infiltrate the CNS, exacerbating neuroinflammation and white matter damage (Salimi & Klein, 2019). Moreover, activated microglia can engage in "synaptic stripping," phagocytizing dendritic spines and synapses, causing synaptic loss, especially in the hippocampus and prefrontal cortex areas critical for memory and executive function (Schlachetzki et al., 2022). Soluble viral proteins (such as gp120, Tat, and Nef) secreted by infected macrophages contribute to excitotoxicity, oxidative stress, and synaptic damage (Marino et al., 2020). The CD16+ monocyte subset, which has a pro-inflammatory profile (Ong et al., 2018), plays a critical role in HIV neuroinvasion due to its high MMP-9 secretion (which leads to BBB breakdown) (Campos et al., 2014) and enhanced chemotaxis (Kruize & Kootstra, 2019).

However, inflammation and immune activation are central mechanisms driving the development of HAND, with various contributing factors. HIV-

infected macrophages release pro-inflammatory cytokines (such as TNF- α , IL-1 β , and IL-6) and chemokines (like MCP-1/CCL2), activating astrocytes and microglia while recruiting additional monocytes into the CNS, sustaining chronic neuroinflammation (Saylor et al., 2016).

Additionally, HIV RNA and proteins activate the NLRP3 inflammasome in macrophages, increasing the release of IL-1 β and IL-18. NLRP3 is primarily found in myeloid cells (monocytes, macrophages, and neutrophils) and acts as a sensor for pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), initiating an inflammatory response (Swanson et al., 2019). This activation occurs in two steps: first, HIV infection primes macrophages by increasing NLRP3 expression, and then specific viral components activate the inflammasome, resulting in the maturation and release of IL-1 β and IL-18 (Chivero et al., 2017).

Activated macrophages and microglia produce quinolinic acid, an N-Methyl-D-aspartate (NMDA) receptor agonist that induces excitotoxicity by overstimulating neurons. NMDA

receptors, which are the primary excitatory neurotransmitter receptors in the human brain, play a crucial role in synaptic plasticity, a neuronal mechanism thought to be fundamental for memory formation. Quinolinic acid also generates ROS, leading to mitochondrial dysfunction and neuronal apoptosis (Lugo-Huitrón et al., 2013).

These pathological processes ultimately result in a range of cognitive deficits, including asymptomatic neurocognitive impairment (subtle deficits detectable only through neuropsychological testing), mild neurocognitive disorder (functional impairment in daily activities), and HIV-associated dementia (severe cognitive and motor decline, which is now rare in the ART era) (Adhikary et al., 2025).

3.3 Liver and Kidney Disease

Common to the mechanism of tissue damage in other organs, chronic inflammation and immune activation driven by HIV-infected monocytes and macrophages play a central role in liver and kidney pathology among PLWH. However, the dynamics underlying the damage differ between the two organs.

