Journal of
Antivirals & Antiretrovirals
ISSN: 1948-5964

de O' Leary et al., J Antivir Antiretrovir 2012, S10
DOI: 10.4172/jaa.S10-003

Review Article Open Access

The Impact of HAART on Advanced Brain Aging: Implications for Mitochondrial Dysfunction and APP Processing

Julia Campos de O' Leary[1], Demian Obregon[1,2,3], Frank Fernandez[1,2], Jun Tan[1,2,3] and Brian Giunta[1,3]*

[1]Neuroimmunology Laboratory, Department of Psychiatry and Behavioral Neurosciences, Morsani College of Medicine, University of South Florida, Tampa, FL, USA
[2]Rashid Laboratory for Developmental Neurobiology, Department of Psychiatry and Neurosciences, Morsani College of Medicine, University of South Florida, Tampa, FL, USA
[3]James A. Haley Veterans' Administration Hospital, Tampa, FL, USA

Abstract

Highly Active Antiretroviral Therapy (HAART) has significantly reduced AIDS-related morbidity and mortality. However the prevalence of HIV-1-Associated Neurocognitive Disorders (HAND) has been on the rise in the post-HAART era. A majority of the side effects of HAART can in part at least be attributed directly, or indirectly, to mitochondrial dysfunction. Indeed the rapid early clinical phase-in of HAART required dose de-escalations secondary to toxicities suggested to be related to drug side effects affecting mitochondria. Central to central nervous system (CNS) function is the amyloid precursor protein (APP), the parent protein from which amyloid-beta (Aβ) peptide is generated. Aβ generation and aggregation as plaques are well known in the age related dementia, Alzheimer's disease (AD). It has been demonstrated that Aβ is common feature of the HIV infected brain as well. Further, reactive oxygen species (ROS) production is upregulated by HAART. Importantly, ROS promote β-secretase expression; a mechanism by which HAART may promote cognitive dysfunction, even in immune-competent HIV infected individuals.

Keywords: Beta-secretase; APP; HAART; Amyloid-β; Microglia

Highly Active Antiretroviral Therapy, HIV Infection and Amyloid-Beta (Aβ)

HIV-associated neuroinflammation is known to occur in even in the face of good virologic control with HAART [1]. As part of this neuroinflammation, the HIV itself promotes deposition of the same amyloid-β peptide (Aβ) found in Alzheimer's disease (AD; for review see [2]). In HIV infected patients, Aβ immunoreactivity has largely been observed predominantly in the neuronal soma, dystrophic axons, and extracellular space [3-5]. Importantly, this Aβ deposition has been correlated with development of neurocognitive impairment [1]. In further support, Xu and colleagues [6] found, upon examination of autopsy brains of HIV Encephalitis (HIVE) and HIV seronegative cases, similar findings. Although intraneuronal Aβ immunoreactivity is also seen in aged control brains, it was significantly increased in HAART-treated HIVE brains. Extracellular Aβ deposition was also found in HAART-treated brains from patients with HIV-associated dementia (HAD) but HAART-untreated HAD brains show only intraneuronal Aβ accumulation [6]; indicating some mechanistic role of HAART in Aβ deposition. The prevalence of this intraneuronal Aβ staining was about 30-40%, and extracellular Aβ was present in 4-13% of HIV-infected brains, with a significantly higher percentage of extracelluar Aβ present in HAART-treated patients [5]. Importantly, Brew and colleagues found cerebrospinal fluid (CSF) Aβ 1-42 and tau levels correlate with HIV-associated cognitive impairment (HAND) [1].

It is possible that extracellular Aβ (eAβ) and intracellular amyloid-beta (iAβ) are present and interact in a cyclic pathway [7,8]. Neuronal loss is a late event in neurodegeneration. Many changes, including synapse dysfunction, electrophysiological properties and morphological atrophy, occur prior to neuronal loss [9]. Although iAβ and its accumulation may be an early event prior to senile plaque and neurofibrillary tangles (NFT), iAβ may alter cellular functions that would subsequently lead to neuronal loss [7].

iAβ is widely detected in neuronal cells and mainly produced by neurons, but glial cells also produce it in the normal human brain [10]. The iAβ accumulation precedes eAβ deposits and plaque formation. In animal models, iAβ accumulation precedes morphological deficits [11,12]. Aβ is generated by the sequential enzymatic cleavage of amyloid precursor protein (APP), and processing may occur within the endoplasmic reticulum (ER) intermediate compartment [13].

