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Role of the Macrophage in HIV-Associated Neurocognitive Disorders and Other Comorbidities in Patients on Effective Antiretroviral Treatment

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Abstract

Combination antiretroviral therapy (ART) has altered the outcomes of HIV infection in treated populations by greatly reducing the incidence of opportunistic infections, cancer, and HIV-associated dementia. Despite these benefits, treated patients remain at high risk of chronic diseases affecting peripheral organs and brain. Generally, these morbidities are attributed to persistence of latent HIV in resting T cells, chronic inflammation, and metabolic effects of ART. This review makes the case that monocytes/macrophages warrant attention as persistent reservoirs of HIV under ART, source of systemic and brain inflammation, and important targets for HIV eradication to control chronic HIV diseases.

The morbidity and mortality of HIV infection have changed significantly in countries with access to ART. HIV infection can now be managed as a chronic condition with continued treatment resulting in stable suppression of virus replication and immunological improvement. Because individuals on successful ART generally do not develop immunodeficiency, the previously fatal complications of opportunistic infections and cancers can be largely prevented. In the central nervous system (CNS), ART dramatically reduced the prevalence of HIV dementia, the most severe form of HIV-associated neurologic diseases (HAND) (Antinori *et al*, 2007) and a major AIDS-defining disease in the pre-ART period (Navia *et al*, 1986). Despite these benefits, treated patients remain at high risk for chronic diseases affecting the circulatory system, gut, lung, and lipid, bone, and energy metabolism. Some of these abnormalities appear to reflect a state of accelerated aging. In addition, a large fraction of HIV patients on ART, an estimated 50%, exhibit milder, sub-dementia forms of HIV-associated brain disease known as asymptomatic neurocognitive impairment (ANI) and mild neurocognitive disorder (MND) (Antinori *et al*,

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FINANCIAL CONFLICTS OF INTEREST

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2007; Harezlak *et al*, 2011; Heaton *et al*, 2010). ANI and MND, rather than dementia, now constitute the majority of HIV neurological cases diagnosed in people on ART with sustained plasma virus suppression and improved or normal CD4 T cell levels (Antinori *et al*, 2007; Harezlak *et al*, 2011; Heaton *et al*, 2010). The key questions in HIV research are, therefore: what are the virological and host mechanisms responsible for these morbidities, and how can these illnesses be prevented, treated, or cured (the latter likely requiring elimination of virus infected cellular reservoirs)?

The current view attributes chronic diseases observed in individuals on ART to chronic inflammation caused by residual HIV in tissues, with additional complications of metabolic effects of prolonged antiviral drug administration (Lake and Currier, 2013; Sandler and Douek, 2012). While ART prevents HIV replication (infection of new cells), a large fraction of patients on effective therapy still have low (several copies/ml) but persistent levels of free virus in plasma which is detectable by sensitive PCR and culture methods (Palmer *et al*, 2008; Siliciano *et al*, 2003). This “residual” plasma viremia is stable, insensitive to antiretroviral therapy, and it presents the major obstacle to HIV cure (reviewed in (Katlama *et al*, 2013; Shan and Siliciano, 2013)). The origins of this virus are not fully known, but one conspicuous cellular niche for HIV persistence is the pool of resting memory CD4+ T cells carrying latent HIV (reviewed in (Shan and Siliciano, 2013)). In the absence of HIV expression, these cells do not undergo viral cytolysis and are not recognized by virus specific cytotoxic T cells, but they can produce virus and spread new infection upon stimulation (Ho *et al*, 2013). Importantly, latently infected T cells were shown to decay at slow rates, with estimated t(1/2) of 44 months, consistent with persistence and stability of residual HIV in plasma (Shan and Siliciano, 2013; Siliciano *et al*, 2003). Extensive efforts are being devoted to testing strategies to induce and eradicate latent HIV in T cells, including by the novel methods of somatic cell gene editing (Hu *et al*, 2014; Shan and Siliciano, 2013). However, T cell reservoirs may not fully account for residual HIV in treated patients. Careful genetic analysis of virus in; patients on therapy (Bailey *et al*, 2006; Palmer *et al*, 2008) or after discontinuation of therapy (Chun *et al*, 2000) found that in the majority of subjects residual and rebounded HIV in plasma, respectively, was genetically distinct from virus present in pre-existing T cell reservoirs, suggesting that these cells are not the sole source of residual viremia. Notably attempts to reactivate latent virus in T cells of patients on ART with immunological stimulators have been thus far unsuccessful (Mitsuyasu *et al*, 2007). HIV reactivation in T cells can be achieved using chromatin modifying agents such as valproic acid or vorinostat (Del Prete *et al*, 2014; Elliott *et al*, 2014; Lehrman *et al*, 2005; Wei *et al*, 2014). However, evidence that increased HIV transcription in T cells caused by these agents may facilitate HIV cure is mixed. Earlier clinical trials suggested depletion of latent HIV infection in T cells after treatment with valproic acid (Lehrman *et al*, 2005), whereas recent study with larger group of patients showed no effects of a potent HDAC inhibitor vorinostat on plasma virus levels, frequency of latently infected cells, and frequency of HIV specific T cells (Elliott *et al*, 2014). Because residual HIV in individuals on effective suppressive ART shows only limited genetic diversification over-time, with no new appearance of ART resistance mutations (Bailey *et al*, 2006; Wong *et al*, 1997), it is unlikely that this virus arises from active virus replication in an unidentified tissue. In some studies, however, residual viremia can be reduced (but not

eliminated) upon intensification of treatment (Baroncelli *et al*, 2015). Together these considerations suggest that other persistently-infected cells, in addition to memory T cells, contribute to stable residual viremia and chronic inflammatory diseases in patients on effective ART.

HIV-infected macrophages are one such cell type worth consideration and several excellent reviews have recently elaborated on this subject (Costiniuk and Jenabian, 2014; Dey *et al*, 2012; Stevenson, 2014; Tan and Sattentau, 2013; Watters *et al*, 2013). Infected macrophages have been found at low but measurable frequencies in lung and duodenal tissue of patients on ART with undetectable plasma virus (Cribbs *et al*, 2015; Zalar *et al*, 2010) and in brain tissues of SIV-infected macaques on ART (Clements *et al*, 2002). The potential role of macrophages as a lasting HIV sanctuary is further supported by HIV biology in these cells. Macrophages are natural target cells for lentiviruses including HIV. Although they are terminally differentiated, non-dividing cells, lentiviruses have evolved the mechanisms to transport viral core to the intact nucleus, integrate viral DNA into transcriptionally active sites on chromosomes, and initiate chronic productive infection in these cells. Macrophages support HIV infection without undergoing viral cytolysis or apoptosis and infected cells are insensitive to the currently available antiretroviral drugs and antiviral CTL; as a consequence infected macrophages have long life span compared to productively infected T cells (Borjabad *et al*, 2011; Busca *et al*, 2012; Cribbs *et al*, 2015; Le Douce *et al*, 2010; Murphy *et al*, 2008; Vojnov *et al*, 2012). Both HIV and SIV have evolved strategies to overcome macrophage restriction factors, contributing to their persistence in these cells (reviewed in (Stevenson, 2014)). The ability of HIV to assemble and accumulate in intracellular compartment connected to extracellular space (reviewed in (Tan and Sattentau, 2013)) may further protect virus from immunological responses and contribute to virus transmission despite ART (Duncan *et al*, 2013). At present, it is an open question whether monocytes/macrophages can also support HIV latency similar to memory T cells. Many of the studies on latency were conducted in transformed macrophage cell lines (Kumar *et al*, 2014); the few published studies of primary cells in patients indicate that at least intestinal and lung macrophages remain productively infected under suppressive ART (Cribbs *et al*, 2015; Zalar *et al*, 2010). Transient SIV latency in macrophages/microglia was documented during early stages of infection in macaques (Barber *et al*, 2006) and one recent report demonstrated presence of unexpressed HIV DNA in macrophages/microglia in autopsy brain tissue from of patients who died with presymptomatic HIV infection (Thompson *et al*, 2011). It should be noted that because HIV infection of macrophages is largely non-lytic and infected cells may be able to avoid host immune responses (Busca *et al*, 2012; Vojnov *et al*, 2012), viral latency may not be essential for their survival as HIV reservoirs under ART. Further studies are needed to determine whether HIV RNA present in residual infected macrophages under ART bears sequence similarity with that of HIV RNA of residual HIV in plasma.