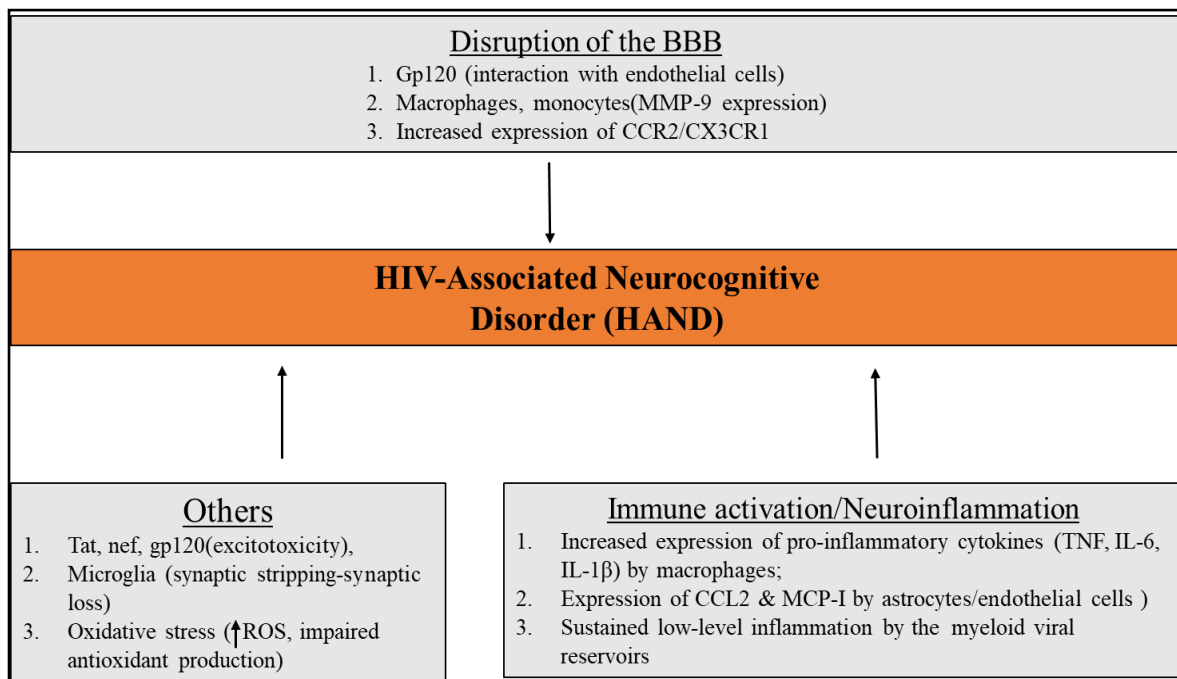


Fig. 1. Mechanisms of HAND. HIV-infected CD16+ monocytes migrate across the BBB enabled by CCR2/MMP-9 expression, seeding CNS reservoirs. Persistent viral proteins (Tat/gp120) and cytokines (TNF- α /IL-1 β) drive neuroinflammation, oxidative stress, and synaptic damage, culminating in cognitive decline

Most of the focus on liver disease has been on individuals co-infected with HCV or HBV. However, even though the apparent net effect of HIV on liver fibrosis is most evident in the presence of a second contributor, such as HCV infection, HBV infection, excessive alcohol use, or metabolic liver disease, HIV infection itself biases the liver toward fibrosis and synergistically promotes these other processes. There is also significant evidence suggesting that even without primary liver disease, HIV itself may cause liver steatosis and fibrosis (Sherman & Thomas, 2022).

Various seemingly overlapping mechanisms have been proposed to explain how HIV may potentiate or cause liver fibrosis, but they all converge on the central role of the hepatic stellate cell (HSC). HSCs are pivotal in liver fibrosis, where the liver develops scar tissue secondary to chronic injury. When HSCs are activated, they can transdifferentiate from a quiescent to an activated phenotype, producing excess extracellular matrix (ECM), which contributes to the development of fibrosis, cirrhosis, and other liver diseases (Hoffmann et al., 2020).

HIV-infected Kupffer cells (resident liver macrophages) and circulating monocytes that migrate to the liver become chronically activated due to viral persistence. They create a pro-inflammatory microenvironment in the liver by releasing TNF- α , IL-6, IL-1 β , and CCL2. (Mosoian et al., 2016), while HIV proteins (Tat, Nef), which directly enhance macrophage activation, may stimulate signaling pathways such as NF- κ B, amplifying cytokine production. Additionally, activated macrophages secrete TGF- β , a key fibrogenic cytokine, and platelet-derived growth factor (PDGF), a potent mitogen (Mosoian et al., 2016). These factors are crucial in transitioning HSCs from a quiescent to an activated state.

