Published in final edited form as:

AIDS. 2014 September 24; 28(15): 2175–2187. doi:10.1097/QAD.0000000000000408.

The importance of monocytes and macrophages in HIV pathogenesis, treatment, and cure

Jennifer H. Campbell[a], **Anna C. Hearps**[b,c], **Genevieve E. Martin**[b], **Kenneth C. Williams**[a], and **Suzanne M. Crowe**[b,c,d]

[a]Department of Biology, Boston College, Chestnut Hill, Massachusetts, USA

[b]Centre for Biomedical Research, Burnet Institute, Melbourne, Victoria, Australia

[c]Department of Infectious Diseases, Monash University, Melbourne, Victoria, Australia

[d]Infectious Diseases Unit, The Alfred Hospital, Melbourne, Victoria, Australia

Abstract

Monocytes and macrophages play critical roles in HIV transmission, viral spread early in infection, and as a reservoir of virus throughout infection. There has been a recent resurgence of interest in the biology of monocyte subsets and macrophages and their role in HIV pathogenesis, partly fuelled by efforts to understand difficulties in achieving HIV eradication. This article examines the importance of monocyte subsets and tissue macrophages in HIV pathogenesis. Additionally, we will review the role of monocytes and macrophages in the development of serious non-AIDS events including cardiovascular disease and neurocognitive impairment, their significance in viral persistence, and how these cells represent an important obstacle to achieving HIV eradication.

Keywords

HIV cure; HIV pathogenesis; macrophage; monocyte; reservoirs

Pathogenesis

Myeloid lineage cells are targets of HIV infection

By harboring HIV long term without cytolysis [1,2], monocytes and macrophages, compared with $CD4^+$ T cells, provide a reservoir of HIV [3,4]. In the circulation, phenotypically unique subpopulations of monocytes exist that are distinguished based on size, granularity, and expression of surface markers [1,2,5]. In healthy people, cells expressing the lipopolysaccharide (LPS) receptor CD14 but not CD16 (classical $CD14^{++}CD16^{-}$ monocytes) make up 80–90% of monocytes [5] (Table 1) [6–8]. Inflammation and peripheral immune activation during HIV infection are associated with increased numbers of

Correspondence to Professor Suzanne M. Crowe, Centre for Biomedical Research, Burnet Institute, Melbourne, Victoria 3001, Australia., Tel: +61 3 9282 2194; fax: +61 3 9282 2142; crowe@burnet.edu.au.

Conflicts of interest

The authors declare that no conflicts of interest exist.

circulating $CD14^{++}CD16^{+}$ (intermediate) and $CD14^{+}CD16^{++}$ (nonclassical) monocytes [9,10], and the degree of $CD16^{+}$ monocyte expansion is closely linked to the rate of disease progression [11]. Then they can reach 10–50% of circulating monocytes depending upon disease state and antiretroviral therapy (ART) status [9–12] (Table 1).

Historically, monocytes have not been considered to be a significant target of HIV infection [14,15]. Early studies indicate that even though they are activated and express HLA-DR, infection is dependent on their differentiation into macrophages [16,17]. However, more recent literature demonstrates that monocytes, particularly the $CD16^{+}$ intermediate and $CD16^{++}$ nonclassical cells, can be infected by HIV [18,19]. Of relevance, monocytes expressing CD16 are thought to have a more mature immune phenotype consistent with macrophages, which may partly account for their ability to become infected.

Relative to $CD4^{+}$ T lymphocytes, monocytes and macrophages are more resistant to productive HIV infection as a result of maturation and activation-dependent host factors. Differential expression of host restriction factors including SAMHD1 (sterile motif and histidine aspartic domain and HD domain-containing protein 1), viperin [virus inhibitory protein, endoplasmic reticulum-associated, interferon (IFN)-inducible)], and members of the APOBEC (apolipoprotein B mRNA editing enzyme) 3G family can affect productive infection of monocytes and macrophages [20–23] (Fig. 1). Classical monocytes, in particular, express the low-molecular-weight forms of APOBEC3A and APOBEC3G that block HIV reverse transcription [18,24]. In contrast, intermediate and nonclassical monocytes express higher-molecular-weight forms of these enzymes that support HIV replication [18,21,24].

By hydrolyzing cellular deoxyribonucleotides and reducing the pool of nucleotides available for reverse transcription [25], SAMHD1 expression restricts viral replication in monocytes and macrophages [26]; cells lacking SAMHD1 are highly susceptible to infection [20]. Mechanisms underlying the antiviral activity of viperin remain unclear; however, viperin levels are increased upon HIV infection of monocytes and macrophages and inhibit production of infectious virus [22]. Recent studies implicate naturally occurring cellular microRNAs (miRNAs-28, -150, -223, -382) in restricting monocyte infection [27]. Chemokines and cytokines in the surrounding environment can also dictate expression of cellular restriction factors in monocytes and macrophages (reviewed in [28]), and influence their levels of productive HIV replication [29].

Monocytes and macrophages as viral reservoirs

Monocytes and macrophages are in anatomic reservoirs including tissues such as the brain and lung and can persist by avoiding immune system detection. In the central nervous system (CNS), parenchymal microglia, meningeal macrophages, choroid plexus macrophages, and perivascular macrophages all express viral co-receptors and are susceptible to HIV infection [30,31]. Perivascular macrophages are the most consistent targets of HIV in the brain [32], and viral DNA can be isolated from these cells throughout infection, indicating that they are viral reservoirs [33].

A recent study in simian imunodeficiency virus (SIV)-infected rhesus macaques underscores the importance of lung alveolar and interstitial macrophages in local viral infection [34]. Alveolar macrophages are a primary viral target in the lung [35]; interstitial macrophages that are repeatedly renewed from monocytes can also be infected [34]. *Pneumocystis jirovecii* coinfection augments viral infection and macrophage activation in the lung [36,37].

In the gastrointestinal tract (GIT) of ART-naive individuals, high levels of chemokines/cytokines (e.g. CCL2, IL1β, CCL5, CXCL9, CXCL10) are produced and activated mucosal macrophages with poor phagocytic activity accumulate [38]. Unlike the CNS and lungs, GIT macrophages downregulate CD4 and CCR5 in response to HIV [39]. Though this remains an open question, downregulation of CD4 and CCR5 may in part result in reduced viral infection in these GIT macrophages.

HIV can also infect marginal zone macrophages in the spleen but conflicting data exist on whether these cells maintain a reservoir of virus [40].

The low frequencies of HIV-infected monocytes and the difficulty in obtaining tissue samples present major barriers to elucidating the dynamics of HIV infection and productive viral replication in human monocytes and macrophages. Experiments in SIV-infected macaques have provided critical insights into the role of monocytes and macrophages in viral persistence and maintenance of tissue reservoirs (reviewed in [41,42]). There are higher levels of SIV-infected monocytes and macrophages in monkeys than HIV-infected cells of this lineage in humans, in part reflecting differences in the primate lentiviral auxiliary protein x (Vpx) between SIV and HIV [26]. By inducing proteasomal degradation of the host restriction factor SAMHD1, Vpx increases monocyte and macrophage susceptibility to SIV infection [26].

In the absence of inflammation, monocytes continuously leave the bone marrow and circulate in blood for 3–5 days before trafficking into tissues [43]. With SIV infection, there is increased egress of classical, nonclassical, and intermediate monocyte subsets from the bone marrow, and these cells remain in the circulation for a short amount of time before entering tissues [44]. We have shown that monocytes from HIV-infected individuals have shortened telomeres. Because monocytes do not divide in the blood, this observation may reflect increased cell division and subsequent shortening of telomeres in bone marrow monocyte precursor cells [45]. These findings suggest that monocyte turnover and release from the bone marrow may also increase during HIV infection [45].

Upon $CD4^+$ T-cell depletion during chronic SIV infection in macaques, macrophages comprise more than 95% of productively infected cells in lymph nodes; high numbers of SIV RNA+ macrophages are also evident in the CNS and lungs [46,47]. Although sequencing studies have found little difference in HIV-1 subspecies in the blood and lungs [48], there appears to be independent evolution of virus in other tissues and phylogenetically distinct transcripts are present in the plasma, spleen, lymph nodes, and CNS [49–52]. Although all viral strains (X4, R5, or T cell vs. macrophage-tropic) can enter the CNS of HIV and SIV-infected humans and monkeys, the bulk of the data demonstrate that macrophage-tropic viruses preferentially replicate in the CNS [49,53–55]. It is quite possible

that $CD4^+$ T cells and monocytes/macrophages can bring virus into the CNS early in infection; analysis of sequence evolution within the CNS has revealed that these macrophage-tropic viruses seed the brain throughout infection and are the major strains that replicate with disease [56,57].

The proportion of intermediate and nonclassical monocytes expressing $CD16^+$ varies between individuals but is higher in ART-naive vs. individuals on ART, with these cells contributing significantly to disease pathogenesis [19,45,58]. The proportion of $CD16^+$ monocytes in virologically suppressed individuals on ART is comparable with that in HIV-infected elite controllers [59]. Despite this, $CD16^+$ monocytes are preferentially infected and recovered from blood even during sustained virologic suppression when compared with classical monocytes [18]. $CD16^+$ monocytes have also been shown to harbor viral variants that are genetically distinct from sequences in resting $CD4^+$ T cells [60]. Taken together, the contribution of monocytes to the viral reservoir may vary throughout infection and with therapy.

Role of monocytes and macrophages in opportunistic infections—With HIV infection, the reduced phagocytic ability of monocytes and macrophages contributes to increased host susceptibility to opportunistic pathogens [61,62]. Both *Mycobacterium tuberculosis* (MTb) and HIV infect alveolar macrophages and coinfection can augment production of tumor necrosis factor (TNF)α, IFN-γ, and CCL2 [63]. In some coinfected patients, tuberculosis (TB)-associated immune reconstitution inflammatory syndrome (TB-IRIS) occurs following ART initiation. It reflects a heightened inflammatory response to MTb, with new or worsening symptoms [64]. TB-IRIS may present in one of two clinical forms: paradoxical TB-IRIS, when symptoms of TB develop or recur during antituberculosis treatment following ART initiation, or unmasked TB-IRIS with an initial clinical presentation of TB, often with a strong inflammatory component, during early ART. Although the pathogenesis of TB-IRIS is not well understood, recent gene expression studies suggest that inherent differences in gene expression by monocytes contribute to the development of TB-IRIS and that monocytes mediate important activities during TB-IRIS [65,66].

Role of monocytes in neuroAIDS

In the ART era, the incidence of HIV-associated dementia has declined, yet the prevalence of milder forms of HIV-associated neurocognitive disorders (HANDs) continues to increase [67,68]. Importantly, development of HAND is associated with higher rates of AIDS-defining illnesses [69] and increased mortality [70]. The events leading to neuronal injury with HAND are not well understood; however, the presence of activated and productively infected macrophages and microglial cells are the best correlates of CNS disease severity [11,71–79] (Table 2). Recent data suggest that the event initiating macrophage activation and accumulation in the CNS is activation, expansion, and viral infection of monocytes trafficking from bone marrow [73–75,80,81]. Supporting this finding, elevated levels of cytokines [interleukin (IL)-6, IL-8, IFNγ] and proteins linked with monocyte activation (sCD14) and chemotaxis (MCP-1, CCL3, CXCL10) in the cerebrospinal fluid (CSF) of

HIV-infected individuals on ART are associated with impaired neurocognition and the severity of neuropathology [76,82].

