Chapter 8
HIV-Associated Neurocognitive Disorder:
The Interaction Between HIV-1 and Dopamine Transporter Structure

Ahmed Abd Elkader Elrashedy
National Research Center, Egypt

ABSTRACT

In the last two decades, several advancement studies have increased the care of HIV-infected individuals. Specifically, the development for preparation of combination antiretroviral therapy has resulted in a dramatic decline in the rate of deaths from AIDS. The term "HIV-associated neurocognitive disorder" (HAND) has been used to distinguish the spectrum of neurocognitive dysfunction associated with HIV infection. HIV can pass to the CNS during the early stages of infection and last in the CNS. CNS inflammation and infection lead to the development of HAND. The brain can serve as a sanctuary for ongoing HIV replication, even when the systemic viral suppression has been achieved. HAND can remain in patients treated with combination antiretroviral therapy, and its effect on survival, quality of life, and everyday functioning make it a significant unresolved problem. This chapter discusses details of the computational modeling studies on mechanisms and structures of human dopamine transporter (hDAT) and its interaction with HIV-1 trans activator of transcription (Tat).

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INTRODUCTION

About 36.7 million people in the world suffer from the acquired immune deficiency syndrome (AIDS) disease caused by human immunodeficiency virus (HIV) and about 1.1 million people have died from this disease, according to the 2016 report of United Nations Programme on HIV/AIDS (UNAIDS) (Who, UNICEF, 2016). (See Figure 1 and Figure 2.) 70% of HIV-infected individuals suffer from HIV-associated neurocognitive disorders (HAND) (Ernst et al., 2009; Zhu et al., 2009; Midde, Gomez, & Zhu, 2012; Robertson et al., 2007).

Even though our knowledge is improving and we're learning more about HAND, there is no specific treatment for curing HAND. HAND affects survival, quality of life, and everyday activities, so the development of a HAND treatment remains important for HIV patients (Heaton et al., 1994).

All over the world, HAND is the major cause of cognitive impairment and persists, even in individuals who've received combination antiretroviral therapy (Heaton et al., 2010a; Tozzi et al., 2007). The spectrum of neurological complications in HAND are generally segregated into three main groups: asymptomatic neurocognitive impairment (ANI; 33%), mild neurocognitive disorders (MND, 20–30%), and severe, albeit rare, HIV-associated dementia (HAD; 2–8%) (Heaton et al., 2010b; McArthur et al., 2010).

The clinical impairments in HAND include attention, memory, learning, motor function, and behavioral changes. As combination antiretroviral therapy becomes more widely distributed in resource-limited settings, survival will improve and the long-term global impact of HAND will become even more important.

Adding to that, early HIV infection of the CNS is believed to contribute to the development of HAND. Evidence shows that the CNS can subsequently serve as a storage tank for ongoing HIV replication, so that limits the opportunity for a complete cure or eradication of the infection (Fois & Brew, 2015). Additionally, the incidence and progression of HAND are usually combined with the intake of recreational drugs like cocaine and methamphetamine (Buch et al., 2011). If HAND can be prevented at early infection stage, the quality of life for the patient will be improved and the economic burden will be lessened on the healthcare system.

Joining together lines of clinical observation, supported by imaging, (Wang et al., 2004; Chang et al., 2008) neuropsychological performance testing (Meade et al., 2011; Kumar et al., 2011) and postmortem examinations (Gelman et al., 2012), have implicated dopamine (DA) dysregulation with the abnormal neurocognitive function observed in HAND (Berger & Arendt, 2000). DA-rich brain regions (basal ganglia and related structures) are highly sensitive to the effects of both HIV infection and substance use.