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Does ART attenuate or prevent HIV encephalopathy?

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By

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Introduction

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Human Immunodeficiency virus (HIV) infections, if left untreated, can cause immune suppression. Many individuals may not be aware that they have HIV until they are tested. HIV can be spread through shared needles, sexual contact, breast milk, and transfer of blood/bodily fluids in open mucosa. HIV progresses to several stages depending on how long a patient remains untreated. The usual time from HIV exposure to the development of symptoms is two to four weeks, although incubation periods as long as ten months have been observed.[1] In the first or acute stage, patients may experience symptoms such as fever, lymphadenopathy, sore throat, rash, myalgia/arthralgia, and headache.[1] Painful mucocutaneous ulceration is a distinctive manifestation of acute HIV infections. In addition, an asymptomatic or dormant phase can occur initially or after the symptomatic phase and last 10-12 years. Progression to acquired immunodeficiency syndrome (AIDS) occurs when the T-cell count falls under 200 cells/cubic millimeter or AIDS-defining illnesses(HIV-related encephalopathy and other CNS disorders) are present. Advanced HIV infection occurs when the T-cells fall below 50 cells/cubic millimeter, increasing the risk for developing malignancies, including CNS lymphoma.[1]

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Many times HIV remains undetected because patients are asymptomatic and thus unaware that they are infected, or they are unaware because they have not had complete STD screening. By the end of 2016, 36.7 million adults and children globally were reportedly living with HIV/AIDS.[2] These facts highlight the importance of early detection and treatment of HIV infections. Antiretroviral therapy (ART) can prevent, stall, or even reverse many of the HIV-related illnesses. Whether ART can prevent or ameliorate HIV-related cognitive impairment is unclear, though.

Background

HIV-related cognitive impairment is a broad term that includes AIDS dementia complex, HIV encephalitis, and HIV encephalopathy (the historical equivalent to a subacute syndrome of progressive cognitive and motor dysfunction). Heikinheimo et al. examined the process of HIV infecting the brain. Initially, the virus is transported from the periphery through the BBB into the CNS with both monocytes and CD4 cells. The monocytes then transfer HIV into macrophages and microglial cells where it replicates. The infected macrophages and microglial cells then elicit an inflammatory reaction, which releases neurotoxins such as glutamate, thus leading to brain damage.[3]

In order to classify these HIV-associated neurocognitive disorders, the Frascati criteria are used. Though not universal, they include three levels of impaired neuropsychological test performance and functional impairment within an umbrella term, known as HIV-associated neurocognitive disorders (HAND).[4] HAND can be further broken down into three sections.

Asymptomatic neurocognitive impairment (ANI)	Mild neurocognitive disorder (MND)	HIV associated dementia
1 standard deviation or more below the mean in at least two cognitive domains on neuropsychological standardized testing without a symptomatic impairment.	one standard deviation or more below the mean in at least two cognitive domains on neuropsychological standardized testing with at least mild symptomatic impairment.	two standard deviations or more below the mean in at least two cognitive domains on neuropsychological standardized testing with impairment in activities of daily living.

1

HIV related cognitive impairment must be differentiated from other sources of encephalopathy including CMV (cytomegalovirus), syphilis, EBV (Epstein-Barr virus), toxoplasmosis, rubella, viral hepatitis, gonococcal, and other infections. Differentiation from these other bacteria/viral origins requires a thorough workup, including a lumbar puncture for

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definitive treatment. This distinction is necessary because treatments for infectious causes are available, whereas definitive treatment for HIV-related cognitive impairment may not be available and most likely would be different.

For treatment of HIV infections, seven classes of antiretroviral drugs are currently available: nucleoside reverse transcriptase inhibitors (NRTIs), nucleotide reverse transcriptase inhibitors (NtRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion inhibitors, entry inhibitors—CCR5 (chemokine co-receptor-5) antagonists, and HIV integrase strand transfer inhibitors (INSTIs).[5] Antiretroviral therapy (ART) is usually given as triple therapy (3 drug combination) for efficacy and prevention of viral resistance. Patients can take a single pill with a combination of 3 antiretrovirals, or a combination of 3 drugs, 2 NRTIs and 1 NNRTI, in separate pills. Combination therapy is necessary to avoid ART resistance, which is well documented and clinically translates into treatment failure and viral load rebound.[6] Combination ART is also known as cART and as the older term, HAART (Highly Active Retroviral Therapy). HAART can have pharmacological toxicities. NRTIs can cause hematologic toxicity, myopathy, cardiomyopathy, lactic acidosis, exocrine pancreas failure, liver failure, bone marrow failure and peripheral neuropathy.[5]

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ART for HIV CNS complications was examined by Pérez-Valero et al. in 2013 who found encouraging evidence for ART efficacy in patients who were HIV positive but virologically suppressed for >1 year.[6] These patients were treated with a protease-inhibitor given as monotherapy or with triple-drug therapy (two nucleoside/nucleotide reverse transcriptase inhibitors plus a protease inhibitor). The study concluded that compared to triple drug antiretroviral therapy, monotherapy with ritonavir/lopinavir or ritonavir/darunavir in patients

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who are virally suppressed was not associated with a higher rate of asymptomatic neurocognitive impairment.[6] Lopinavir or darunavir is the actual antiviral agent. In both combinations, ritonavir functions by inhibiting the metabolism of lopinavir (or darunavir), thus boosting levels of lopinavir (or darunavir). When evaluated for cognitive impairment, no specific differences in global deficit score were observed between these groups. Thus, monotherapy (single-drug treatment with a protease inhibitor combined with a booster drug) appeared to be as effective as triple-drug therapy in these patients.