Furthermore, HIV-infected macrophages generate ROS, which directly activate HSCs and enhance TGF- β signaling, exacerbating the process of tissue damage. In addition, HIV-induced gut barrier dysfunction allows translocation of microbial components, especially lipopolysaccharides (LPS), to the liver. These bind to TLR4 on Kupffer cells, further amplifying cytokine production (e.g., IL-1 β via NLRP3 inflammasome activation) (Hoffmann et al., 2020). Ultimately, the resulting accumulation of ECM disrupts liver architecture, leading to cirrhosis and impaired hepatic function.

HIV-infected monocytes and macrophages significantly contribute to HIV-associated kidney disease, particularly HIV-associated nephropathy (HIVAN) and immune-complex-mediated glomerulonephritis, through direct viral infection, chronic inflammation, and podocyte injury. HIVAN, characterized by focal segmental glomerulosclerosis with collapsing glomerulopathy and tubulointerstitial inflammation, is underpinned by various pathological processes. HIV-infected macrophages expressing pro-inflammatory cytokines (TNF- α , IL-6, and TGF- β) promote fibrosis and glomerular scarring (Medapalli, He & Klotman, 2011). Additionally, infected macrophages release IL-1 β via NLRP3 inflammasomes, amplifying glomerular damage (Ekabe et al., 2021). Podocytes can also be infected, but through non-conventional mechanisms (HIV-receptor-independent). One such mechanism is through virological synapses and tunneling nanotubes between CD4+ T cells, macrophages, and renal cells. These facilitate HIV spread among these different cell types (Hughes et al., 2021). Infection of podocytes triggers apoptosis, loss of function, and dedifferentiation, all contributing to glomerular damage (Hughes et al., 2021).

3.4 Cancer

While ART has reduced the incidence of AIDS-defining cancers, PLWH still experience an elevated risk for certain non-AIDS-defining cancers due to multiple mechanisms, including improvements in life expectancy with ART, immunosenescence, and the loss of control over oncogenic infections due to HIV-related immune suppression. But additionally, macrophage-derived chronic inflammation and immune activation create a microenvironment conducive to carcinogenesis (Grulich et al., 2007). Hodgkin lymphoma and cancers of the lung, anus, liver, which are non-AIDS malignancies have become more prevalent in PLWH (Wang, Silverberg & Abrams, 2014).

While ART has significantly reduced the incidence of AIDS-defining cancers, PLWH still face an increased risk for certain non-AIDS-defining cancers. This heightened risk arises from various factors, including the prolonged life expectancy associated with ART, immunosenescence, and diminished control over oncogenic infections due to HIV-related immune suppression (Wang, Silverberg & Abrams, 2014). Furthermore, macrophage-driven immune dysregulation contributes to a microenvironment