There are several hypothetical pathways that may result in iAβ accumulation [7]. First, iAβ may be formed in the ER, recognized as a misfolded protein, and then translocated to the cytosol where it is ubiquitinated and sent to the proteasomes for degradation [14]. Since this degradation process decreases with aging, or medication toxicities, inefficient clearance of Aβ could result in iAβ accumulation. Secondly, secreted Aβ may be internalized into endosomes [15,16], increasing the membrane permeability of lysosomes [17], and thus, promote leaks into the cytosol. Thirdly, iAβ may occur due to passive leakage along any component of the secretory pathway. Fourth, eAβ passively diffuses through the plasma membrane into the cytosol or is actively brought in by surface receptors [18]. Finally, oxidative DNA damage induces iAβ accumulation resulting p53 mRNA increase in the nuclei leading to Bax and caspase-6 activation and subsequent execution of the cell apoptotic pathway [19].

Importantly, cellular toxicity of iAβ may be cell-type specific, because it induces cell death only in human primary neurons, but not in human primary astrocytes, murine neuroblastoma cells (NT2a), LaN1 or M17 cells [19]. It also appears that the Aβ oligomers, but not fibrils, may be the more toxic species [19], and that the iAβ toxicity may be attributed to these Aβ oligomeric forms.

***Corresponding author:** Brian Giunta M.D., Ph.D, Neuroimmunology Laboratory, Department of Psychiatry and Behavioral Neurosciences, Morsani College of Medicine, University of South Florida, Tampa, FL, USA, E-mail: bgiunta@health.usf.edu

Received April 03, 2012; **Accepted** May 14, 2012; **Published** May 16, 2012

Citation: de O' Leary JC, Obregon D, Fernandez F, Tan J, Giunta B (2012) The Impact of HAART on Advanced Brain Aging: Implications for Mitochondrial Dysfunction and APP Processing. J Antivir Antiretrovir S10. doi:10.4172/jaa.S10-003

Thus it is not surprising that accumulation of iAβ is correlated with apoptotic cell death. Alterations in axonal structure and transport may account for the iAβ neurotoxicity and its role in memory function. Accumulation of iAβ increases the number of Golgi apparatus elements, lysosomes and lipofuscin bodies in the hippocampus [20], and also leads to axonopathy with the formation of axonal spheroids as well as myelin ovoids.

There are at least two forms of eAβ, high molecular weight insoluble Aβ fibrils that accumulate in the extracellular space as senile plaques [21] and soluble forms of Aβ that correlate with synaptic dysfunction and cognitive decline [22,23] which include: (a) soluble small globular structures of synthetic Aβ termed Aβ-derived diffusible ligands (ADDLs) [24,25], (b) curvilinear structures of protofibrils [26], and (c) Aβ oligomers; especially nanomers and dodecamers [27].

While Aβ oligomers and ADDL do not seem to progress into insoluble fibrils and plaques, they can interact with cell surface receptors or the cell membrane to gain access into the cells, hence contributing to iAβ load. Likewise, the Aβ fibrils, present as insoluble deposits, could reverse into soluble Aβ monomers. The solubilized Aβ may subsequently gain access into the cells *via* receptor or membrane mediated mechanisms as described if not degraded by the appropriate proteases such as insulin degrading enzyme (IDE) and neprilysin [28].

The positron emission tomography (PET) tracer ^{11}C-labeled Pittsburgh Compound-B (^{11}C-PIB) specifically binds fibrillar Aβ plaques and can be detected [29]. In a recent case-control study, cognitively unimpaired, HIV infected patients had an ^{11}C-PiB scan within 2 years of concomitant CSF studies and neuropsychometric testing. As would be expected, none of the HIV+ participants had fibrillar amyloid plaques as assessed by increased ^{11}C-PiB Mean Cortical Binding Potential (MCBP) or binding potential within four cortical regions [30]; lending further support to the findings of Brew and colleagues [1]. In the following review we suggest it is possible Aβ biogenesis is increased by the upregulation of β-secretase (BACE) through mitochondrial reactive oxygen species (ROS) activity imparted by HAART.

Disruption of Mitochondrial Function by HAART

Highly active antiretroviral therapy (HAART) has significantly reduced AIDS-related morbidity and mortality. However the prevalence of HIV-1-associated neurocognitive disorders (HAND) has been on the rise in the post-HAART era [31-33]. HAART, and particularly the nucleoside reverse transcriptase inhibitors (NRTI) (especially didanosine, stavudine, zalcitabine, and to a lesser extent zidovudine (AZT), abacavir and lamivudine [3TC]), has been positively correlated with serious adverse reactions.

Most of these can in part at least be attributed directly or indirectly to mitochondrial dysfunction [34-37]. Mitochondria are key organelles in energy production in all nucleated human cells. This energy, in the form of ATP, is produced through the oxidative phosphorylation pathway. Furthermore, mitochondria perform an array of other biological functions and modulate factors involved in cell apoptosis [38].

