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EDITORIAL COMMENTARY

Antiretroviral Treatment of Acute HIV Infection Normalizes Levels of Cerebrospinal Fluid Markers of Central Nervous System (CNS) Inflammation: A Consequence of a Reduced CNS Reservoir?

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(See the Major Article by Hellmuth et al, on pages 1885–91.)

Antiretroviral treatment (ART) has transformed human immunodeficiency virus (HIV) infection from a generally lethal infection into a chronic disease, enabling persons living with HIV (PLWH) to have a near-normal life. Still, HIV-infected individuals continue to have a shorter life expectancy than the general population, which may in part be explained by differences in lifestyle factors such as smoking, alcohol consumption, and drug use among PLWH [1]. Persistent immune activation and inflammation may also contribute to increased age-related morbidity and mortality in PLWH. Levels of immune activation markers commonly continue to be increased despite suppressive ART. This is probably driven by HIV release from latently infected resting T cells that are randomly activated, as well as other cells. Other sources may be microbial translocation, lifestyle factors, and coinfections, such as that due to cytomegalovirus [1, 2]. The clinical consequences of this low-grade chronic immune activation are not fully known, but it is clear that increased levels of inflammatory biomarkers are predictive of subsequent morbidity and mortality [3, 4].

It is beneficial to initiate ART in patients with high $CD4^+$ T-cell counts, rather than postponing treatment [5]. The reduction of systemic inflammation by ART may help explain many of the benefits [4]. Nevertheless, not all comorbidities are reduced by early initiation of ART in persons with high $CD4^+$ T-cell counts. For example, cardiovascular complications (or surrogate markers of cardiovascular disease), pulmonary disease markers, and neurocognitive dysfunction did not appear to improve significantly with early ART initiation in the START trial, despite major declines in infections and infection-related cancers [6–8]. While the relatively young age of START participants, in addition to measurement issues, may have contributed to the lack of any clear beneficial impact of immediate ART initiation on these morbidities, it is also possible, that irreversible HIV-associated organ injury in the relevant tissues (ie, the vasculature, lung, and brain) may not yet have been established at such early disease stages [9].

HIV is a neurotropic virus and can be found in the central nervous system (CNS) early after infection [10]. While infected $CD4^+$ T cells often traffic through the cerebrospinal fluid (CSF) during untreated disease, an active, productive infection is also established within the CNS itself, mainly in microglia and brain macrophages, leading to chronic CNS immune activation that may contribute to neuronal damage if left untreated [11]. Similar to its effect outside the CNS, ART substantially decreases intrathecal immune activation, although not to normal levels [12]. Notably, $CD4^+$ T-cell trafficking through the CSF is often reduced to near normal levels with ART [13]. Yet, CSF levels of neopterin, a pteridine marker of primarily macrophage activation [14], have been found to be stably increased in the majority of PLWH who begin treatment during the chronic phase of HIV infection and also after long-term receipt (ie, for >10 years) of suppressive ART [15, 16].

By contrast, Hellmuth et al [17] report in this issue of *The Journal of Infectious Diseases* that, in the CSF, levels of markers of residual CNS inflammation are essentially normalized when ART is initiated early, during acute HIV infection (AHI), while plasma levels of markers remain abnormal [17]. This important finding has several potential implications. The most plausible explanation for the difference is that a stable, permanent infection of cells in the CNS is established later than in systemic viral reservoirs, which are highly concentrated in memory T-cell compartments within the first days of systemic HIV infection [9]. This hypothesis is supported by a recent study

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examining anti-HIV antibody formation as a surrogate marker for antigen load and the size of the viral reservoir [18] in patients followed longitudinally during early HIV infection [19]. While serum anti-HIV antibodies emerged in blood by day 30 in untreated early infection, CSF antibodies reached similar levels about 2 weeks later. In addition, high antibody levels, comparable to those observed in chronically infected subjects, were reached several months later in CSF, compared with blood. Furthermore, while treatment of chronic infection resulted in only small reductions in levels of anti-HIV antibodies in both CSF and serum, treatment during early infection substantially reduced CSF levels of antibodies, sometimes to levels close to those in HIV-negative controls, whereas antibody levels in serum were less affected [19]. To the extent that differential CSF and blood antibodies indicate HIV persistence, these data strongly suggest a relative delay in the establishment of the CNS reservoir, compared with the systemic HIV reservoir. If true, this provides an opportunity for early treatment to have a greater impact on the magnitude of long-term CNS infection, supported by the normalization of CSF levels of immune activation biomarkers by early ART initiation, as reported by Hellmuth et al [17].

CNS infection is generally well controlled by systemic suppressive ART, although sometimes the HIV RNA load is increased in the CSF despite suppression of the plasma viral load, a phenomenon referred to as "CSF viral escape" [20]. Occasionally, CSF viral escape is accompanied by neurological and neurocognitive signs and symptoms (symptomatic CSF escape) [21]. However, asymptomatic escape, found when lumbar puncture is performed in study protocols, is more common [22, 23]. CSF escape is associated with increased intrathecal immune activation and may be related to the size of the CNS HIV reservoir, although this has not been definitely proven. Correspondingly, the residual CSF viral load below the limit of quantification of standard assays also correlates with the degree of CSF immune activation in PLWH receiving suppressive ART [24, 25], reinforcing the view that intrathecal immune activation is driven by persistent virus in the CNS. Nevertheless, similar to findings during systemic infection [26], treatment intensification does not seem to decrease the residual CSF viral load or inflammation [27, 28], suggesting there is no ongoing HIV replication during effective treatment. Altogether, these data suggest a close association between the CNS reservoir and CSF immune activation.

Macrophages and microglia are the main target cells for HIV replication in the CNS, which is different from systemic infection, where lymphocytic infection dominates [29]. This, together with CNS being an immune-privileged anatomic compartment protected by the blood-brain barrier, provides a foundation for compartmentalized HIV-1 replication within the CNS reservoir [30]. The CNS reservoir has not yet been adequately characterized, either in morphological terms or with regard to the mechanisms leading to its establishment and maintenance. A better understanding of the CNS reservoir formation prior to treatment and of its preservation during ART is important when exploring HIV eradication strategies, but also if one is to avoid severe CNS adverse events during the course of HIV cure studies [31]. It would be of great benefit for cure strategies if the HIV CNS reservoir were substantially reduced by early ART, as indicated in the study by Hellmuth et al [17].

The clinical implications of normalized intrathecal immune activation in PLWH treated during acute HIV infection are unclear. Will the long-term risk for cerebrovascular events, HIV-associated neurocognitive disease, and non–HIV-associated dementia, such as Alzheimer disease and vascular dementia, decline? Although there are some indications of an association between immune activation and these conditions [32, 33], there is yet no evidence that early initiation of ART prevents neurological or neurocognitive diseases.

Notes

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