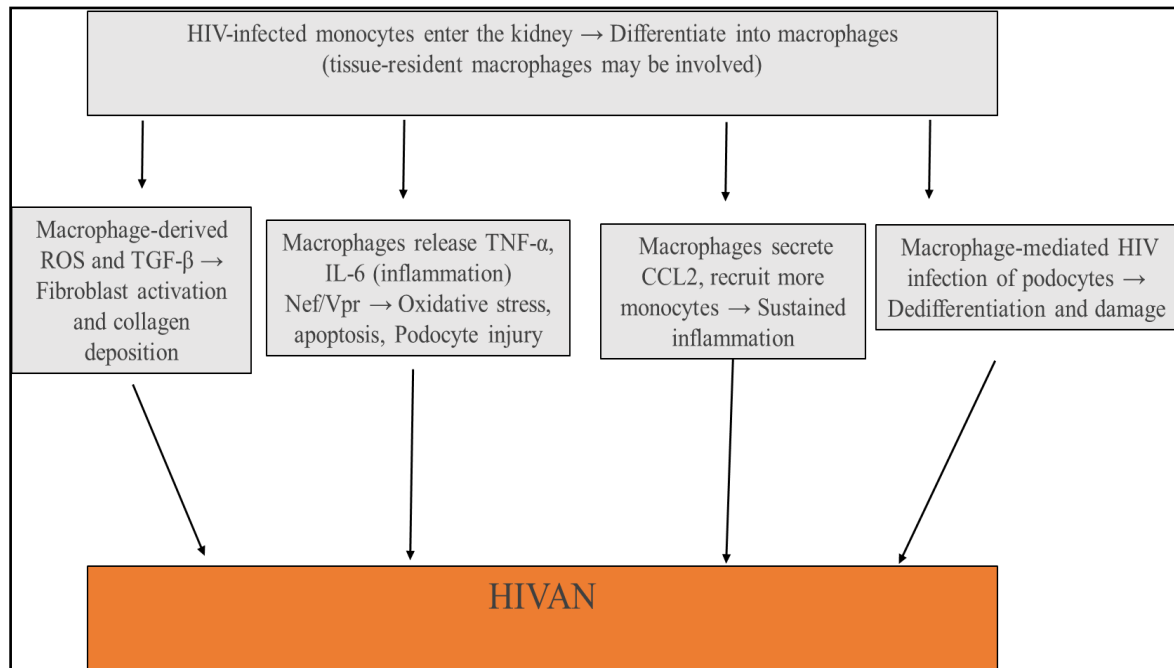


Fig. 2. Mechanisms of HIV-associated nephropathy (HIVAN)

that favors carcinogenesis (Grulich et al., 2007). Consequently, non-AIDS malignancies, such as Hodgkin lymphoma and cancers of the lung, anus, and liver, have become more prevalent among PLWH (Wang, Silverberg & Abrams, 2014).

The chronic inflammatory state induced by the increased secretion of proinflammatory cytokines from HIV-infected monocytes and macrophages promotes DNA damage, inhibits apoptosis in malignant cells, and supports tumor cell proliferation (Grivennikov, Greten & Karin, 2010). For instance, IL-6 activates JAK-STAT3 signaling in epithelial cells by binding to its receptor (IL-6R). Activating this signaling pathway leads to downstream effects on gene expression and cellular behavior, including driving the expression of genes involved in cell survival, proliferation, angiogenesis, and metastasis, ultimately facilitating oncogenic transformation in certain cells (Thuya et al., 2025).

Secondly, HIV alters macrophage polarization, steering them toward a pro-tumor M2-like phenotype, characterized by increased PD-L1, IL-10, and TGF- β expression. These factors suppress the cytotoxic T-cell responses and encourage the expansion of regulatory T-cells (Tregs), which favors immune escape by tumours (Li et al., 2024). Furthermore, chronic HIV activation boosts the population of

monocyte-derived myeloid-derived suppressor cells (MDSCs), which impede the functions of NK and CD8+ T-cells. MDSCs are linked to aggressive tumor growth and poorer outcomes in HIV-related cancers (Tumino et al., 2022).

Moreover, metabolic reprogramming within the tumor microenvironment—exemplified by increased glycolysis in HIV-infected monocytes and macrophages—results in the production of lactate. The lactate acidifies the tumor environment, suppresses antitumor immunity, and promotes metastasis. Additionally, the elevated production of ROS from dysfunctional mitochondria in these HIV-infected cells causes DNA damage in adjacent cells. This damage affects oncogenes and tumor suppressor genes, thereby increasing the risk of carcinogenesis (Zhou et al., 2022).

4. THERAPEUTIC IMPLICATIONS

Given the substantial evidence highlighting the crucial involvement of monocytes and macrophages in the development of nADEs, targeting the mechanisms by which these cells contribute to these pathologies presents a promising strategy for alleviating chronic inflammation and enhancing clinical outcomes in PLWH in the era of viral suppression. Non-specific, potential therapeutic approaches include:

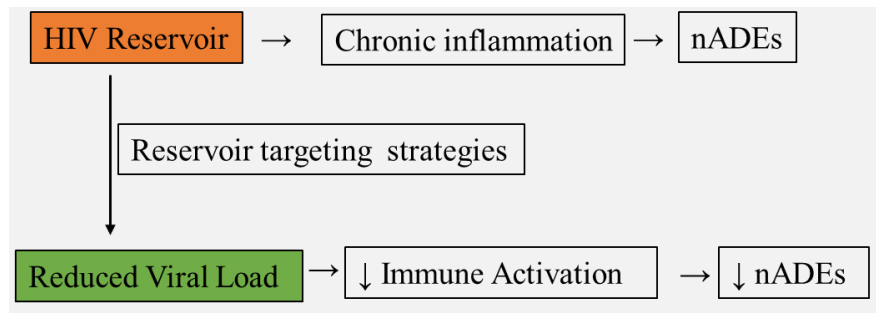


Fig. 3. Conceptual Basis for Employing Reservoir Targeting Strategies

Table 1. Plausible mechanisms of amelioration of nADEs following successful reservoir reduction/elimination

nADE	Mechanism of amelioration
Neurocognitive (HAND)	↓ HIV-infected microglia, ↓ neuroinflammation
Cardiovascular	↓ IL-6/TNF- α → ↓ endothelial dysfunction
Liver/Kidney Fibrosis	↓ TGF- β → ↓ collagen deposition

4.1 Reservoir-Targeting Strategies

The persistence of latent or transcriptionally active viruses in myeloid cells despite ART remains a major barrier to cure efforts and a major contributor to the chronic immune dysfunction underlying the development of nADEs. Reservoir-targeting strategies aim to eliminate persistent HIV and reduce chronic inflammation, directly addressing the root cause of nADEs. While challenges remain (e.g., myeloid reservoir penetration (Chun, Moir & Fauci, 2015)), combined approaches promise to improve long-term outcomes for PLWH. Eliminating HIV reservoirs in monocytes and macrophages is critical for achieving a cure and lowering the risk of nADEs.

Recent research provides evidence supporting strategies to target these reservoirs by employing latency-reversing agents such as TLR agonists (Li et al., 2023) and gene-editing technologies using CRISPR to excise HIV DNA from infected macrophages (Das et al., 2019). The ultimate aim is to reduce reservoir load, lower immune activation and inflammation, and decrease the incidence of nADEs.

4.2 Anti-Inflammatory Therapies

Agents that modulate the activation of monocytes and macrophages, such as statins, aspirin, and cytokine inhibitors (e.g., IL-6 and TNF- α blockers), may help reduce inflammation and lower the risk of nADEs. Specifically, statins can influence vascular atherosclerotic inflammation

by directly enhancing the function of endothelial cells, vascular smooth muscle cells, platelets, and immune cells. Additionally, rosiglitazone, a PPAR-gamma agonist, has demonstrated potential in halting brain inflammation and inhibiting HIV replication in murine models of HIV encephalitis.

4.3 Restoring Immune Homeostasis

Interventions designed to restore the functional properties of monocytes and macrophages, such as enhancing phagocytosis and promoting anti-inflammatory phenotypes, may contribute to mitigating tissue damage and improving overall outcomes. In particular, modulating macrophage function by shifting polarization from pro-inflammatory M1 to anti-inflammatory M2 (and vice versa) could have significant implications for HIV pathogenesis and the development of non-antibody-dependent enhancement (nADEs) (Luo et al., 2024).

5. CONCLUSION

Monocytes and macrophages play crucial roles in the pathogenesis of HIV disease and the development of nADEs. Their functions as viral reservoirs, drivers of chronic inflammation, and mediators of tissue damage underscore the need for targeted therapeutic strategies to address these mechanisms. While current challenges such as low myeloid cell penetration, reservoir heterogeneity, and limited CNS penetration still need to be overcome, understanding and modulating the functions of monocytes and

macrophages presents a promising strategy for reducing the burden of nADEs and enhancing the long-term health outcomes of PLWH.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

The author hereby declares that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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