NRTIs have traditionally been suggested to be major culprit in HAART-induce mitochondrial toxicity due to their ability to inhibit Pol-γ, the DNA polymerase responsible for the synthesis of mitochondrial DNA [34,39,40]. Nevertheless, accumulating evidence points to a more complex relationship between these organelles and NRTIs, as well as non-nuceloside reverse transcriptase inhibitors (NNRTIs) such as efavirenz (EFV) and Protease Inhibitors (PI). The rapid early clinical phase-in of HAART required dose de-escalations secondary to toxicities suggested to be related to drug side effects on mitochondria [38]. For example, it has been shown the HAART drug combination of zidovudine (AZT) and the PI, indinavir (IDV) can disrupt the function and viability of endothelial cells due to loss of mitochondrial membrane potential; partially reversible with the thiol antioxidant N-acetylcysteine amide [32]. In adipocytes from HAART treated patients, it has also been shown that NRTI administration correlated positively with mitochondrial DNA depletion [41,42] suggesting an etiology for the lipodystrophy imparted by HAART. There are also coherent experimental and clinical arguments for the existence of mitochondrial toxicity following perinatal exposure to AZT, alone or in combination with the NRTI 3TC [43,44]. Further it has been demonstrated that placental tissue of HIV-1-infected HAART-exposed pregnancies undergoes mitochondrial DNA depletion with secondary respiratory chain compromise [45] and also that HAART treated pregnant mothers can have children with mitochondrial dysfunction [46]. It has also been found in synaptosomes and isolated mitochondria, as well as human subjects [47,48] that the NRTI, didanosine, can induce oxidative stress, cause the release of cytochrome c, reduce the levels of anti-apoptotic proteins, and increase the levels of pro-apoptotic proteins [49].

Elevation of ROS, APP Processing and Aβ Biogenesis

Central to CNS neural function is the amyloid precursor protein (APP), the parent protein from which amyloid-beta (Aβ) peptide is generated. Aβ generation and aggregation as plaques are the hallmark pathology of Alzheimer's Disease (AD; [15,50-53]). The peptides have been evidenced to be neurotoxic, as they are reported mediators of inflammation [54,55], and oxidative stress [56]. Aβ peptides are produced *via* the amyloidogenic pathway of APP proteolysis, which involves the actions of β and γ-secretases [15]. Initially, β-secretase (BACE) cleaves APP, creating an Aβ-containing carboxyl-terminal fragment known as β-C-terminal fragment (β-CTF) [57,58]. In the human brain $A\beta_{40}$ is the predominant form whereas $A\beta_{42}$ represents about 10% Aβ in the brain and has a greater propensity to form neurotoxic oligomeric and aggregated species (for review, see [59]). NFT, like amyloid, have also been implicated as a central pathological feature of AD. They are misfolded and hyperphosphorylated tau, a microtubule formation protein element (for review see [60]). The accumulation of Aβ can adversely affect disrcrete molecular pathways, thus facilitating tau phosphorylation, aggregation, and accumulation of abnormal hyperphosphorylated tau. Aβ and abnormal hyperphosphorylated tau synergize to accelerate neurodegenerative mechanisms involved in aging, metabolism, cellular detoxification, and mitochondrial dysfunction, resulting in neuritic plaque formation [61]. Levels of BACE - 1 are increased in vulnerable regions of the AD brain, but the underlying mechanisms are not known.

Importantly, it has been demonstrated that ROS stimulate β-secretase expression [62], suggesting a mechanism by which HAART-induced ROS promotes β-secretase transcription, thereby promoting production of pathological levels of Aβ linked cognitive dysfunction in AD which could be applied to HAND. Indeed deposition of Aβ is common feature of HIV infection [5,63,64]. Mitochondrial dysfunction has been observed in postmortem brains of AD patients [65] just as

in HAART-treated HIV-infected patients [66]. Indeed, mitochondrial dysfunction in both AD [67-69] and HAART-treated patients [66,70-74] is characterized by elevated ROS generation [75], decreased electron transport chain activity, most markedly in cytochrome c oxidase, and altered Krebs cycle enzyme activities [32,45,76,77]. It has been suggested that mitochondria play a pivotal role in the irreversible loss of neuronal function and in the neuronal cell death that occurs during the pathogenesis of both conditions [49,78].

Several studies have indicated mitochondria may be a direct target of AD–associated proteins and peptides such as full-length APP, Aβ peptide, tau, and truncated ApoE4 [79-83] just as HAART directly targets mitochondria. APP and Aβ have both been localized to mitochondria, where they may cause a disruption of basic mitochondrial functions including oxidative phosphorylation or protein import [82]; similar to HAART. Complex IV (of the electron transport chain) seem to be a direct target of both Aβ and truncated ApoE4 [80,84] well as NRTI.