Persistently increased numbers and/or percentages of $CD16^+$ monocytes are more tightly linked to the development of neurological disease than the number of HIV-infected cells in the CNS or CSF viral load [75,83]. Infection of $CD16^+$ monocytes increases the capacity of these cells to migrate across the blood-brain barrier (BBB) [84] wherein they can stimulate productive viral replication in the brain [80]. Monocytes expressing the CD16 receptor are immunophenotypically similar to perivascular macrophages in the CNS, in that the majority of $CD16^+$ monocytes express the haptoglobin-hemoglobin scavenger receptor CD163, and all $CD163^+$ perivascular macrophages in the CNS express CD16 [76,85,86]. Although HIV does not directly infect neurons, increased production of proinflammatory chemokines/cytokines and other excitotoxic factors by perivascular macrophages and activated microglia contribute to neuronal injury and death [87,88] (Fig. 2). Release of inflammatory chemokines/cytokines (MCP-1, CX3CL1, CXCL10, CCL3, IL-1β, TNFα, IFNα) within the CNS also stimulates up regulation of adhesion molecules on the brain microvascular endothelia [89,90], thereby recruiting monocytes to the BBB and promoting their transmigration into the brain [91].

It is generally assumed that HIV enters the brain within infected monocytes, but this has not been directly demonstrated. Evidence that HIV enters the CNS soon after peripheral infection was demonstrated by accidental iatrogenic infection [92]. In SIV-infected rhesus macaques, gliosis, glial nodules, and scattered productively infected cells are evident in frontal lobes, temporal lobes, and white matter shortly after infection [93,94]. Interestingly, after initial seeding of virus, SIV RNA and p27 are not found until evidence of AIDS, probably the result of late seeding of the CNS by macrophages [95].

Evidence suggests that monocytes dictate the timing and severity of neurological sequelae during HIV infection. In virologically suppressed HIV-infected individuals on ART, levels of sCD163 in the plasma are associated with neurocognitive decline, suggesting that persistent activation of $CD16^+$ monocytes plays a role in CNS disease [96]. Furthermore, experiments in rhesus monkeys using the thymidine analog 5′-bromo-2′-deoxyuridine (BrdU) to monitor monocyte dynamics during infection have underscored the importance of monocytes in CNS disease. In SIV-infected animals, the magnitude of BrdU+ monocytes released from bone marrow is a more accurate indicator of the rate of AIDS progression than plasma virus or $CD4^+$ T-cell count [44]. Rapid development and histopathologic severity of SIV encephalitis are associated with the degree of $BrdU^+$ monocyte expansion during the first 4 weeks of infection [97]. Moreover, sCD163 in plasma correlates with the percentage of BrdU-labeled monocytes and $CD16^+$ monocytes [97]. These findings suggest that innate immune activation early in infection is critical for determining overall disease outcomes. Finally, in ART-naive individuals, HIV DNA levels in CD16+ monocytes are closely linked to the development and severity of neuropathology. This observation implicates the size of the monocyte HIV reservoir in neuropathogenesis [98,99].

Role of monocytes in serious non-AIDS events

HIV-infected individuals are at increased risk for a range of comorbidities including cardiovascular disease (CVD), non-AIDS malignancies, neurocognitive disorders, renal, bone and liver dysfunction, and frailty [100]. These conditions, collectively known as serious non-AIDS events (SNAEs), now represent the major cause of mortality in virologically suppressed HIV-infected individuals [101]. Persistent HIV-related inflammation and innate immune activation, both incompletely restored by ART, are thought to underpin the increased risk of these diseases, rather than T-cell activation [102]. This is supported by high plasma levels of inflammatory markers (e.g., hsCRP and IL-6 [103]) and monocyte activation (sCD14) [104]) that predict all-cause mortality in HIV-infected individuals. Chronic low-level endotoxemia in HIV-infected individuals can result from microbial translocation across the gut mucosa [105]. Subsequent passage of microbial products via the portal vein into the liver can lead to monocyte activation, altered coagulation, and systemic inflammation. This eventually can result in end-organ damage and development of SNAEs.

Low bone mineral density (BMD; reviewed in [106]) and osteoporosis [107] are common in HIV-infected people. Although T-cell activation has been linked to low BMD [108], monocyte/macrophage activation has not been directly implicated [109]. HIV infection is also associated with an increased risk of frailty and a lower age of onset [110]. Markers of monocyte activation including neopterin and CXCL10 [111] are associated with frailty in uninfected persons, but data are limited in HIV-infected individuals.

Monocyte activation and cardiovascular disease in HIV infection

HIV infection is associated with an approximately two-fold relative risk of CVD [112], persisting after adjustment for traditional risk factors. Moreover, CVD risk prediction algorithms including the Framingham Risk Score may underestimate the degree of atherosclerosis during HIV infection, with 56.4% of HIV-infected individuals with a low estimated CVD risk having evidence of subclinical atherosclerosis [113]. The prevalence of atherosclerosis in this low-risk group was independently associated with levels of oxidized LDL and MCP-1 [113], which promote monocyte recruitment to the subendothelial space where atherosclerotic lesions develop (reviewed in [114]).

Measures of HIV disease progression including viral load and $CD4^+$ T-cell count and markers of T-cell activation are poor predictors of CVD risk and events in HIV-infected individuals [115]. These clinical outcomes are increasingly being shown to correlate with inflammatory markers such as hsCRP, IL-6, and TNF, and monocyte activation [116–118].

Monocyte activation during HIV infection persists despite ART [45,58]. We and others have shown that monocyte expression of CD11b and CX3CR1 are associated with carotid intima–media thickness (cIMT; a surrogate measure of atherosclerosis) in HIV-infected individuals [119,120], whereas others demonstrate that monocyte activation phenotype in HIV-infected individuals is similar to uninfected individuals with CVD [6]. The proportion of inflammatory $CD16^+$ monocytes is increased in untreated HIV infection and predicts progression of coronary artery calcium, independent of traditional risk factors [115].

Monocytes play a critical role in atherosclerosis; they migrate across activated endothelial cells into fatty streaks within the subendothelium, where they mature into macrophages and endocytose lipids (Fig. 3). Monocytes can egress from the subendothelial space and remove lipid to prevent plaque progression [121]; however under inflammatory conditions, they are more likely to be retained and develop into lipid-laden foam cells. Lipid uptake by foam cells results in necrosis, inflammation, and expansion of the atherosclerotic core, whereas increased matrix metalloproteinase activity by resident macrophages increases plaque instability and promotes rupture [122].

The relationship between monocyte/macrophage activation and CVD is supported by biomarker data. In HIV-infected individuals, plasma sCD163 levels are associated with noncalcified coronary plaques [123,124] and arterial inflammation [125]. Increased levels of sCD14 and LPS are independently associated with increased cIMT, in some [126,127] although not all cohorts [128]. Elevated sCD14 is also independently associated with coronary artery calcification [129]. Importantly, the association between monocyte activation and CVD risk (Table 3) [113,115,118,120,123–125,127,129,130] observed in cohorts of ART-treated individuals is independent of protease inhibitor use (linked to increased CVD risk in HIV infection) [131]. The increased prevalence of atherosclerosis and monocyte activation (evidenced by increased sCD163 levels) in HIV elite controllers who maintain viral suppression without ART [132] highlights the critical role of immune activation in HIV-related CVD risk independent of viral and ART parameters.

Despite these associations, mechanistic explanations for how monocytes contribute to CVD in HIV infection are lacking. We recently demonstrated that elevated numbers of $CD163^+$ macrophages in the hearts of SIV-infected monkeys correlate with the severity of fibrosis and overall cardiac damage [133]. Further, we found an increased percentage of $CD16^+$ monocytes by 8 days postinfection in animals that developed cardiac disease and fibrosis (K. Williams unpublished results). We have previously shown that HIV impairs the ability of monocytes to egress from an in-vitro plaque model [134], which may promote their retention in atherosclerotic lesions *in vivo*. Our recent findings indicate that monocytes from HIV-infected individuals have a heightened potential to form foam cells [135]. Further work is essential to elucidate the association of HIV-associated inflammation and immune activation with atherogenesis.

Treatment and cure

In the era of effective ART, the new challenges in HIV treatment involve ameliorating the increased risk of SNAEs and moving toward a ‘functional HIV cure’, meaning undetectable viremia and no evidence of disease progression in the absence of ART.

Targeting inflammation to prevent serious non-AIDS events

Therapeutic strategies to prevent co-morbidities such as CVD in HIV-infected individuals need to target the component of this risk driven by inflammation and monocyte activation. The ability of the anti-inflammatory statin rosuvastatin to improve cardiovascular and skeletal health in HIV infection by simultaneously targeting inflammation and dyslipidemia is currently being evaluated in the SATURN-HIV trial. Preliminary data indicate

rosuvastatin can reduce markers of monocyte activation, including sCD14 and tissue factor expression on monocytes, independent of its lipid-lowering effects [7]. This activity is also associated with increased bone mineral density [109]. Thus, anti-inflammatory drugs may be able to ameliorate markers of inflammation and monocyte activation in ART-treated individuals. Whether this effect translates to a reduction in SNAEs will be an area of intense interest in coming years.

HIV eradication

Experiments involving the transplantation of HIV-resistant CCR5Δ32 stem cells into an HIV-infected individual (the 'Berlin patient') have demonstrated that a sterilizing cure for HIV infection may be possible; however, this approach is definitely not a universal option for cure [136]. In this regard, after a period of sustained virologic suppression, cessation of ART was associated with HIV rebound in two HIV-infected individuals who received bone marrow transplantation with wild-type CCR5 stem cells [137]. This observation indicated that latent infection in long-lived cells and tissues can persist despite bone marrow transplantation and long-term ART [138].

HIV-infected individuals may also be 'functionally cured' of HIV, meaning that although HIV DNA and RNA persist in cells and tissues, they maintain undetectable plasma viral loads without ART [139]. Despite low levels of HIV in the plasma of elite controllers, replication-competent virus can be found in resting $CD4^+$ T cells [140] and infrequently in circulating monocytes [141]. Elucidating the molecular mechanisms by which replication-competent virus is suppressed in these cellular reservoirs will be critical to design a therapeutic strategy that might affect a functional cure.

Persistent infection in latently infected cells

In the vast majority of virologically suppressed HIV-infected individuals on ART, reservoirs of latently infected cells (including resting $CD4^+$ T cells and $CD16^+$ monocytes in the bone marrow, thymus, blood, brain, and other tissues) persist, containing replication-competent, transcriptionally silent, latent provirus. This represents a major barrier to the eradication of HIV [142–144] (Fig. 4).

Although latently infected $CD4^+$ T cells, particularly central memory T cells, comprise the majority of the HIV reservoir, analysis of viral sequences isolated during episodic increases in viral load in ART-treated individuals suggests this virus is coming from cells other than $CD4^+$ T cells [145]. Importantly, even in the presence of ART, activated $CD16^+$ monocytes are capable of perpetuating HIV replication through ongoing cell-to-cell transfer of virions and efficient infection of $CD4^+$ T cells [146,147].

Efficacy of antiretroviral therapy in targeting monocytes and macrophages

Intensification of ART using maraviroc and raltegravir can reduce the size of the peripheral latently infected $CD4^+$ T-cell reservoir [148]; however, specific data on the impact of ART intensification on the monocyte/macrophage reservoir are lacking. Initiating therapy early after seroconversion reduces the number of latently infected $CD4^+$ T cells in the blood, GIT [149], and brain [150] and decreases HIV DNA to levels that are similar to that in elite

controllers [151]. These findings suggest that both intensifying treatment and initiating ART during early infection can decrease the overall size of the latent HIV reservoir.

The biologic characteristics of monocytes and macrophages, however, may reduce the efficacy of such strategies in these cells. HIV-infected monocytes are more resistant than $CD4^+$ T cells to the effects of antiretroviral compounds, although newer classes of drugs may hold more promise. Early in-vitro work indicated that chronically infected monocytes/macrophages are less susceptible to the effects of the nucleoside reverse transcriptase inhibitor (NRTI) zidovudine than acutely infected $CD4^+$ T cells [152]. Although protease inhibitors are effective in stopping the release of infectious virions from productively infected macrophages, these drugs are less effective against latent infection [153,154] and high concentrations of protease inhibitors are required to suppress HIV replication in these cells [155].

The CCR5 inhibitor maraviroc can reach high concentrations in the GIT and reduce the size of the gut reservoir [156]. Maraviroc can also directly prevent infection of monocyte-derived macrophages *ex vivo*, thus potentially impacting the size of reservoirs in these cells *in vivo*. However, specific studies in HIV-infected individuals are currently lacking [156].

The integrase inhibitor raltegravir is equally potent in macrophages as in lymphocytes [157] and can reach therapeutic concentrations in the CSF [158]. This result is advantageous for targeting infected cells including macrophages in the brain. However, although multiple mutations are required to confer raltegravir resistance in T cells, this can be achieved via a single mutation in macrophages [159].

Factors contributing to persistent inflammation and HIV infection in the CNS despite effective therapy include limited neuropenetrance of many antiretroviral drugs [160,161] and neurotoxicity of some antiviral drugs capable of penetrating the CNS [162,163]. They may potentiate inflammation and immune activation. Even when therapy is initiated during primary infection, CNS immune activation is still evident more than 4 years after effective ART [164] and 80–90% of virologically suppressed HIV-infected individuals at autopsy have prominent activated and productively infected macrophages in the CNS [165]. This finding suggests that neuropenetrance of ART may not be sufficient to prevent HIV-related neuronal damage and target macrophage reservoirs of HIV in the brain. Three recent studies indicate that the ability of an antiviral drug to target CNS macrophages is the most accurate indicator of its utility in treating clinical symptoms associated with CNS HIV infection [75,83,151]. These data, along with the fact that viral sequences from the brains of HIV-infected individuals have macrophage-tropic motifs [56,166], demonstrate that to be effective in the CNS the therapy needs to target monocytes and macrophages.

Strategies other than activation of latent T-cell reservoirs are needed to achieve HIV eradication

Recent research toward a cure for HIV has focused on activation of latently infected T cells to induce HIV transcription, followed by elimination of these infected cells (reviewed in [167]). Although a number of drugs such as the phorbol ester prostratin [168] and histone deacetylase inhibitors including vorinostat [169,170] may also activate latent infection in

monocytes and macrophages, there is no defined strategy to subsequently reduce the size of the viral reservoir, as these cells are resistant to ART-induced cell death. Thus, more plausible biologic approaches are required, particularly those that target immune cells in addition to lymphocytes, including monocytes and macrophages. These tactics merit serious consideration as a strategy to eradicate HIV or to effect significant and sustained change on the size of the HIV reservoir. Although directly eliminating HIV-infected monocytes/macrophages would seem an attractive approach to eradicate viral reservoirs, to date there are no current approaches for this. But, immune therapies that target monocyte/macrophage activation or differentiation might be considered to slow or stop HIV-related diseases or pathogenesis.

Conclusion

HIV-infected monocytes and macrophages contribute to viral persistence throughout infection providing an important reservoir of HIV and perpetuating HIV replication through ongoing cell-to-cell transfer of virions. These cells also play a critical role as inflammatory mediators of HIV-associated CNS disease, CVD, and other SNAEs. Eradication of HIV is not possible with current therapy. Strategies toward a cure thus far have overlooked the contributions of non-T-cell reservoirs to ongoing viral persistence. The future challenges for both treatment and toward a cure require the development of innovative and more effective therapeutics that target persistent HIV in these additional cellular reservoirs.

Acknowledgements

S.C. is supported by an NHMRC Principal Research Fellowship. The authors gratefully acknowledge the contribution to this work of the Victorian Operational Infrastructure Support Program received by the Burnet Institute. This work was also supported by NIH NS040237 (KWC).

References

1. Crowe S, Mills J, McGrath MS. Quantitative immunocyto-fluorographic analysis of CD4 surface antigen expression and HIV infection of human peripheral blood monocyte/macrophages. AIDS Res Hum Retroviruses 1987;3:135–145. [PubMed: 3113464]
2. Gendelman HE, Orenstein JM, Martin MA, Ferrua C, Mitra R, Phipps T, et al. Efficient isolation and propagation of human immunodeficiency virus on recombinant colony-stimulating factor 1-treated monocytes. J Exp Med 1988;167:1428–1441. [PubMed: 3258626]
3. Zhu T, Muthui D, Holte S, Nickle D, Feng F, Brodie S, et al. Evidence for human immunodeficiency virus type 1 replication in vivo in CD14(+) monocytes and its potential role as a source of virus in patients on highly active antiretroviral therapy. J Virol 2002;76:707–716. [PubMed: 11752161]
4. Bacchus C, Cheret A, Avettand-Fenoël V, Nembot G, Mélard A, Blanc C, et al. A single HIV-1 cluster and a skewed immune homeostasis drive the early spread of HIV among resting CD4+ cell subsets within one month post infection. PLoS One 2013;8:e64219. [PubMed: 23691172]
5. Ziegler-Heitbrock L, Ancuta P, Crowe S, Dalod M, Grau V, Hart DN, et al. Nomenclature of monocytes and dendritic cells in blood. Blood 2010;116:e74–e80. [PubMed: 20628149]
6. Funderburg NT, Zidar DA, Shive C, Lioi A, Mudd J, Mussel-white LW, et al. Shared monocyte subset phenotypes in HIV-1 infection and in uninfected subjects with acute coronary syndrome. Blood 2012;120:4599–4608. [PubMed: 23065151]
7. Funderburg NT, Jiang Y, Debanne SM, Storer N, Labbato D, Clagett B, et al. Rosuvastatin treatment reduces markers of monocyte activation in HIV infected subjects on antiretroviral therapy. Clin Infect Dis 2013;58:588–595. [PubMed: 24253250]

8. Ziegler-Heitbrock L, Hofer TPJ. Toward a refined definition of monocyte subsets. Front Immunol 2013;4:23. [PubMed: 23382732]
9. Weber C, Belge KU, Hundelshausen von P, Draude G, Steppich B, Mack M, et al. Differential chemokine receptor expression and function in human monocyte subpopulations. J Leukoc Biol 2000;67:699–704. [PubMed: 10811011]
10. Thieblemont N, Weiss L, Sadeghi HM, Estcourt C, Haeffner-Cavaillon N. CD14lowCD16high: a cytokine-producing monocyte subset which expands during human immunodeficiency virus infection. Eur J Immunol 1995;25:3418–3424. [PubMed: 8566032]
11. Pulliam L, Gascon R, Stubblebine M, McGuire D, McGrath MS. Unique monocyte subset in patients with AIDS dementia. Lancet 1997;349:692–695. [PubMed: 9078201]
12. Han J, Wang B, Han N, Zhao Y, Song C, Feng X, et al. CD14(high)CD16(+) rather than CD14 (low) CD16(+) monocytes correlate with disease progression in chronic HIV-infected patients. J Acquir Immune Defic Syndr 2009;52:553–559. [PubMed: 19950429]
13. Barbour JD, Jalbert EC, Chow DC, Gangcuangco LM, Norris PJ, Keating SM, et al. Reduced CD14 expression on classical monocytes and vascular endothelial adhesion markers independently associate with carotid artery intima media thickness in chronically HIV-1 infected adults on virologically suppressive anti-retroviral therapy. Atherosclerosi 2014; 232:52–58.
14. Jurriaans S, Dekker JT, de Ronde A. HIV-1 viral DNA load in peripheral blood mononuclear cells from seroconverters and long-term infected individuals. AIDS 1992;6:635–641. [PubMed: 1503683]
15. Bagasra O, Pomerantz RJ. Human immunodeficiency virus type I provirus is demonstrated in peripheral blood monocytes in vivo: a study utilizing an in situ polymerase chain reaction. AIDS Res Hum Retroviruses 1993;9:69–76. [PubMed: 8427715]
16. Bergamini A, Bolacchi F, Pesce CD, Carbone M, Cepparulo M, Demin F, et al. Increased CD4 and CCR5 expression and human immunodeficiency virus type 1 entry in CD40 ligand-stimulated macrophages. J Infect Dis 2002; 185:1567–1577. [PubMed: 12023762]
17. Sonza S, Maerz A, Deacon N, Meanger J, Mills J, Crowe S. Human immunodeficiency virus type 1 replication is blocked prior to reverse transcription and integration in freshly isolated peripheral blood monocytes. J Virol 1996;70:3863–3869. [PubMed: 8648722]
18. Ellery PJ, Tippett E, Chiu Y-L, Paukovics G, Cameron PU, Solomon A, et al. The CD16+ monocyte subset is more permissive to infection and preferentially harbors HIV-1 in vivo. J Immunol 2007;178:6581–6589. [PubMed: 17475889]
19. Jaworowski A, Kamwendo DD, Ellery P, Sonza S, Mwapasa V, Tadesse E, et al. CD16+ monocyte subset preferentially harbors HIV-1 and is expanded in pregnant Malawian women with Plasmodium falciparum malaria and HIV-1 infection. J Infect Dis 2007;196:38–42. [PubMed: 17538881]
20. Berger A, Sommer AFR, Zwarg J, Hamdorf M, Welzel K, Esly N, et al. SAMHD1-deficient CD14+ cells from individuals with Aicardi-Goutières syndrome are highly susceptible to HIV-1 infection. PLoS Pathog 2011;7:e1002425. [PubMed: 22174685]
21. Berger G, Durand S, Fargier G, Nguyen X-N, Cordeil S, Bouaziz S, et al. APOBEC3A is a specific inhibitor of the early phases of HIV-1 infection in myeloid cells. PLoS Pathog 2011; 7:e1002221. [PubMed: 21966267]
22. Nasr N, Maddocks S, Turville SG, Harman AN, Woolger N, Helbig KJ, et al. HIV-1 infection of human macrophages directly induces viperin which inhibits viral production. Blood 2012;120:778–788. [PubMed: 22677126]
23. Nguyen LA, Kim D-H, Daly MB, Allan KC, Kim B. Host SAMHD1 protein promotes HIV-1 recombination in macrophages. J Biol Chem 2014;289:2489–2496. [PubMed: 24352659]
24. Peng G, Greenwell-Wild T, Nares S, Jin W,Lei KJ, Rangel ZG, et al. Myeloid differentiation and susceptibility to HIV-1 are linked to APOBEC3 expression. Blood 2007;110:393–400. [PubMed: 17371941]
25. Lahouassa H, Daddacha W, Hofmann H, Ayinde D, Logue EC, Dragin L, et al. SAMHD1 restricts the replication of human immunodeficiency virus type 1 by depleting the intracellular pool of deoxynucleoside triphosphates. Nat Immunol 2012; 13:223–228. [PubMed: 22327569]

26. Laguette N, Sobhian B, Casartelli N, Ringeard M, Chable-Bessia C, Ségéral E, et al. SAMHD1 is the dendritic- and myeloid-cell-specific HIV-1 restriction factor counteracted by Vpx. Nature 2011;474:654–657. [PubMed: 21613998]
27. Wang X, Ye L, Hou W, Zhou Y, Wang Y-J, Metzger DS, et al. Cellular microRNA expression correlates with susceptibility of monocytes/macrophages to HIV-1 infection. Blood 2009; 113:671–674. [PubMed: 19015395]
28. Williams KC, Burdo TH. HIV and SIV infection: the role of cellular restriction and immune responses in viral replication and pathogenesis. APMIS 2009;117:400–412. [PubMed: 19400864]
29. Kilareski EM, Shah S, Nonnemacher MR, Wigdahl B. Regulation of HIV-1 transcription in cells of the monocyte-macrophage lineage. Retrovirology 2009;6:118. [PubMed: 20030845]
30. He J, Chen Y, Farzan M, Choe H, Ohagen A, Gartner S, et al. CCR3 and CCR5 are co-receptors for HIV-1 infection of microglia. Nature 1997;385:645–649. [PubMed: 9024664]
31. Lavi E, Strizki JM, Ulrich AM, Zhang W, Fu L, Wang Q, et al. CXCR-4 (Fusin), a co-receptor for the type 1 human immunodeficiency virus (HIV-1), is expressed in the human brain in a variety of cell types, including microglia and neurons. Am J Pathol 1997;151:1035–1042. [PubMed: 9327737]
32. Williams KC, Corey S, Westmoreland SV, Pauley D, Knight H, deBakker C, et al. Perivascular macrophages are the primary cell type productively infected by simian immunodeficiency virus in the brains of macaques: implications for the neuropathogenesis of AIDS. J Exp Med 2001;193:905–915. [PubMed: 11304551]
33. Sinclair E, Gray F, Ciardi A, Scaravilli F. Immunohistochemical changes and PCR detection of HIV provirus DNA in brains of asymptomatic HIV-positive patients. J Neuropathol Exp Neurol 1994;53:43–50. [PubMed: 8301319]
34. Cai Y, Sugimoto C, Arainga M, Alvarez X, Didier ES, Kuroda MJ. In vivo characterization of alveolar and interstitial lung macrophages in rhesus macaques: implications for understanding lung disease in humans. J Immunol 2014; 192:2821–2829. [PubMed: 24534529]
35. Jambo KC, Banda DH, Kankwatira AM, Sukumar N, Allain TJ, Heyderman RS, et al. Small alveolar macrophages are infected preferentially by HIV and exhibit impaired phagocytic function. Mucosal Immunol 2014;7:1116–1126. [PubMed: 24472847]
36. Zhang J, Zhu J, Imrich A, Cushion M, Kinane TB, Koziel H. Pneumocystis activates human alveolar macrophage NF-kappaB signaling through mannose receptors. Infect Immun 2004; 72:3147–3160. [PubMed: 15155616]
37. Segal LN, Methé BA, Nolan A, Hoshino Y, Rom WN, Dawson R, et al. HIV-1 and bacterial pneumonia in the era of antiretroviral therapy. Proc Am Thorac Soc 2011;8:282–287. [PubMed: 21653529]
38. Allers K, Fehr M, Conrad K, Epple H-J, Schürmann D, Geelhaar-Karsch A, et al. Macrophages accumulate in the gut mucosa of untreated HIV-infected patients. J Infect Dis 2014;209:739–748. [PubMed: 24133185]
39. Shen R, Meng G, Ochsenbauer C, Clapham PR, Grams J, Novak L, et al. Stromal down-regulation of macrophage CD4/CCR5 expression and NF-(B activation mediates HIV-1 nonpermissiveness in intestinal macrophages. PLoS Pathog 2011;7:e1002060. [PubMed: 21637819]
40. Zaritsky LA, Dery A, Leong WY, Gama L, Clements JE. Tissue-specific interferon alpha subtype response to SIV infection in brain, spleen, and lung. J Interferon Cytokine Res 2013; 33:24–33. [PubMed: 23050948]
41. Hirsch VM, Lifson JD. Simian immunodeficiency virus infection of monkeys as a model system for the study of AIDS pathogenesis, treatment, and prevention. Adv Pharmacol 2000; 49:437–477. [PubMed: 11013771]
42. Williams K, Burdo TH. Monocyte mobilization, activation markers, and unique macrophage populations in the brain: observations from SIV infected monkeys are informative with regard to pathogenic mechanisms of HIV infection in humans. J Neuroimmune Pharmacol 2012;7:363–371. [PubMed: 22167311]
43. Whitelaw DM. Observations on human monocyte kinetics after pulse labeling. Cell Tissue Kinet 1972;5:311–317. [PubMed: 5044622]

44. Hasegawa A, Liu H, Ling B, Borda JT, Alvarez X, Sugimoto C, et al. The level of monocyte turnover predicts disease progression in the macaque model of AIDS. Blood 2009; 114:2917–2925. [PubMed: 19383966]
45. Hearps AC, Maisa A, Cheng W-J, Angelovich TA, Lichtfuss GF, Palmer CS, et al. HIV infection induces age-related changes to monocytes and innate immune activation in young males which persist despite cART. AIDS 2012;26:843–853. [PubMed: 22313961]
46. Clements JE, Babas T, Mankowski JL, Suryanarayana K, Piatak M, Tarwater PM, et al. The central nervous system as a reservoir for simian immunodeficiency virus (SIV): steady-state levels of SIV DNA in brain from acute through asymptomatic infection. J Infect Dis 2002;186:905–913. [PubMed: 12232830]
47. Igarashi T, Imamichi H, Brown CR, Hirsch VM, Martin MA. The emergence and characterization of macrophage-tropic SIV/HIV chimeric viruses (SHIVs) present in CD4+ T cell-depleted rhesus monkeys. J Leukoc Biol 2003;74:772–780. [PubMed: 14595005]
48. Heath L, Fox A, McClure J, Diem K, van't Wout AB, Zhao H, et al. Evidence for limited genetic compartmentalization of HIV-1 between lung and blood. PLoS One 2009; 4:e6949. [PubMed: 19759830]
49. Cheng-Mayer C, Weiss C, Seto D, Levy JA. Isolates of human immunodeficiency virus type 1 from the brain may constitute a special group of the AIDS virus. Proc Natl Acad Sci U S A 1989;86:8575–8579. [PubMed: 2813413]
50. Wong JK, Ignacio CC, Torriani F, Havlir D, Fitch NJ, Richman DD. In vivo compartmentalization of human immunodeficiency virus: evidence from the examination of pol sequences from autopsy tissues. J Virol 1997;71:2059–2071. [PubMed: 9032338]
51. Chen H, Wood C, Petito CK. Comparisons of HIV-1 viral sequences in brain, choroid plexus and spleen: potential role of choroid plexus in the pathogenesis of HIV encephalitis. J Neurovirol 2000; 6:498–506. [PubMed: 11175322]
52. Stingele K, Haas J, Zimmermann T, Stingele R, Hübsch-Müller C, Freitag M, et al. Independent HIV replication in paired CSF and blood viral isolates during antiretroviral therapy. Neurology 2001;56:355–361. [PubMed: 11171901]
53. Ghorpade A, Nukuna A, Che M, Haggerty S, Persidsky Y, Carter E, et al. Human immunodeficiency virus neurotropism: an analysis of viral replication and cytopathicity for divergent strains in monocytes and microglia. J Virol 1998;72:3340–3350. [PubMed: 9525661]
54. Gorry PR, Bristol G, Zack JA, Ritola K, Swanstrom R, Birch CJ, et al. Macrophage tropism of human immunodeficiency virus type 1 isolates from brain and lymphoid tissues predicts neurotropism independent of coreceptor specificity. J Virol 2001;75:10073–10089. [PubMed: 11581376]
55. Peters PJ, Bhattacharya J, Hibbitts S, Dittmar MT, Simmons G, Bell J, et al. Biological analysis of human immunodeficiency virus type 1 R5 envelopes amplified from brain and lymph node tissues of AIDS patients with neuropathology reveals two distinct tropism phenotypes and identifies envelopes in the brain that confer an enhanced tropism and fusigenicity for macrophages. J Virol 2004;78:6915–6926. [PubMed: 15194768]
56. Salemi M, Lamers SL, Yu S, de Oliveira T, Fitch WM, McGrath MS. Phylodynamic analysis of human immunodeficiency virus type 1 in distinct brain compartments provides a model for the neuropathogenesis of AIDS. J Virol 2005;79:11343–11352. [PubMed: 16103186]
57. Strickland SL, Gray RR, Lamers S, Burdo T, Huenink E, Nolan D, et al. Efficient transmission and persistence of low frequency SIVmac251 variants in CD8-depleted rhesus macaques with different neuropathology. J Gen Virol 2012; 93:925–938. [PubMed: 22302881]
58. Martin GE, Gouillou M, Hearps AC, Angelovich TA, Cheng AC, Lynch F, et al. Age-associated changes in monocyte and innate immune activation markers occur more rapidly in HIV infected women. PLoS One 2013;8:e55279. [PubMed: 23365694]
59. Krishnan S, Wilson EMP, Sheikh V, Rupert A, Mendoza D, Yang J, et al. Evidence for innate immune system activation in hiv type 1-infected elite controllers. J Infect Dis 2014;209: 931–939. [PubMed: 24185941]

60. Mavigner M, Delobel P, Cazabat M, Dubois M, L'faqihi-Olive F-E, Raymond S, et al. HIV-1 residual viremia correlates with persistent T-cell activation in poor immunological responders to combination antiretroviral therapy. PLoS One 2009; 4:e7658. [PubMed: 19876401]
61. Kedzierska K, Ellery P, Mak J, Lewin SR, Crowe SM, Jaworowski A. HIV-1 down-modulates gamma signaling chain of Fc gamma R in human macrophages: a possible mechanism for inhibition of phagocytosis. J Immunol 2002;168:2895–2903. [PubMed: 11884460]
62. Leeansyah E, Wines BD, Crowe SM, Jaworowski A. The mechanism underlying defective Fcgamma receptor-mediated phagocytosis by HIV-1-infected human monocyte-derived macrophages. J Immunol 2007; 178:1096–1104. [PubMed: 17202373]
63. Périssé ARS, Smeaton L, Chen Y, La Rosa A, Walawander A, Nair A, et al. Outcomes among HIV-1 infected individuals first starting antiretroviral therapy with concurrent active TB or other AIDS-defining disease. PLoS One 2013;8:e83643. [PubMed: 24391801]
64. Meintjes G, Lawn SD, Scano F, Maartens G, French MA, Worodria W, et al. Tuberculosis-associated immune reconstitution inflammatory syndrome: case definitions for use in resource-limited settings. Lancet Infect Dis 2008;8:516–523. [PubMed: 18652998]
65. Tran HTT, Van den Bergh R, Loembe MM, Worodria W, Mayanja-Kizza H, Colebunders R, et al. Modulation of the complement system in monocytes contributes to tuberculosis-associated immune reconstitution inflammatory syndrome. AIDS 2013;27:1725–1734. [PubMed: 23807270]
66. Tran HTT, Van den Bergh R, Vu TN, Laukens K, Worodria W, Loembe MM, et al. The role of monocytes in the development of tuberculosis-associated immune reconstitution inflammatory syndrome. Immunobiology 2014;219:37–44. [PubMed: 23958034]
67. Heaton RK, Clifford DB, Franklin DR, Woods SP, Ake C, Vaida F, et al. HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER Study. Neurology 2010;75:2087–2096. [PubMed: 21135382]
68. Heaton RK, Franklin DR, Ellis RJ, McCutchan JA, Letendre SL, Leblanc S, et al. HIV-associated neurocognitive disorders before and during the era of combination antiretroviral therapy: differences in rates, nature, and predictors. J Neurovirol 2011;17:3–16. [PubMed: 21174240]
69. Vivithanaporn P, Heo G, Gamble J, Krentz HB, Hoke A, Gill MJ, et al. Neurologic disease burden in treated HIV/AIDS predicts survival: a population-based study. Neurology 2010; 75:1150–1158. [PubMed: 20739646]
70. Tozzi V, Balestra P, Serraino D, Bellagamba R, Corpolongo A, Piselli P, et al. Neurocognitive impairment and survival in a cohort of HIV-infected patients treated with HAART. AIDS Res Hum Retroviruses 2005;21:706–713. [PubMed: 16131310]
71. Cosenza MA, Zhao M-L, Si Q, Lee SC. Human brain parenchymal microglia express CD14 and CD45 and are productively infected by HIV-1 in HIV-1 encephalitis. Brain Pathol 2002; 12:442–455. [PubMed: 12408230]
72. Gelman BB, Lisinicchia JG, Morgello S, Masliah E, Commins D, Achim CL, et al. Neurovirological correlation with HIV-associated neurocognitive disorders and encephalitis in a HAART-era cohort. J Acquir Immune Defic Syndr 2013; 62:487–495. [PubMed: 23242157]
73. Williams K, Westmoreland S, Greco J, Ratai E, Lentz M, Kim W-K, et al. Magnetic resonance spectroscopy reveals that activated monocytes contribute to neuronal injury in SIV neuroAIDS. J Clin Invest 2005;115:2534–2545. [PubMed: 16110325]
74. Campbell JH, Burdo TH, Autissier P, Bombardier JP, Westmoreland SV, Soulas C, et al. Minocycline inhibition of monocyte activation correlates with neuronal protection in SIV neuroAIDS. PLoS One 2011;6:e18688. [PubMed: 21494695]
75. Kusao I, Shiramizu B, Liang C-Y, Grove J, Agsalda M, Troelstrup D, et al. Cognitive performance related to HIV-1-infected monocytes. J Neuropsychiatry Clin Neurosci 2012; 24:71–80. [PubMed: 22450616]
76. Fischer-Smith T, Croul S, Sverstiuk AE, Capini C, L'Heureux D, Regulier EG, et al. CNS invasion by CD14+/CD16+ peripheral blood-derived monocytes in HIV dementia: perivascular accumulation and reservoir of HIV infection. J Neurovirol 2001;7:528–541. [PubMed: 11704885]
77. Kamat A, Lyons JL, Misra V, Uno H, Morgello S, Singer EJ, et al. Monocyte activation markers in cerebrospinal fluid associated with impaired neurocognitive testing in advanced HIV infection. J Acquir Immune Defic Syndr 2012; 60:234–243. [PubMed: 22569268]

78. Lyons JL, Uno H, Ancuta P, Kamat A, Moore DJ, Singer EJ, et al. Plasma sCD14 is a biomarker associated with impaired neurocognitive test performance in attention and learning domains in HIV infection. J Acquir Immune Defic Syndr 2011; 57:371–379. [PubMed: 21646912]

79. Ancuta P, Kamat A, Kunstman KJ, Kim E-Y, Autissier P, Wurcel A, et al. Microbial translocation is associated with increased monocyte activation and dementia in AIDS patients. PLoS One 2008;3:e2516. [PubMed: 18575590]

80. Kim W-K, Corey S, Alvarez X, Williams K. Monocyte/macrophage traffic in HIV and SIV encephalitis. J Leukoc Biol 2003; 74:650–656. [PubMed: 12960230]

81. Williams DW, Eugenin EA, Calderon TM, Berman JW. Monocyte maturation, HIV susceptibility, and transmigration across the blood brain barrier are critical in HIV neuropathogenesis. J Leukoc Biol 2012;91:401–415. [PubMed: 22227964]

82. Kamat A, Misra V, Cassol E, Ancuta P, Yan Z, Li C, et al. A plasma biomarker signature of immune activation in HIV patients on antiretroviral therapy. PLoS One 2012;7:e30881. [PubMed: 22363505]

83. Shikuma CM, Nakamoto B, Shiramizu B, Liang C-Y, Degruttola V, Bennett K, et al. Antiretroviral monocyte efficacy score linked to cognitive impairment in HIV. Antivir Ther (Lond) 2012;17:1233–1242. [PubMed: 23018140]

84. Wang H, Sun J, Goldstein H. Human immunodeficiency virus type 1 infection increases the in vivo capacity of peripheral monocytes to cross the blood-brain barrier into the brain and the in vivo sensitivity of the blood-brain barrier to disruption by lipopolysaccharide. J Virol 2008;82:7591–7600. [PubMed: 18508884]

85. Williams K, Alvarez X, Lackner AA. Central nervous system perivascular cells are immunoregulatory cells that connect the CNS with the peripheral immune system. Glia 2001; 36:156–164. [PubMed: 11596124]

86. Kim W-K, Alvarez X, Fisher J, Bronfin B, Westmoreland S, McLaurin J, et al. CD163 identifies perivascular macrophages in normal and viral encephalitic brains and potential precursors to perivascular macrophages in blood. Am J Pathol 2006;168:822–834. [PubMed: 16507898]

87. Xiong H, Zeng YC, Lewis T, Zheng J, Persidsky Y, Gendelman HE. HIV-1 infected mononuclear phagocyte secretory products affect neuronal physiology leading to cellular demise: relevance for HIV-1-associated dementia. J Neurovirol 2000; 6 (Suppl 1):S14–23. [PubMed: 10871761]

88. Persidsky Y, Zheng J, Miller D, Gendelman HE. Mononuclear phagocytes mediate blood-brain barrier compromise and neuronal injury during HIV-1-associated dementia. J Leukoc Biol 2000; 68:413–422. [PubMed: 10985259]

89. Nottet HS, Persidsky Y, Sasseville VG, Nukuna AN, Bock P, Zhai QH, et al. Mechanisms for the transendothelial migration of HIV-1-infected monocytes into brain. J Immunol 1996; 156:1284–1295. [PubMed: 8558009]

90. Persidsky Y, Stins M, Way D, Witte MH, Weinand M, Kim KS, et al. A model for monocyte migration through the blood-brain barrier during HIV-1 encephalitis. J Immunol 1997; 158:3499–3510. [PubMed: 9120312]

91. Williams DW, Calderon TM, Lopez L, Carvallo-Torres L, Gaskill PJ, Eugenin EA, et al. Mechanisms of HIV entry into the CNS: increased sensitivity of HIV infected CD14+CD16+ monocytes to CCL2 and key roles of CCR2, JAM-A, and ALCAM in diapedesis. PLoS One 2013;8:e69270. [PubMed: 23922698]

92. Davis LE, Hjelle BL, Miller VE, Palmer DL, Llewellyn AL, Merlin TL, et al. Early viral brain invasion in iatrogenic human immunodeficiency virus infection. Neurology 1992; 42:1736–1739. [PubMed: 1513462]

93. Chakrabarti L, Hurtrel M, Maire MA, Vazeux R, Dormont D, Montagnier L, et al. Early viral replication in the brain of SIV-infected rhesus monkeys. Am J Pathol 1991;139:1273–1280. [PubMed: 1750503]

94. Clay CC, Rodrigues DS, Ho YS, Fallert BA, Janatpour K, Reinhart TA, et al. Neuroinvasion of fluorescein-positive monocytes in acute simian immunodeficiency virus infection. J Virol 2007;81:12040–12048. [PubMed: 17715237]

95. Soulas C, Conerly C, Kim W-K, Burdo TH, Alvarez X, Lackner AA, et al. Recently infiltrating MAC387(+) monocytes/macrophages a third macrophage population involved in SIV and HIV encephalitic lesion formation. Am J Pathol 2011;178:2121–2135. [PubMed: 21514427]

96. Burdo TH, Weiffenbach A, Woods SP, Letendre S, Ellis RJ, Williams KC. Elevated sCD163 is a marker of neurocognitive impairment in HIV infection. AIDS 2013;27:1387–1395. [PubMed: 23435298]

97. Burdo TH, Soulas C, Orzechowski K, Button J, Krishnan A, Sugimoto C, et al. Increased monocyte turnover from bone marrow correlates with severity of SIV encephalitis and CD163 levels in plasma. PLoS Pathog 2010;6:e1000842. [PubMed: 20419144]

98. Valcour VG, Shiramizu BT, Shikuma CM. HIV DNA in circulating monocytes as a mechanism to dementia and other HIV complications. J Leukoc Biol 2010;87:621–626. [PubMed: 20130221]

99. Valcour VG. HIV, aging, and cognition: emerging issues. Top Antivir Med 2013;21:119–123. [PubMed: 23981600]

100. Hearps AC, Martin GE, Rajasuriar R, CroweSM. Inflammatory Co-morbidities in HIV+ Individuals: Learning Lessons from Healthy Ageing. Curr HIV/AIDS Rep 2014;11:20–34. [PubMed: 24414166]

101. Hsu DC, Sereti I, Ananworanich J. Serious Non-AIDS events: Immunopathogenesis and interventional strategies. AIDS Res Ther 2013;10:29. [PubMed: 24330529]

102. Tenorio AR, Zheng Y, Bosch RJ, Krishnan S, Rodriguez B, Hunt PW, et al. Soluble markers of inflammation and coagulation, but not T-cell activation, are predictors of non-AIDS-defining morbid events during suppressive antiretroviral treatment. J Infect Dis 2014 (in press).

103. Kuller LH, Tracy R, Belloso W, De Wit S, Drummond F, Lane HC, et al. Inflammatory and coagulation biomarkers and mortality in patients with HIV infection. PLoS Med 2008; 5:e203. [PubMed: 18942885]

104. Sandler NG, Wand H, Roque A, Law M, Nason MC, Nixon DE, et al. Plasma levels of soluble CD14 independently predict mortality in HIV infection. J Infect Dis 2011;203:780–790. [PubMed: 21252259]

105. Bukh AR, Melchjorsen J, Offersen R, Jensen JMB, Toft L, Støvring H, et al. Endotoxemia is associated with altered innate and adaptive immune responses in untreated HIV-1 infected individuals. PLoS One 2011;6:e21275. [PubMed: 21731690]

106. Bone Hoy J., fracture and frailty. Curr Opin HIV AIDS 2011; 6:309–314. [PubMed: 21537171]

107. Brown TT, Qaqish RB. Antiretroviral therapy and the prevalence of osteopenia and osteoporosis: a meta-analytic review. AIDS 2006;20:2165–2174. [PubMed: 17086056]

108. Gazzola L, Bellistri GM, Tincati C, lerardi V, Savoldi A, del Dole A, et al. Association between peripheral T-Lymphocyte activation and impaired bone mineral density in HIV-infected patients. J Transl Med 2013; 11:51. [PubMed: 23448662]

109. Erlandson KM, O'Riordan M, Labbato D, McComsey GA. Relationships between inflammation, immune activation, and bone health among HIV-infected adults on stable antiretroviral therapy. J Acquir Immune Defic Syndr 2014; 65:290–298. [PubMed: 24525466]

110. Desquilbet L, Jacobson LP, Fried LP, Phair JP, Jamieson BD, Holloway M, et al. HIV-1 infection is associated with an earlier occurrence of a phenotype related to frailty. J Gerontol A Biol Sci Med Sci 2007;62:1279–1286. [PubMed: 18000149]

111. Qu T, Yang H, Walston jD, Fedarko NS, Leng SX. Upregulated monocytic expression of CXC chemokine ligand 10 (CXCL-10) and its relationship with serum interleukin-6 levels in the syndrome of frailty. Cytokine 2009;46:319–324. [PubMed: 19342252]

112. Hemkens LG, Bucher HC. HIV infection and cardiovascular disease. Eur Heart J 2014;35:1373–1381. [PubMed: 24408888]

113. Parra S, Coll B, Aragonés G, Marsillach J, Beltrán R, Rull A, et al. Nonconcordance between subclinical atherosclerosis and the calculated Framingham risk score in HIV-infected patients: relationships with serum markers of oxidation and inflammation. HIV Med 2010;11:225–231. [PubMed: 19845792]

114. Moore KJ, Sheedy FJ, Fisher EA. Macrophages in atherosclerosis: a dynamic balance. Nat Rev Immunol 2013;13: 709–721. [PubMed: 23995626]

115. Baker JV, Hullsiek KH, Singh A, Wilson E, Henry K, Lichtenstein K, et al. Immunologic predictors of coronary artery calcium progression in a contemporary HIV cohort. AIDS 2013;28:831–840.
116. Duprez DA, Neuhaus J, Kuller LH, Tracy R, Belloso W, De Wit S, et al. Inflammation, coagulation and cardiovascular disease in HIV-infected individuals. PLoS ONE 2012;7:e44454. [PubMed: 22970224]
117. De Luca A, de Gaetano Donati K, Colafigli M, Cozzi-Lepri A, De Curtis A, Gori A, et al. The association of high-sensitivity c-reactive protein and other biomarkers with cardiovascular disease in patients treated for HIV: a nested case-control study. BMC Infect Dis 2013;13:414. [PubMed: 24004495]
118. Shikuma CM, Barbour JD, Ndhlovu LC, Keating SM, Norris PJ, Budoff M, et al. Plasma monocyte chemoattractant protein-1 and tumor necrosis factor-(levels predict the presence of coronary artery calcium in HIV-infected individuals independent of traditional cardiovascular risk factors. AIDS Res Hum Retroviruses 2014;30:142–146. [PubMed: 23984974]
119. Hsue PY, Scherzer R, Hunt PW, Schnell A, Bolger AF, Kalapus SC, et al. Carotid intima-media thickness progression in HIV-infected adults occurs preferentially at the carotid bifurcation and is predicted by inflammation. J Am Heart Assoc 2012; 1:e000422.
120. Westhorpe CLV, Maisa A, Spelman T, Hoy JF, Dewar EM, Karapanagiotidis S, et al. Associations between surface markers on blood monocytes and carotid atherosclerosis in HIV-positive individuals. Immunol Cell Biol 2014;92:133–138. [PubMed: 24296810]
121. Llodrá J, Angeli V, Liu J, Trogan E, Fisher EA, Randolph GJ. Emigration of monocyte-derived cells from atherosclerotic lesions characterizes regressive, but not progressive, plaques. Proc Natl Acad Sci USA 2004;101:11779–11784. [PubMed: 15280540]
122. Ghattas A, Griffiths HR, Devitt A, Lip GYH, Shantsila E. Monocytes in coronary artery disease and atherosclerosis: where are we now? J Am Coll Cardiol 2013;62:1541–1551. [PubMed: 23973684]
123. Burdo TH, Lo J, Abbara S, Wei J, DeLelys ME, Preffer F, et al. Soluble CD163, a novel marker of activated macrophages, is elevated and associated with noncalcified coronary plaque in HIV-infected patients. J Infect Dis 2011;204:1227–1236. [PubMed: 21917896]
124. Fitch KV, Srinivasa S, Abbara S, Burdo tH, Williams KC, Eneh P, et al. Noncalcified coronary atherosclerotic plaque and immune activation in HIV-infected women. J Infect Dis 2013; 208:1737–1746. [PubMed: 24041790]
125. Subramanian S, Tawakol A, Burdo TH, Abbara S, Wei J, Vijayakumar J, et al. Arterial inflammation in patients with HIV. JAMA 2012;308:379–386. [PubMed: 22820791]
126. Merlini E, Luzi K, Suardi E, Barassi A, Cerrone M, Martinez JS, et al. T-cell phenotypes, apoptosis and inflammation in HIV+ patients on virologically effective cART with early atherosclerosis. PLoS One 2012;7:e46073. [PubMed: 23029393]
127. Kelesidis T, Kendall MA, Yang OO, Hodis HN, Currier JS. Biomarkers of microbial translocation and macrophage activation: association with progression of subclinical atherosclerosis in HIV-1 infection. J Infect Dis 2012;206:1558–1567. [PubMed: 23066162]
128. Longenecker CT, Funderburg NT, Jiang Y, Debanne S, Storer N, Labbato DE, et al. Markers of inflammation and CD8 T-cell activation, but not monocyte activation, are associated with subclinical carotid artery disease in HIV-infected individuals. HIV Med 2013;14:385–390. [PubMed: 23332012]
129. Longenecker CT, Jiang Y, Orringer CE, Gilkeson RC, Debanne S, Funderburg NT, et al. Soluble CD14 is independently associated with coronary calcification and extent of subclinical vascular disease in treated HIV infection. AIDS 2014; 28:969–977. [PubMed: 24691204]
130. Barbour JD, Jalbert EC, Chow DC, Gangcuangco LMA, Norris PJ, Keating SM, et al. Reduced CD14 expression on classical monocytes and vascular endothelial adhesion markers independently associate with carotid artery intima media thickness in chronically HIV-1 infected adults on virologically suppressive antiretroviral therapy. Atherosclerosis 2014; 232: 52–58. [PubMed: 24401216]

131. DAD study group. Friis-M0ller N, Reiss P, Sabin CA, Weber R, Monforte AD, et al. Class of antiretroviral drugs and the risk of myocardial infarction. N Engl J Med 2007;356:1723–1735. [PubMed: 17460226]

132. Pereyra F, Lo J, Triant VA, Wei J, Buzon Mj, Fitch KV, et al. Increased coronary atherosclerosis and immune activation in HIV-1 elite controllers. AIDS 2012;26:2409–2412. [PubMed: 23032411]

133. Walker JA, Sulciner ML, Nowicki KD, Miller AD, Burdo TH, Williams KC. Elevated numbers of CD163(+) macrophages in hearts of simian immunodeficiency virus-infected monkeys correlate with cardiac pathology and fibrosis. AIDS Res Hum Retroviruses 2014;30:685–694. [PubMed: 24524407]

134. Westhorpe CLV, Zhou J, Webster NL, Kalionis B, Lewin SR, Jaworowski A, et al. Effects of HIV-1 infection in vitro on transendothelial migration by monocytes and monocyte-derived macrophages. J Leukoc Biol 2009;85:1027–1035. [PubMed: 19286896]

135. Maisa A, Pereira CF, Angelovich TA, Zhou JL, Muller WA, Hearps AC, et al. TNF drives foam cell formation by monocytes from HIV+ donors in an in vitro atherosclerosis model. [Abstract 256]. 21st Conference on Retroviruses and Opportunistic Infections, Boston MA, March 2014.

136. Hütter G, Nowak D, Mossner M, Ganepola S, Müssig A, Allers K, et al. Long-term control of HIV by CCR5 Delta32/Delta32 stem-cell transplantation. N Engl J Med 2009;360:692–698. [PubMed: 19213682]

137. Henrich TJ, Gandhi RT. Early treatment and HIV-1 reservoirs: a stitch in time? J Infect Dis 2013;208:1189–1193. [PubMed: 23852126]

138. Henrich T, Hill AL, Goldstein E, Rosenbloom DIS, Hanhauser E, Kuritzkes DR. Mathematical modeling of HIV-1 latent reservoir dynamics following hematopoietic stem cell transplantation. [Abstract 130]. 6th International Workshop on HIV Persistence, Miami FL, 12 2013.

139. Migueles SA, Connors M. Long-term nonprogressive disease among untreated HIV-infected individuals: clinical implications of understanding immune control of HIV. JAMA 2010; 304:194–201. [PubMed: 20628133]

140. Blankson JN, Bailey JR, Thayil S, Yang H-C, Lassen K, Lai J, et al. Isolation and characterization of replication-competent human immunodeficiency virus type 1 from a subset of elite suppressors. J Virol 2007;81:2508–2518. [PubMed: 17151109]

141. Spivak AM, Salgado M, Rabi SA, O'Connell KA, Blankson JN. Circulating monocytes are not a major reservoir of HIV-1 in elite suppressors. J Virol 2011;85:10399–10403. [PubMed: 21795348]

142. Sonza S, Mutimer HP, Oelrichs R, Jardine D, Harvey K, Dunne A, et al. Monocytes harbour replication-competent, nonlatent HIV-1 in patients on highly active antiretroviral therapy. AIDS 2001;15:17–22. [PubMed: 11192864]

143. Lambotte O, Taoufik Y, de Goer MG, Wallon C, Goujard C, Delfraissy JF. Detection of infectious HIV in circulating monocytes from patients on prolonged highly active antiretroviral therapy. J Acquir Immune Defic Syndr 2000;23:114–119. [PubMed: 10737425]

144. Ho Y-C, Shan L, Hosmane NN, Wang J, Laskey SB, Rosenbloom DIS, et al. Replication-competent noninduced proviruses in the latent reservoir increase barrier to HIV-1 cure. Cell 2013;155:540–551. [PubMed: 24243014]

145. Sahu GK, Paar D, Frost SDW, Smith MM, Weaver S, Cloyd MW. Low-level plasma HIVs in patients on prolonged suppressive highly active antiretroviral therapy are produced mostly by cells other than CD4 T-cells. J Med Virol 2009; 81:9–15. [PubMed: 19031450]

146. Duncan CJA, Russell RA, Sattentau QJ. High multiplicity HIV-1 cell-to-cell transmission from macrophages to CD4+ T cells limits antiretroviral efficacy. AIDS 2013;27:2201–2206. [PubMed: 24005480]

147. Peressin M, Proust A, Schmidt S, Su B, Lambotin M, Biedma ME, et al. Efficient transfer of HIV-1 in trans and in cis from Langerhans dendritic cells and macrophages to autologous T lymphocytes. AIDS 2014;28:667–677. [PubMed: 24451159]

148. Gutiérrez C, Hernández-Novoa B, Vallejo A, Serrano-Villar S, Abad-Fernandez M, Madrid N, et al. Dynamics of the HIV-1 latent reservoir after discontinuation of the intensification of

antiretroviral treatment: results of two clinical trials. AIDS 2013;27:2081–2088. [PubMed: 24384589]

149. Josefsson L, Stockenstrom von S, Faria NR, Sinclair E, Bacchetti P, Killian M, et al. The HIV-1 reservoir in eight patients on long-term suppressive antiretroviral therapy is stable with few genetic changes over time. Proc Natl Acad Sci USA 2013; 110:E4987–E4996. [PubMed: 24277811]
150. Strain MC, Little SJ, Daar ES, Haavlir DV, Gunthard HF, Lam RY, et al. Effect of treatment, during primary infection, on establishment and clearance of cellular reservoirs of HIV-1. J Infect Dis 2005;191:1410–1418. [PubMed: 15809898]
151. Buzon MJ, Codoner FM, Frost SDW, Pou C, Puertas MC, Massanella M, et al. Deep molecular characterization of HIV-1 dynamics under suppressive HAART. PLoS Pathog 2011;7:e1002314. [PubMed: 22046128]
152. Crowe SM, McGrath MS, Elbeik T, Kirihara J, Mills J. Comparative assessment of antiretrovirals in human monocyte-macrophages and lymphoid cell lines acutely and chronically infected with the human immunodeficiency virus. J Med Virol 1989;29:176–180. [PubMed: 2533247]
153. Solas C, Lafeuillade A, Halfon P, Chadapaud S, Hittinger G, Lacarelle B. Discrepancies between protease inhibitor concentrations and viral load in reservoirs and sanctuary sites in human immunodeficiency virus-infected patients. Antimicrob Agents Chemother 2003;47:238–243. [PubMed: 12499197]
154. Aquaro S, Svicher V, Schols D, Pollicita M, Antinori A, Balzarini J, et al. Mechanisms underlying activity of antiretroviral drugs in HIV-1-infected macrophages: new therapeutic strategies. J Leukoc Biol 2006;80:1103–1110. [PubMed: 16931601]
155. Perno CF, Newcomb FM, Davis DA, Aquaro S, Humphrey RW, Caliò R, et al. Relative potency of protease inhibitors in monocytes/macrophages acutely and chronically infected with human immunodeficiency virus. J Infect Dis 1998; 178:413–422. [PubMed: 9697721]
156. Brown KC, Patterson KB, Malone SA, Shaheen NJ, Prince HMA, Dumond JB, et al. Single and multiple dose pharmacokinetics of maraviroc in saliva, semen, and rectal tissue of healthy HIV-negative men. J Infect Dis 2011;203:1484–1490. [PubMed: 21502084]
157. Scopelliti F, Pollicita M, Ceccherini-Silberstein F, Di Santo F, Surdo M, Aquaro S, et al. Comparative antiviral activity of integrase inhibitors in human monocyte-derived macrophages and lymphocytes. Antiviral Res 2011; 92:255–261 . [PubMed: 21867733]
158. Yilmaz A, Gisslén M, Spudich S, Lee E, Jayewardene A, Aweeka F, et al. Raltegravir cerebrospinal fluid concentrations in HIV-1 infection. PLoS ONE 2009; 4:e6877. [PubMed: 19721718]
159. Marsden MD, Avancena P, Kitchen CMR, Hubbard T, Zack JA. Single mutations in HIV integrase confer high-level resistance to raltegravir in primary human macrophages. Antimicrob Agents Chemother 2011;55:3696–3702. [PubMed: 21628534]
160. Cysique LA, Waters EK, Brew BJ. Central nervous system antiretroviral efficacy in HIV infection: a qualitative and quantitative review and implications for future research. BMC Neurol 2011; 11:148. [PubMed: 22107790]
161. del Palacio M, Alvarez S, Muñoz-Fernández MÁ. HIV-1 infection and neurocognitive impairment in the current era. Rev Med Virol 2012;22:33–45. [PubMed: 21990255]
162. Schweinsburg BC, Taylor MJ, Alhassoon OM, Gonzalez R, Brown GG, Ellis RJ, et al. Brain mitochondrial injury in human immunodeficiency virus-seropositive (HIV+) individuals taking nucleoside reverse transcriptase inhibitors. J Neurovirol 2005;11:356–364. [PubMed: 16206458]
163. Robertson K, Liner J, Meeker RB. Antiretroviral neurotoxicity. J Neurovirol 2012;18:388–399. [PubMed: 22811264]
164. Edén A, Price RW, Spudich S, Fuchs D, Hagberg L, Gisslén M. Immune activation of the central nervous system is still present after >4 years of effective highly active antiretroviral therapy. J Infect Dis 2007;196:1779–1783. [PubMed: 18190258]
165. Kumar AM, Borodowsky I, Fernandez B, Gonzalez L, Kumar M. Human immunodeficiency virus type 1 RNA Levels in different regions of human brain: quantification using real-time reverse transcriptase-polymerase chain reaction. J Neurovirol 2007;13:210–224. [PubMed: 17613711]

166. Lamers SL, Gray RR, Salemi M, Huysentruyt LC, McGrath MS. HIV-1 phylogenetic analysis shows HIV-1 transits through the meninges to brain and peripheral tissues. Infect Genet Evol 2011;11:31–37. [PubMed: 21055482]

167. Katlama C, Deeks SG, Autran B, Martinez-Picado J, van Lunzen J, Rouzioux C, et al. Barriers to a cure for HIV: new ways to target and eradicate HIV-1 reservoirs. Lancet 2013;381:2109–2117. [PubMed: 23541541]

168. Kulkosky J, Culnan DM, Roman J, Dornadula G, Schnell M, Boyd MR, et al. Prostratin: activation of latent HIV-1 expression suggests a potential inductive adjuvant therapy for HAART. Blood 2001;98:3006–3015. [PubMed: 11698284]

169. Archin NM, Espeseth A, Parker D, Cheema M, Hazuda D, Margolis DM. Expression of latent HIV induced by the potent HDAC inhibitor suberoylanilide hydroxamic acid. AIDS Res Hum Retroviruses 2009;25:207–212. [PubMed: 19239360]

170. Archin NM, Liberty AL, Kashuba AD, Choudhary SK, Kuruc JD, Crooks AM, et al. Administration of vorinostat disrupts HIV-1 latency in patients on antiretroviral therapy. Nature 2012; 487:482–485. [PubMed: 22837004]

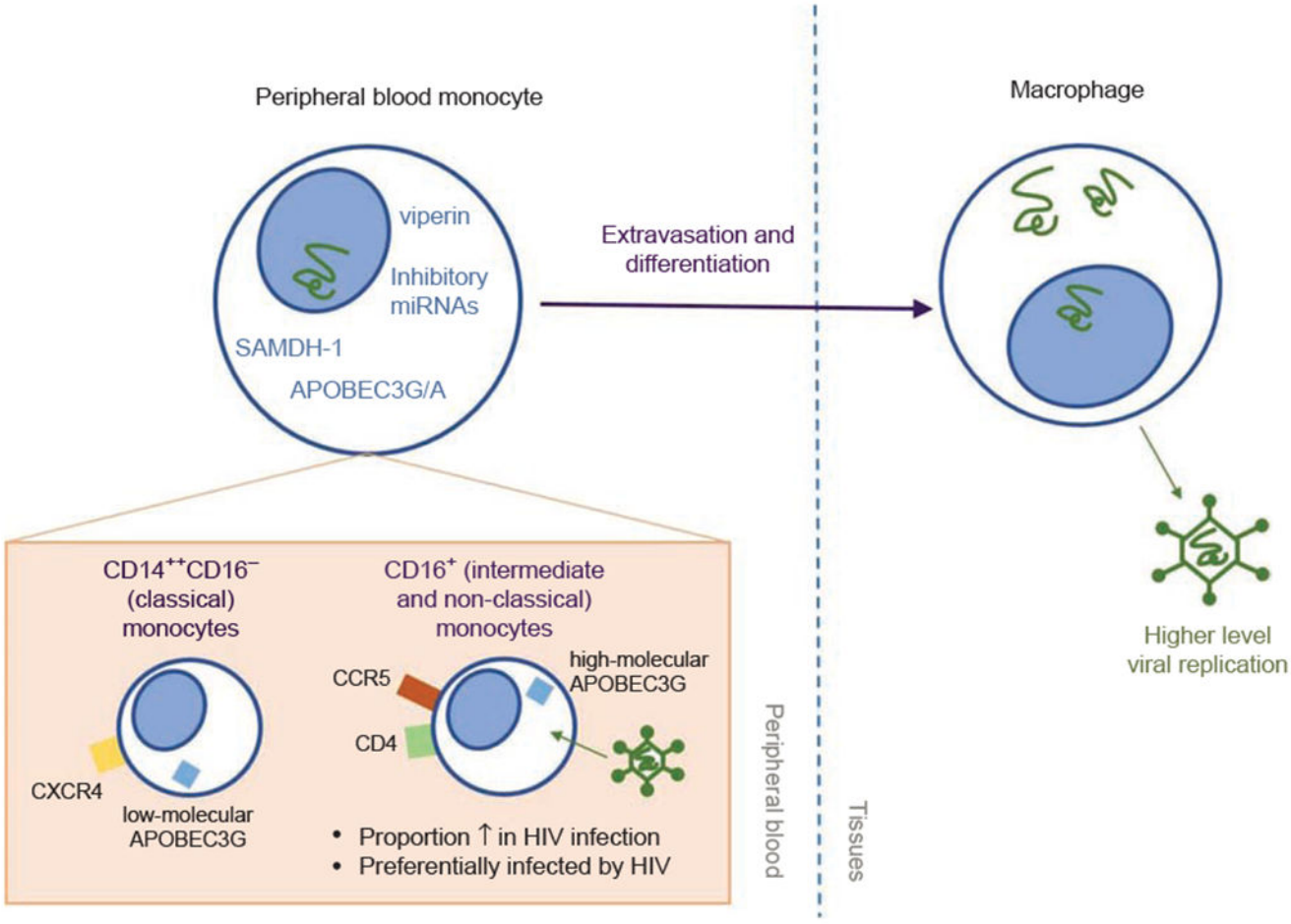

Fig. 1. Monocytes and macrophages are important targets of HIV.

Variable levels of expression of HIV co-receptors, as well as intracellular inhibitory factors, are responsible for differences in HIV infection and replication between macrophages and monocytes, and between monocyte subsets.

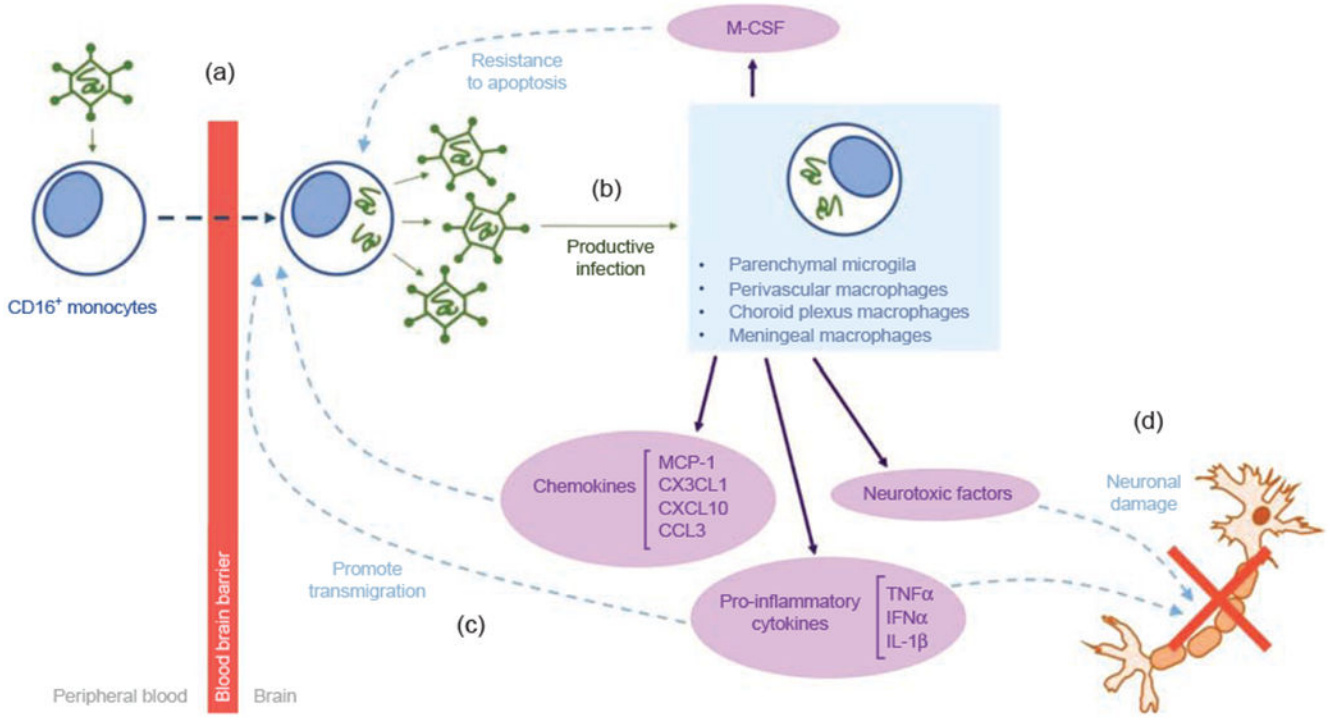

Fig. 2. Role of monocytes and macrophages in the development of neurocognitive impairment during FI IV infection.

(a) Infection of $CD16^+$ monocytes by HIV promotes transmigration into the brain where (b) productive infection allows for the evolution of CCR5/macrophage tropic virus. (c) Chemokines and cytokines produced by infected cells promote further transmigration and ongoing infection and (d) induce the neuronal damage that leads to neurocognitive decline.

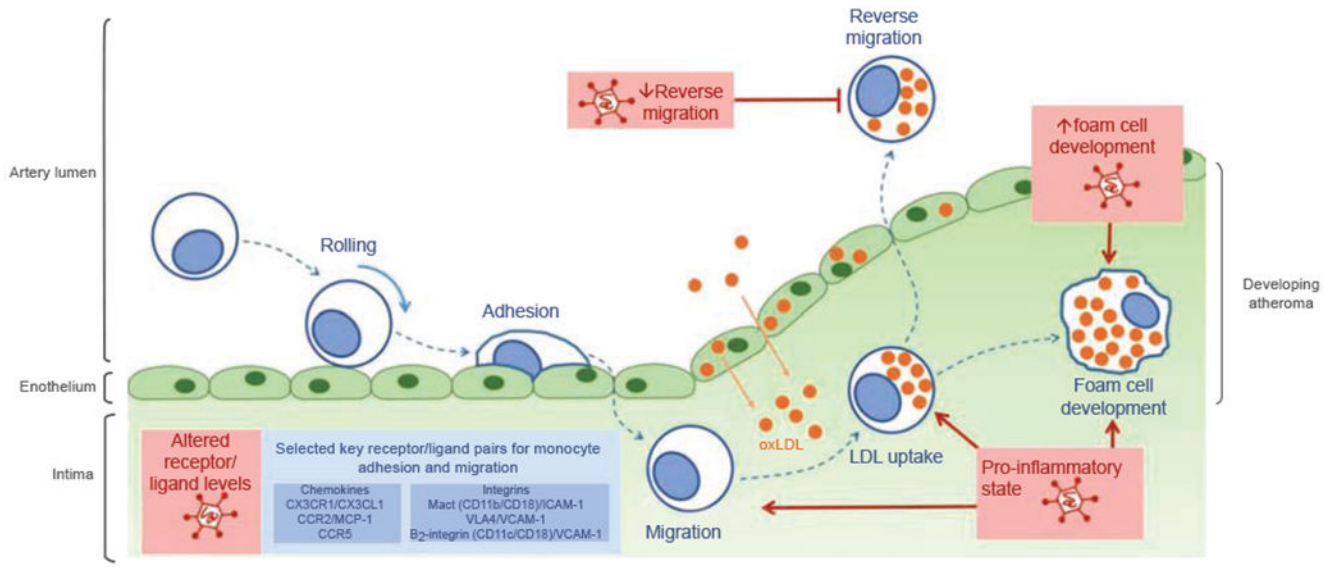

Fig. 3. A model for the role of monocytes in the development of atherosclerosis in HIV-infected individuals.

Migration of monocytes across the blood vessel endothelium and the development of foam cells is the initiating step in the development of atherosclerosis. Alternatively, these monocytes can migrate out of the intima, carrying pro-atherosclerotic LDL away from the vessel wall. During HIV infection, several alterations in monocyte dynamics promote migration of monocytes and foam cell formation, rather than reverse migration. oxLDL, oxidized low density lipoprotein.

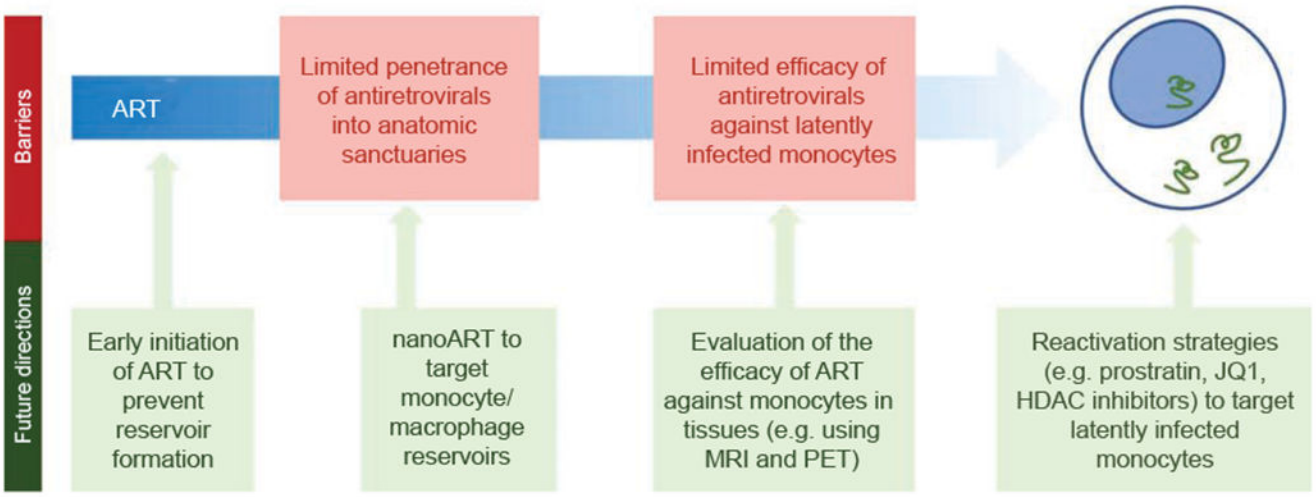

Fig. 4. The relevance of monocytes to HIV treatment and cure strategies.

Overview of the barriers which limit the ability of antiretroviral therapy (ART) to target monocytes and macrophages in tissues, and potential strategies to address these.

Table 1.

Changes in the percentage of classical, intermediate, and nonclassical monocyte subpopulations under various conditions.

	Classical $CD14^{++}$ $CD16^{-}$ monocytes	Intermediate $CD14^{++}$ $CD16^{+}$ monocytes	Nonclassical $CD14^{+}$ $CD16^{++}$ monocytes
Healthy individuals [6,8]	80–90%	11.2–28.2%	3.5–9.9%
Uncontrolled viremia [6] (viral load >400 copies/ml)		38.8% (29.6–59.8%)	17.1% (13.0–27.5%)
Controlled viremia [6,13] (viral load <400 copies/ml)	71.1%	20.7% (15.6%–28.2%)	9.3% (6.0–15.2%)
ART-treated individuals [7] (<3 years of therapy)		23.4% (18.6%–35.9%)	10.0% (7.5–14.3%)

AIDS. Author manuscript; available in PMC 2019 January 14.

Table 2.

Monocyte-specific correlates of neurocognitive decline or neuronal injury in HIV infection.

Compartment	Measure of monocyte dysfunction associated with neurocognitive decline or neuronal injury
Brain	High HIV viral load [72]; increased perivascular $CD14^+/CD16^+$ mononuclear cells [76]
Cerebrospinal fluid	Elevated sCD14 [76,77]
Blood	Elevated $CD16^+$ monocytes [11,73,74]; high HIV DNA levels in $CD16^+$ monocytes [75]; elevated sCD14 [78,79]

Table 3.

Markers of monocyte activation, recruitment into plaques and foam cell formation are associated with radiological measures of cardiovascular disease.

Monocyte	Characteristics	Associated measure of cardiovascular disease
Subset	CD16+ monocytes	CAC progression [115]
Phenotype	CD11b expression	cIMT [120]
	CX3CR1 expression	cIMT [120]
Activation markers	sCD163 level	Noncalcified coronary plaque size [123,124]; arterial wall inflammation [125]
	sCD14 level	cIMT progression [127]; CAC [129]
Recruitment	MCP-1 level	cIMT [113]; CAC [118]
	oxidized LDL level	cIMT [113]
	sVCAM1 level	cIMT [130]

CAC, coronary artery calcium; cIMT, carotid intima–media thickness; LDL, low-density lipoprotein.