ART has been successful in arresting or reducing HIV infection and in forestalling CNS complications in virologically suppressed HIV patients. Because HIV cognitive impairment can occur in 15% up to 50% of HIV infected patients, it is crucial to determine whether ART is effective for prevention and treatment of HIV cognitive impairment.[6]

Discussion

The frequency of HIV-associated dementia (HAD) decreased with the introduction of antiretroviral therapy (ART). Evidence for this decline was found by Monforte et al. in a prospective observational study involving 9,803 patients across Europe from 1994-2002. Participants not on HAART therapy, who had a low CD4 cell count and high plasma viral load, had a significantly increased risk of developing CNS diseases (including dementia) compared with those persons on HAART therapy.[7] A limitation of the study includes that data on toxoplasmosis and cryptococcosis were not collected in detail and were not collected in the data. In addition, an increasing proportion of patients stopped specific prophylaxis after HAART induced increase of CD4 cell counts. This meant that. Strengths in the study include a strong

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association with high CD4 counts and low viral load correlated with a lower risk of developing CNS diseases. This study supports the benefit of HAART in the reduction of CNS diseases.

Contrary to the above findings, Cysique et al. found several adverse neuropsychiatric effects with NNRTIs, specifically efavirenz (EFV), which has good CNS penetration. These adverse drug effects occurred more frequently in patients with preexisting neurologic issues and had the potential to worsen neurocognitive deficits. Thus, the drug efavirenz is no longer used in the management of neurocognitive disorders. In addition, efavirenz is avoided in patients with psychiatric conditions because of emerging evidence of increased suicidality with efavirenz use.[4] The study shows that poor adherence has been shown to be associated with the severity of cognitive impairment, especially in older adults and with complex regimens. The strengths Cysique et al. study included the emphasis of the need to address methodological limitations of published studies. In addition, this study emphasized the need for large and representative cross-disciplinary longitudinal investigations across the HIV illness span.[4] This study was a review, which can be a limitation. Nonetheless, other drugs for ART therapy, such as a combination pill (bictegravir, emtricitabine and tenofovir alafenamide), do not have detrimental CNS effects, and if otherwise appropriate, should be considered for both better compliance and overall management.

In an observational study by Fogel et al., a controlled trial examined 24 features sometimes associated with HAND in participants. Two groups were studied. One group consisted of 40 patients diagnosed HIV who were in the older cohort (55–73 years of age). The younger cohort was made up of 30 patients, aged 32– 50 years of age. Participants were examined for HAND while on cART for a total of five years. All participants treated with cART-

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did not demonstrate significant central nervous system deficits meeting Frascati criteria. The older cohort had more cases of HAND compared to the younger cohort, but also had a higher prevalence of hyperlipidemia.[11] Of the two cohorts, the older cohort had more neurocognitive impairment. The HAND in this older group might have been due in part to atherosclerotic vascular dementia, indicating that HAND was less frequent in older patients who did not have hyperlipidemia. However, HIV-associated neurocognitive disorders were found in members of the younger cohort who abused drugs (methamphetamine, in particular), whereas these CNS disorders were less frequent in younger persons who did not abuse drugs.[11] The strengths of this study included the diversity of the cohort. There was a 14 year difference between the means of the two age groups in the cohort. In addition, the inclusion of multiple risk factors in the analysis provided more detail.

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In an observational follow-up study of HIV-infected patients who were first enrolled in a neurological and neuropsychological examination during 1986–1990, Heikinheimo et al. examined 80 HIV patients taking ART who did not have heavy alcohol consumption, central nervous system disorders, or psychiatric disease. Groups were examined according to the durations of ART, including the start dates and any interruptions. Outcomes measured included neurological and neuropsychological examinations, MRI of the brain, and laboratory tests, including blood CD4 cells and plasma HIV-1 RNA. Although polyneuropathy, fatigue, and mild depression were found, severe neurological abnormalities were absent. Many of these Finnish HIV-1-infected patients who received adequate anti-HIV therapy retained good neurological and neurocognitive function despite of a history of HIV infection for as long as 30 years.[2] This

study was limited by a small sample size; however, it highlighted how beneficial ART therapy can be for preventing HIV-related neurocognitive dysfunction.

In the 2017 prospective cohort study by Coban et al. 3313 participants with HIV were randomized to different ART protocols. Participants were previously ART-naïve. Their ages ranged from 22-60 years old. Most had viral suppression for 2 or more years after the initiation of ART. In the individuals studied, viral loads were suppressed with ART. Neurocognitive impairment was still found in both younger and older participants, although less frequent overall compared with patients who did not receive ART. However, even after adjusting for covariates, older participants were more likely to have neurocognitive impairment than younger individuals. The odds of neurocognitive impairment at follow-up visits among the HIV infected increased by nearly 20% for each decade of advancing age. Nonetheless, the rate of neurocognitive impairment decreased overall, the longer participants were on ART.[12] A strength of this study was the large cohort size randomly assigned to initial ART for 2 years. A limitation was its observational design. The observed relationships represent associations which may not be causative. In addition, few subjects were over the age of 60, limiting the data of older patients.

In the 2016 review study by Chan et al. the persistence of HIV-associated neurocognitive disorders despite combination ART (cART) was revealed. However, this neurologic complication was less frequent the earlier cART was started. When neurocognitive disorders were found, they might have been due to cerebrovascular risk factors.[13] CNS viral escape syndrome is the replication of virus in the CNS compartment, despite ART. Both CNS HIV escape and CD8 encephalitis expand the understanding of cognitive impairment in people living with HIV on

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cART. Both show that CNS viral replication and widespread neuroinflammation can persist with CART supression.[13] Furthermore, the rare CNS viral escape syndrome can be diagnosed in patients who have long standing HIV and are virologically suppressed on antiretroviral therapy (ART).

In a study performed by Heikinheimo et al, 2015, 80 HIV+ patients were selected from the greater Helsinkin area from an outpatient Infectious disease clinic. The patients underwent neurological and neuropsychological examinations including brain MRIs between 1986 through 2013. Of the participants, 9 patients suffered from fatigue, 5 developed neuropathies, and 3 had lacunar infarcts. In addition, two patients had brain atrophy. In summary, polyneuropathy, fatigue, and depression were common, but severe neurological abnormalities were absent.[2]

A retrospective study by Lescure et al. investigated 14 HIV infected patients treated with cART who had documented encephalitis originally of unknown cause. These individuals had unusual brain MRI imaging that showed multiple, linear, gadolinium-enhanced perivascular lesions. Tests for CD8 encephalitis (which is characterized by diffuse perivascular and intraparenchymal CD8 infiltration), included MRIS, lumbar punctures, and brain biopsies. CD8 encephalitis was diagnosed in 13 out of 14 of these patients, thus suggesting that cART was not effective for this particular CNS disorder. Sometimes patients develop subacute progressive cognitive deficits that are unexplained by other conditions and accompanied by detectable CSF HIV RNA levels.[4] This means that although patients are well controlled with HART, they still develop HAND. In addition, CD8 encephalitis in HIV-infected patients receiving cART is a clinical entity that should be added to the list of HIV complications.[14]

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In summary, the evidence from these studies was mixed. Evidence from several studies suggested that cART was beneficial in the prevention and treatment of HIV-associated neurocognitive disorders. The decreased viral load achieved through cART is the proposed mechanism of decreasing HIV-related CNS inflammation. However, efavirenz alone was associated with HIV-related neurocognitive decline, which might have been an adverse drug effect. In the meantime, any CNS adverse effects due to cART need to be researched further. Future research should also examine any factors or comorbidities that might predispose HIV infected patients to HIV-neurocognitive disorders and to further characterize the CD8 encephalitis that might be an adverse drug reaction due to cART.

Conclusion

Findings from many studies suggested that cART was beneficial for treating and preventing cognitive impairment. Other studies revealed evidence that although cART was beneficial, it was also associated with CD8 encephalitis. In all cases, a risk versus benefit analysis was done. ART was found to be beneficial in suppression of viral load in patients initiating treatment. Nonetheless, older patients had HAND more frequently than younger patients. In many cases of HIV-neurocognitive deficits or HAND, patients had comorbidities such as hypertension, hyperlipidemia, and previous methamphetamine use, making the cause of the CNS decline less certain. In addition other factors, including age, medication adherence, and severity and duration of HIV infection can affect the frequency of HIV cognitive disorders. Some evidence suggests that earlier treatment with cART may be more beneficial for preventing HIV-neurocognitive disorders. Hence, early diagnosis and treatment are important.

Areas for future research includes more studies on CNS viral escape syndrome. In addition, finding patients without comorbidities is useful for isolating the cause of differences in cases. In addition, studies are needed comparing patients with HIV and hypertension versus those with HIV without hypertension.

Clinicians and patients need to be informed about patient adherence, comorbidities, as well as the side effects of HAART. As studied, the side effects of HAART, including CD8 encephalitis, need to be further studied.[14] In addition, the importance of treatment of HIV needs to be emphasized to patients to prevent HAND. The barrier of obtaining medication is bridged by Public Health. Public Health provides free PREP (pre exposure prophylaxis) as well as resources for treatment to patients with HIV regardless of insurance status.[15] Preliminary evidence of how to use ART is promising and should guide clinicians and patients in medical decision-making. Decreasing viral load is important for decreasing the rate of transmission of the virus as well as overall mortality.

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Reference

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Commented [RS39]: No periods after initials, except the last. Remove the ampersand (&).

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Melanie: can you help me correctly cite this?