Aging, Chronic HAART Administration and Development of Cognitive Deficits

Despite this dramatic improvement in AIDS related morbidity and mortality, high rates of HAND continue to be reported [6,85-88]. Indeed HAND, chronic HIV infection, and aging may all possibly contribute to the development of new forms of neurodegenerative processes based on mitochondrial dysfunction, ensuing upregulation of BACE1, which in turns promotes amyloidogenic APP processing and formation Aβ plaques. All of this would be reflected in accelerated aging-like neurocognitive deficits. The life span increase imparted by HAART also brings patients to an age in which AD is more common and the development of adverse effects of long term medication with HAART may present [89,90].

In support, we recently found that antiretroviral compounds might increase Aβ generation and decrease its clearance by inhibiting microglial phagocytosis, affecting both, amyloidogenic fronts, generation and clearance [90]. Specifically, we found high levels of $A\beta_{1-42}$ peptide remaining in the cultured media after N9 microglial cells were treated with antiretrovirals alone or in combination upon completion of phagocytosis assay [90]. In addition, a majority of the compounds tested also significantly reduced levels of phagosomal (cell associated) $A\beta_{1-42}$ suggesting that HAART can cause microglial phagocytosis inhibition [90]. The most significant amyloidogenic effects were observed with combined HAART, suggesting certain HAART medications may have additive amyloidogenic effects when combined [90]. Recent clinical studies [87,91] further suggests that in well controlled HIV infection, HAART can have a negative effective on cognitive function. It was found, from 167 HIV patients with a median nadir CD4 count of 436 cells/mm^3 and 4.5 median years on HAART, that neurocognitive functioning actually improved after HAART discontinuation [91]. This improvement continued over the course of the 96-week follow-up of the study among the patients remaining off HAART [91]. They observed continued improvement from 48 weeks out (third testing) from the study, indicating that the improvements were not attributed to practice or learning effects. Antiretrovirals that enter the CNS were widely represented in their HAART regimens. They also noted a lack of substantial neurocognitive improvement with resumption of HAART [91]. This study is interesting in that removal of the HAART from patients under good viremic control improved cognition. One would expect that resumption of HAART may again induce cognitive problems however this was not the case. Therefore follow-up studies will need to be performed to determine the underlying mechanism of this phenomenon. Most recently it was shown that efavirenz (EFV) is associated with cognitive disorders in even asymptomatic HIV-infected patients [87]. Further, a randomized controlled study [92] found subjects receiving EFV-containing regimens for 48 weeks showed less improvement from baseline on instruments examining speed of information processing and executive function than patients not on EFV, suggesting EFV use may promote neurocognitive decline. This is also supported by findings of Robertson et al. 2010 [91], in which patients with preserved immune function on EFV regimens showed greater improvement on Trails-Making Tests A and B and WAIS digit symbol after antiretroviral treatment interruption than the non-EFV control group. Of note, the trail-making test measures visual attention and task switching. The instrument consists of two parts in which the subject is instructed to connect a set of 25 dots as rapidly as possible while still maintaining accuracy. It is able to provide data regarding visual search speed, scanning, speed of processing, mental flexibility, and executive functioning [93]. Additionally it is sensitive to detecting several cognitive impairments [93] and both tests in this study have been found to be sensitive and specific to detecting HAND [94,95]. The lack of observed further cognitive decline upon HAART reinitiation in these patients may be related to not following the cohort long enough for the chronic effects of HAART in the CNS to re-initiate. It might also be due to limited power. As it has been suggested that earlier initiation of HAART may improve clinical outcomes, the effect of HAART vs. that of unchecked HIV replication on cognitive function will require further prospective studies [91,96].

Finally, considerable neuroinflammation coupled with mononuclear phagocyte activation has been found in HAART medicated brains, particularly in the hippocampus. Anthony and colleagues [97] found a high level of microglial/macrophage activation that is comparable with the levels seen, pre-HAART, in HIVE and AIDS cases. This result was maximal in the hippocampus where microglial/macrophage upregulation in the HAART-treated group exceeded that seen in HIVE. In the basal ganglia, HAART-treated cases showed significantly higher levels of CD68-positive microglia/macrophages than in control brains, and in the hippocampus levels were significantly higher than those seen in control cases, pre-HAART AIDS, and presymptomatic brains. Overall there is a significant degree of ongoing neuroinflammation in HAART-treated patients, particularly in the hippocampus. This may pose a threat for the future health of individuals maintained long-term on HAART therapy. [97]. Neuroinflamaton is also a feature of both aging and AD (for review see [98]). We and others have shown this resultant elevated secretion of pro-inflammatory cytokines including IFN-γ, TNF-α, and IL-1β can increase Aβ generation and reduce Aβ clearance [6,98,99,100].

In summary it is clear that at least certain HAART regimens, especially those containing EFV, have the potential to cause cognitive decline, despite good control of the HIV itself [87]. Further, it is known that CNS Aβ production is a common feature of the HAART treated brain [3,5] which correlates with cognitive deficits [1]. Therefore, as the aging and efficaciously treated HIV-infected population continues to grow, there will likely be a need to phase in less toxic HAART regimens [101] and/or develop adjunctive neuroprotective, or prophylactic treatments for these undesirable side-effects.

Acknowledgments

This work is supported by NIH/NIMH 1K08MH082642-01A1 (BG), NIH/NIA AG04418/Project 2 (JT) and NIH/NINDS grant R01NS048335 (JT).

References

1. Brew BJ, Pemberton L, Blennow K, Wallin A, Hagberg L (2005) CSF amyloid beta42 and tau levels correlate with AIDS dementia complex. Neurology 65: 1490-1492.
2. Finch CE, Morgan TE (2007) Systemic inflammation, infection, ApoE alleles, and Alzheimer disease: a position paper. Curr Alzheimer Res 4: 185-189.
3. Esiri MM, Biddolph SC, Morris CS (1998) Prevalence of Alzheimer plaques in AIDS. J Neurol Neurosurg Psychiatry 65: 29-33.
4. Izycka-Swieszewska E, Zółtowska A, Rzepko R, Gross M, Borowska-Lehman J (2000) Vasculopathy and amyloid beta reactivity in brains of patients with acquired immune deficiency (AIDS). Folia Neuropathol 38: 175-182.
5. Green DA, Masliah E, Vinters HV, Beizai P, Moore DJ, et al. (2005) Brain deposition of beta-amyloid is a common pathologic feature in HIV positive patients. AIDS 19: 407-411.
6. Xu J, Ikezu T (2009) The comorbidity of HIV-associated neurocognitive disorders and Alzheimer's disease: a foreseeable medical challenge in post-HAART era. J Neuroimmune Pharmacol 4: 200-212.
7. Li M, Chen L, Lee DH, Yu LC, Zhang Y (2007) The role of intracellular amyloid beta in Alzheimer's disease. Prog Neurobiol 83: 131-139.
8. Walsh DM, Selkoe DJ (2007) A beta oligomers - a decade of discovery. J Neurochem 101: 1172-1184.
9. Wirths O, Multhaup G, Czech C, Blanchard V, Moussaoui S, et al. (2001) Intraneuronal Abeta accumulation precedes plaque formation in beta-amyloid precursor protein and presenilin-1 double-transgenic mice. Neurosci Lett 306: 116-120.
10. Hayes GM, Howlett DR, Griffin GE (2002) Production of beta-amyloid by primary human foetal mixed brain cell cultures and its modulation by exogenous soluble beta-amyloid. Neuroscience 113: 641-646.
11. Echeverria V, Ducatenzeiler A, Alhonen L, Janne J, Grant SM, et al. (2004) Rat transgenic models with a phenotype of intracellular Abeta accumulation in hippocampus and cortex. J Alzheimers Dis 6: 209-219.
12. Echeverria V, Ducatenzeiler A, Dowd E, Jänne J, Grant SM, et al. (2004) Altered mitogen-activated protein kinase signaling, tau hyperphosphorylation and mild spatial learning dysfunction in transgenic rats expressing the beta-amyloid peptide intracellularly in hippocampal and cortical neurons. Neuroscience 129: 583-592.
13. Pellegrini L, Passer BJ, Tabaton M, Ganjei JK, D'Adamio L (1999) Alternative, non-secretase processing of Alzheimer's beta-amyloid precursor protein during apoptosis by caspase-6 and -8. J Biol Chem 274: 21011-21016.
14. VanSlyke JK, Musil LS (2002) Dislocation and degradation from the ER are regulated by cytosolic stress. J Cell Biol 157: 381-394.
15. Selkoe DJ (1996) Cell biology of the beta-amyloid precursor protein and the genetics of Alzheimer's disease. Cold Spring Harb Symp Quant Biol 61: 587-596.
16. Selkoe DJ, Yamazaki T, Citron M, Podlisny MB, Koo EH, et al. (1996) The role of APP processing and trafficking pathways in the formation of amyloid beta-protein. Ann N Y Acad Sci 777: 57-64.
17. Yang AJ, Chandswangbhuvana D, Margol L, Glabe CG (1998) Loss of endosomal/lysosomal membrane impermeability is an early event in amyloid Abeta1-42 pathogenesis. J Neurosci Res 52: 691-698.
18. Nagele RG, D'Andrea MR, Anderson WJ, Wang HY (2002) Intracellular accumulation of beta-amyloid(1-42) in neurons is facilitated by the alpha 7 nicotinic acetylcholine receptor in Alzheimer's disease. Neuroscience 110: 199-211.
19. Zhang Y, McLaughlin R, Goodyer C, LeBlanc A (2002) Selective cytotoxicity of intracellular amyloid beta peptide1-42 through p53 and Bax in cultured primary human neurons. J Cell Biol 156: 519-529.
20. Lopez EM, Bell KF, Ribeiro-da-Silva A, Cuello AC (2004) Early changes in neurons of the hippocampus and neocortex in transgenic rats expressing intracellular human a-beta. J Alzheimers Dis 6: 421-431.
21. Price DL, Sisodia SS (1998) Mutant genes in familial Alzheimer's disease and transgenic models. Annu Rev Neurosci 21: 479-505.
22. McLean CA, Cherny RA, Fraser FW, Fuller SJ, Smith MJ, et al. (1999) Soluble pool of Abeta amyloid as a determinant of severity of neurodegeneration in Alzheimer's disease. Ann Neurol 46: 860-866.
23. Wang J, Dickson DW, Trojanowski JQ, Lee VM (1999) The levels of soluble versus insoluble brain Abeta distinguish Alzheimer's disease from normal and pathologic aging. Exp Neurol 158: 328-337.
24. Catalano SM, Dodson EC, Henze DA, Joyce JG, Krafft GA, et al. (2006) The role of amyloid-beta derived diffusible ligands (ADDLs) in Alzheimer's disease. Curr Top Med Chem 6: 597-608.
25. Lambert MP, Barlow AK, Chromy BA, Edwards C, Freed R, et al. (1998) Diffusible, nonfibrillar ligands derived from Abeta1-42 are potent central nervous system neurotoxins. Proc Natl Acad Sci USA 95: 6448-6453.
26. Deshpande A, Mina E, Glabe C, Busciglio J (2006) Different conformations of amyloid beta induce neurotoxicity by distinct mechanisms in human cortical neurons. J Neurosci 26: 6011-6018.
27. Jacobsen JS, Wu CC, Redwine JM, Comery TA, Arias R, et al. (2006) Early-onset behavioral and synaptic deficits in a mouse model of Alzheimer's disease. Proc Natl Acad Sci USA 103: 5161-5166.
28. El-Amouri SS, Zhu H, Yu J, Gage FH, Verma IM, et al. (2007) Neprilysin protects neurons against Abeta peptide toxicity. Brain Res 1152: 191-200.
29. Rabinovici GD, Furst AJ, O'Neil JP, Racine CA, Mormino EC, et al. (2007) 11C-PIB PET imaging in Alzheimer disease and frontotemporal lobar degeneration. Neurology 68: 1205-1212.
30. Ances BM, Christensen JJ, Teshome M, Taylor J, Xiong C, et al. (2010) Cognitively unimpaired HIV-positive subjects do not have increased 11C-PiB: a case-control study. Neurology 75: 111-115.
31. Schouten J, Cinque P, Gisslen M, Reiss P, Portegies P (2011) HIV-1 infection and cognitive impairment in the cART era: a review. AIDS 25: 561-575.
32. Manda KR, Banerjee A, Banks WA, Ercal N (2011) Highly active antiretroviral therapy drug combination induces oxidative stress and mitochondrial dysfunction in immortalized human blood-brain barrier endothelial cells. Free Radic Biol Med 50: 801-810.
33. Gerstoft J, Kirk O, Obel N, Pedersen C, Mathiesen L, et al. (2003) Low efficacy and high frequency of adverse events in a randomized trial of the triple nucleoside regimen abacavir, stavudine and didanosine. AIDS 17: 2045-2052.
34. Apostolova N, Blas-Garcia A, Esplugues JV (2011) Mitochondrial interference by anti-HIV drugs: mechanisms beyond Pol-γ inhibition. Trends Pharmacol Sci 32: 715-725.
35. Casula M, Weverling GJ, Wit FW, Timmermans EC, Stek M Jr (2005) Mitochondrial DNA and RNA increase in peripheral blood mononuclear cells from HIV-1-infected patients randomized to receive stavudine-containing or stavudine-sparing combination therapy. J Infect Dis 192: 1794-1800.
36. Schweinsburg BC, Taylor MJ, Alhassoon OM, Gonzalez R, Brown GG, et al. (2005) Brain mitochondrial injury in human immunodeficiency virus-seropositive (HIV+) individuals taking nucleoside reverse transcriptase inhibitors. J Neurovirol 11: 356-364.
37. Côté HC, Brumme ZL, Craib KJ, Alexander CS, Wynhoven B, et al. (2002) Changes in mitochondrial DNA as a marker of nucleoside toxicity in HIV-infected patients. N Engl J Med 346: 811-820.
38. Cossarizza A, Moyle G (2004) Antiretroviral nucleoside and nucleotide analogues and mitochondria. AIDS 18: 137-151.
39. Saitoh A, Fenton T, Alvero C, Fletcher CV, Spector SA (2007) Impact of nucleoside reverse transcriptase inhibitors on mitochondria in human immunodeficiency virus type 1-infected children receiving highly active antiretroviral therapy. Antimicrob Agents Chemother 51: 4236-4242.
40. Walker UA (2003) Update on mitochondrial toxicity: where are we now. J HIV Ther 8: 32-35.

41. Nolan D, Hammond E, Martin A, Taylor L, Herrmann S, et al. (2003) Mitochondrial DNA depletion and morphologic changes in adipocytes associated with nucleoside reverse transcriptase inhibitor therapy. AIDS 17: 1329-1338.

42. Shikuma CM, Hu N, Milne C, Yost F, Waslien C, et al. (2001) Mitochondrial DNA decrease in subcutaneous adipose tissue of HIV-infected individuals with peripheral lipoatrophy. AIDS 15: 1801-1809.

43. Poirier MC, Divi RL, Al-Harthi L, Olivero OA, Nguyen V, et al. (2003) Long-term mitochondrial toxicity in HIV-uninfected infants born to HIV-infected mothers. J Acquir Immune Defic Syndr 33: 175-183.

44. Barret B, Tardieu M, Rustin P, Lacroix C, Chabrol B, et al. (2003) Persistent mitochondrial dysfunction in HIV-1-exposed but uninfected infants: clinical screening in a large prospective cohort. AIDS 17: 1769-1785.

45. Gingelmaier A, Grubert TA, Kost BP, Setzer B, Lebrecht D, et al. (2009) Mitochondrial toxicity in HIV type-1-exposed pregnancies in the era of highly active antiretroviral therapy. Antivir Ther 14: 331-338.

46. Brogly SB, Ylitalo N, Mofenson LM, Oleske J, Van Dyke R, et al. (2007) In utero nucleoside reverse transcriptase inhibitor exposure and signs of possible mitochondrial dysfunction in HIV-uninfected children. AIDS 21: 929-938.

47. Maggiolo F, Roat E, Pinti M, Nasi M, Gibellini L, et al. (2010) Mitochondrial changes during D-drug-containing once-daily therapy in HIV-positive treatment-naive patients. Antivir Ther 15: 51-59.

48. Thoden J, Lebrecht D, Venhoff N, Neumann J, Muller K, et al. (2008) Highly active antiretroviral HIV therapy-associated fatal lactic acidosis: quantitative and qualitative mitochondrial DNA lesions with mitochondrial dysfunction in multiple organs. AIDS 22: 1093-1094.

49. Opii WO, Sultana R, Abdul HM, Ansari MA, Nath A, et al. (2007) Oxidative stress and toxicity induced by the nucleoside reverse transcriptase inhibitor (NRTI)--2',3'-dideoxycytidine (ddC): relevance to HIV-dementia. Exp Neurol 204: 29-38.

50. Funamoto S, Morishima-Kawashima M, Tanimura Y, Hirotani N, Saido TC, et al. (2004) Truncated carboxyl-terminal fragments of beta-amyloid precursor protein are processed to amyloid beta-proteins 40 and 42. Biochemistry 43: 13532-13540.

51. Sambamurti K, Greig NH, Lahiri DK (2002) Advances in the cellular and molecular biology of the beta-amyloid protein in Alzheimer's disease. Neuromolecular Med 1: 1-31.

52. Golde TE, Eckman CB, Younkin SG (2000) Biochemical detection of Abeta isoforms: implications for pathogenesis, diagnosis, and treatment of Alzheimer's disease. Biochim Biophys Acta 1502: 172-187.

53. Huse JT, Doms RW (2000) Closing in on the amyloid cascade: recent insights into the cell biology of Alzheimer's disease. Mol Neurobiol 22: 81-98.

54. Suo Z, Tan J, Placzek A, Crawford F, Fang C,et al. (1998) Alzheimer's beta-amyloid peptides induce inflammatory cascade in human vascular cells: the roles of cytokines and CD40. Brain Res 807: 110-117.

55. Bradt BM, Kolb WP, Cooper NR (1998) Complement-dependent proinflammatory properties of the Alzheimer's disease beta-peptide. J Exp Med 188: 431-438.

56. Hensley K, Carney JM, Mattson MP, Aksenova M, Harris M, et al. (1994) A model for beta-amyloid aggregation and neurotoxicity based on free radical generation by the peptide: relevance to Alzheimer disease. Proc Natl Acad Sci U S A 91: 3270-3274.

57. Yan R, Bienkowski MJ, Shuck ME, Miao H, Tory MC, et al. (1999) Membrane-anchored aspartyl protease with Alzheimer's disease beta-secretase activity. Nature 402: 533-537.

58. Vassar R, Bennett BD, Babu-Khan S, Kahn S, Mendiaz EA, et al. (1999) Beta-secretase cleavage of Alzheimer's amyloid precursor protein by the transmembrane aspartic protease BACE. Science 286: 735-741.

59. Jacobsen JS, Reinhart P, Pangalos MN (2005) Current concepts in therapeutic strategies targeting cognitive decline and disease modification in Alzheimer's disease. NeuroRx 2: 612-626.

60. Jellinger KA, Bancher C (1998) Neuropathology of Alzheimer's disease: a critical update. J Neural Transm Suppl 54: 77-95.

61. Blurton-Jones M, Laferla FM (2006) Pathways by which Abeta facilitates tau pathology. Curr Alzheimer Res 3: 437-448.

62. Tamagno E, Guglielmotto M, Aragno M, Borghi R, Autelli R, et al. (2008) Oxidative stress activates a positive feedback between the gamma- and beta-secretase cleavages of the beta-amyloid precursor protein. J Neurochem 104: 683-695.

63. Achim CL, Adame A, Dumaop W, Everall IP, Masliah E, et al. (2009) Increased accumulation of intraneuronal amyloid beta in HIV-infected patients. J Neuroimmune Pharmacol 4: 190-199.

64. Alisky JM (2007) The coming problem of HIV-associated Alzheimer's disease. Med Hypotheses 69: 1140-1143.

65. Bosetti F, Brizzi F, Barogi S, Mancuso M, Siciliano G, et al. (2002) Cytochrome c oxidase and mitochondrial F1F0-ATPase (ATP synthase) activities in platelets and brain from patients with Alzheimer's disease. Neurobiol Aging 23: 371-376.

66. Streck EL, Ferreira GK, Scaini G, Rezin GT, Gonçalves CL, et al. (2011) Non-nucleoside reverse transcriptase inhibitors efavirenz and nevirapine inhibit cytochrome C oxidase in mouse brain regions. Neurochem Res 36: 962-966.

67. Parker WD Jr, Filley CM, Parks JK (1990) Cytochrome oxidase deficiency in Alzheimer's disease. Neurology 40: 1302-1303.

68. Lin MT, Simon DK, Ahn CH, Kim LM, Beal MF (2002) High aggregate burden of somatic mtDNA point mutations in aging and Alzheimer's disease brain. Hum Mol Genet 11: 133-145.

69. Mancuso M, Filosto M, Bosetti F, Ceravolo R, Rocchi A, et al. (2003) Decreased platelet cytochrome c oxidase activity is accompanied by increased blood lactate concentration during exercise in patients with Alzheimer disease. Exp Neurol 182: 421-426.

70. Sternfeld T, Schmid M, Tischleder A, Mudra S, Schlamp A, et al. (2007) The influence of HIV infection and antiretroviral therapy on the mitochondrial membrane potential of peripheral mononuclear cells. Antivir Ther 12: 769-778.

71. ter Hofstede HJ, Borm GF, Koopmans PP (2007) Oral glucose loading for detection of mitochondrial toxicity during HAART in HIV-infected patients. Curr HIV Res 5: 389-393.

72. Ghosn J, Guiguet M, Jardel C, Benyaou R, Zeller V, et al. (2005) Muscle and liver lactate metabolism in HAART-treated and naive HIV-infected patients: the MITOVIR study. Antivir Ther 10: 543-550.

73. Boothby M, McGee KC, Tomlinson JW, Gathercole LL, McTernan PG, et al. (2009) Adipocyte differentiation, mitochondrial gene expression and fat distribution: differences between zidovudine and tenofovir after 6 months. Antivir Ther 14: 1089-1100.

74. Mallon PW, Sedwell R, Rogers G, Nolan D, Unemori P, et al. (2008) Effect of rosiglitazone on peroxisome proliferator-activated receptor gamma gene expression in human adipose tissue is limited by antiretroviral drug-induced mitochondrial dysfunction. J Infect Dis 198: 1794-1803.

75. