The challenge of HIV associated neurocognitive disorder

For more than 30 years the world has been challenged by HIV. In addition to attacking the immune system, the virus can enter the peripheral and central nervous systems, with potentially devastating effects. The various neurological complications associated with HIV, including those caused by opportunistic infections and malignant disease are referred to as neuroAIDS, a major component of which is HIV associated neurocognitive disorder (HAND). In its least damaging form, symptoms go un-noticed by patients, and it is known as asymptomatic neurocognitive impairment. Severity increases through mild neurocognitive disorder to its most severe form, HIV associated dementia (HAD). HAND impairs cognitive activity, including memory, learning, attention, problem solving, and decision making. Symptoms can vary from confusion to forgetfulness, behavioural changes, and nerve pain. This issue of The *Lancet Infectious Diseases*, includes a Review of clinical manifestations and management of HAND by David Clifford and Beau Ances, which will be presented at the *Cell–Lancet* translational medicine conference: *What will it take to achieve an AIDS-free world?*

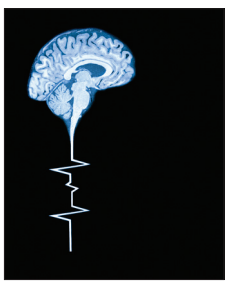
In the course of HAND, HIV crosses the blood–brain barrier in monocytes at an early stage of infection and can in the CNS persist without symptoms for decades. Once in the CNS, HIV can infect microglia and macrophages. Upon HIV infection of macrophage and microglial cells, glutamate—the main excitatory neurotransmitter in the brain—accumulates in the extracellular space. During HAND, it is thought that glutamate excess is associated with neurotoxicity mediated by gp120, tat, and other HIV proteins.

Before the development of antiretroviral therapy (ART), the virus could have a devastating effect on the brains of those infected. In 1996, the introduction of ART in developed countries substantially reduced morbidity and mortality rates in HIV infected patients. The incidence of HIV-dementia also decreased: about 16% of people with HIV were affected before ART, but less than 5% of those with access to effective treatment develop dementia today. However, ART does not eliminate the virus, and individuals receiving ART still develop milder neurocognitive impairment. Thus, there is a need for a more complete therapeutic approach to treatment of HAND.

Goals for the management of HAND include suppression of HIV through ART optimisation and the treatment of associated psychiatric, neurological, and neuropsychological dysfunctions, including mood disorders. The high incidence of HAND in the ART era is linked to the difficulty that certain drugs have in crossing the blood–brain barrier to get into the CNS. Letendre and colleagues introduced a ranking system—CNS penetration effectiveness (CPE)—that classifies molecules on the basis of their ability to enter the CNS and achieve control of HIV replication. Some observational and uncontrolled studies have shown no link between CPE and cognitive outcomes. In other studies, higher CPE was associated with poor cognitive outcomes suggesting a possible neurotoxic effect of ART. A cohort study by Robertson and co-workers shows cognitive improvements in patients who stop ART.

Such conflicting findings might arise from the different study designs and methods used. However, the goal of future studies and trials will be to find new drugs able to reach adequate concentrations in the CNS that are able to suppress viral replication without neurotoxic effects. Since depression and anxiety may be important confounders in the diagnosis of HAND and reduce quality of life, HIV-positive individuals should be screened for mood disorders, and given appropriate treatment. Combinations of standard ART with new drugs that both protect nerve cells from toxins and reduce inflammation are urgently needed. Several strategies need to be used to prevent glutamate excess; antagonists of NMDA receptors have been popular therapeutic targets but not without side-effects. Inhibitors of enzymes involved in the production of glutamate might also be alternative targets.

The treatment of HAND remains challenging because of the multiple mechanisms involved. Therefore, a multi-stranded therapeutic approach will be needed and advances will be depend on the identification of drug-like inhibitors, as well as the development of predictive neuroAIDS animal models. Discovering what may be going on in the CNS after many years of apparent HIV infection control is an urgent and important challenge in HIV medicine. ■ *The Lancet Infectious Diseases*



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The *Lancet–Cell* translational medicine conference *What will it take to achieve an AIDS-free world?* takes place in San Francisco, CA, USA Nov 3–5
See http://www.translationalmedicine-lancet-cell.com/HIV/

See **Review** page 976–86

For more on **HAND** see http://www.iasusa.org/sites/default/files/tam/19-4-137.pdf

For **the paper by Letendre and colleagues** see *Ann Neurol* 2004; **56:** 416–23. DOI:10.1002/ana.20198

For **the paper by Robertson and co-workers** see *Neurology* 2010; **74:** 1260–66. http://dx.doi.org/10.1212/WNL.0b013e3181d9ed09