Another important consideration regarding role of macrophages as viral reservoirs is the longevity or turnover of infected cells under long term therapy. In contrast to infected T cells, the dynamics of HIV-infected macrophages is largely unknown (Costiniuk and Jenabian, 2014). In one longitudinal study in a small number of patients in Thailand, a

subset of subjects maintained HIV DNA positive CD14+ monocytes in blood for 3.5 years of follow up since initiation of treatment while CD14+ depleted lymphocytes were HIV negative during last year of follow up (Shiramizu *et al*, 2012). Tissue macrophages may have longer life spans than circulating monocytoid cells (Murphy *et al*, 2008). The half-life of human perivascular macrophages has been estimated in months to years, whereas microglia turnover more slowly, years to a lifetime (Kofler and Wiley, 2011). In the setting of disease, microglia turnover may be faster and approximate that of perivascular macrophages (Kofler and Wiley, 2011). In non-human primates, monocytes turn over more rapidly in response to viral infection and are replaced at a higher rate from bone marrow (Burdo *et al*, 2010). It is conceivable that the increased turnover observed in blood actually involves the invasion of bone marrow derived monocytes into tissues. This scenario is supported by bioinformatics analysis demonstrating the similarity of HIV sequences in brain, blood, and bone marrow, suggesting a directionality of virus trafficking (Liu *et al*, 2000). It is conceivable that HIV-infected macrophages and microglia could be replaced by uninfected cells with long-term anti-retroviral therapy. However, even with the limited information on macrophage longevity (Cribbs *et al*, 2015; Shiramizu *et al*, 2012; Zalar *et al*, 2010), strategies to target infected macrophages for HIV eradication should also be considered.

While macrophages may serve as an important source of residual virus under ART, the subversion of the physiological functions of these cells by HIV infection, combined with longevity of infected macrophages, play important roles in HIV pathogenesis at many levels of human physiology (Assimakopoulos *et al*, 2014; Brown, 2015; Burdo *et al*, 2013; Cavarelli and Scarlatti, 2014). Paradoxically, the wide-spread use of ART, through diminution of CD4 T cell depletion, has exposed the core lentiviral nature of HIV as a pathogen adapted to survive and cause slow progressive disease, including in the nervous system, through colonization of macrophages. The role of macrophages and microglia in HAND has been known for many years. HIV enters the CNS early after primary infection (Valcour *et al*, 2012), likely by migration of infected monocytes (Saini and Potash, 2014; Valcour *et al*, 2013) through blood-brain barrier (Persidsky *et al*, 2000). Subsequently, HIV persists in the brain in microglia and perivascular macrophages, and to a lesser extent astrocytes, and the process of viral neuropathogenesis is believed to be mediated by inflammatory and cytotoxic products secreted by these cells (Lipton and Gendelman, 1995). This is particularly evident in the case of HIV/SIV encephalitis where the levels of neuronal damage correlate with HIV brain burdens (Budka, 2005). However, even in the pre-ART era, it was clear that high levels of HIV replication in the brain are not required for sustaining HIV brain disease. In many patients, dementia correlates better with activated macrophages/microglia than productive virus infection in the brain (Glass *et al*, 1995). Immune activation of macrophages/microglia and astrocytes, although to a much more modest degree can also be observed in patients on ART with MND (Tavazzi *et al*, 2014). The HIV brain burdens in these patients are often below level of detection (Gelman *et al*, 2013). These results suggest that MND and HAD may represent a disease continuum linked by the common mechanism of glial cell activation. This mechanism may include expression of viral and cellular inflammatory products by chronically-infected glial cells, with the possibility that pharmacologic regimens including antiretroviral drugs with high CNS

penetration may improve cognitive performance in some (Smurzynski *et al*, 2011) but not all tested patients (Marra *et al*, 2009). In support of the role of inflammation, *per se*, it has been shown that soluble CD14 (sCD14), a soluble form of the monocyte endotoxin receptor present on monocytes and macrophages correlates with CD4 nadir and both are strong predictors of the severity of neurocognitive impairment (Ellis *et al*, 2011; Fischer-Smith *et al*, 2001; Lyons *et al*, 2011; McCombe *et al*, 2013). CD4+ T cell nadir is also predictive of opportunistic infections as well as death from all causes in patients on ART (Pulliam *et al*, 1997; Sandler *et al*, 2011). This raises the possibility that monocyte/macrophage activation is important, not just in the CNS pathologies, but in the overall HIV pathogenesis. In fact, because ART neither completely restores immunologic functions nor prevents cognitive deficits in HIV infection, it is conceivable that inflammatory processes initiated in the periphery may affect both immunity and neurocognitive performance.

One of the aspects of the HIV brain disease field that has greatly contributed to our understanding of HIV pathogenesis in general has been the characterization of the role of monocytes/macrophages subsets in disease. Monocytes with a more mature phenotype (CD14+/CD16+) have been shown to be increased in blood in HIV infection, with even higher frequency of expression in HIV dementia (Pulliam *et al*, 1997). It is also evident that CD16+ monocytes are decreased with ART treatment and furthermore, the frequency of CD14+/CD163+/CD16+ monocytes in circulation correlates directly with viral load and inversely with CD4+ T cell count (Fischer-Smith *et al*, 2008a). The notion that this monocyte subset invades the CNS has been demonstrated by *in vitro* (Pulliam *et al*, 1997) and by immunohistochemical studies in human and macaque CNS by Rappaport's group and others (Fischer-Smith *et al*, 2008a; Fischer-Smith *et al*, 2001; Williams *et al*, 2001a) as well as in visceral tissues (Tavazzi *et al*, 2014; Walker *et al*, 2014; Yearley *et al*, 2006).

The connection between HIV/SIV infection, macrophages and immune suppression has also been suggested based on immune polarization. An increase in M2-"like" cells, possibly alternatively activated or regulatory macrophages (Caescu *et al*, 2015; Murray *et al*, 2014), could be responsible for both CNS disease, other comorbid conditions in AIDS, as well as immune dysfunction. Macrophage Colony Stimulating Factor (M-CSF) expression is increased in HIV infection, likely driving production on monocytes from bone marrow and differentiation toward M2. M2 macrophages (as generated in response to M-CSF) are preferentially infected by HIV (Kalter *et al*, 1991); this may have profound consequences for increasing macrophage targets for infection, and at the same time, polarization immune responses in toward immune suppression.

An additional intersecting pathway between peripheral and brain manifestations of HIV infection is chronic interferon (IFN) stimulation and the consequent dysregulation of interferon stimulated genes (Borjabad *et al*, 2011; Gelman *et al*, 2013; Pulliam, 2014; Pulliam *et al*, 2014; Roberts *et al*, 2004). In fact, the ability to control Type I interferon responses may also explain why sooty mangabeys and African green monkeys do not get AIDS from SIV infection, whereas rhesus macaques are susceptible to disease (Jacquelin *et al*, 2009), although there are dissenting views (Bosinger *et al*, 2013). In the CNS, Type I IFN was shown to control HIV and SIV expression in the brain and neuropathogenesis (Clements *et al*, 2002; He *et al*, 2014) but also contributed to brain disease in some systems

(Sas *et al*, 2009). We suspect that there is a connection in both peripheral and brain diseases between altered monocyte/macrophage homeostasis, immune polarization and the interferon response. IFN-α is known to induce the M2 cytokine, IL-10 (Aman *et al*, 1996), by recruiting IFN Regulatory Factor 1 and Stat 3 (Ziegler-Heitbrock *et al*, 2003). IL-10, together with M-CSF have also been demonstrated to promote the development of CD14+/CD16+ monocytes (Li *et al*, 2005). As IL-10 is an important immunosuppressive Th2/M2 cytokine, the process leading to expansion of CD14+/CD163+/CD16+ monocytes/macrophages likely has profound implications in the development of CNS disease and immunosuppression.

While macrophage/microglial and also astrocytic infection of the CNS represent important obstacles for HIV eradication, altered inflammatory pathways likely provide more direct explanations for both the neurocognitive impairment and immune dysfunction remaining in successfully treated patients. In the setting of ART, despite adequate control of viral replication, inflammatory pathways, including IFN-activated genes, remain activated above basal levels, contributing to the neuro- and immune-pathogenesis. These processes would serve to promote the accumulation of M2 and/or regulatory macrophages in CNS as well as other organs, as we have observed in patients with HIVE (Tavazzi *et al*, 2014). In view of the importance of altered monocyte/macrophage homeostasis, trafficking and immune polarization (Burdo *et al*, 2010; Fischer-Smith *et al*, 2008a; Fischer-Smith *et al*, 2008b; Fischer *et al*, 2014; Hasegawa *et al*, 2009; Williams *et al*, 2001a; Williams *et al*, 2001b), there is an urgent need for pharmacologic strategies applied to HIV infection in order to successfully modulate inflammation and immune polarization. Such an effort will require interdisciplinary approaches combining support from relevant NIH grant programs (i.e., NIAID, NIMH, NINDS as well as other institutes) and an evolution in the mind-set of the academic and industry scientists which has up to now been highly successful, but for the most part focused on viral targets for therapeutic intervention. The timely interactions and synergy between AIDS and HAND programs at NIH provides a unique opportunity to address common pathogenic pathways in diverse manifestations of HIV infection under ART.

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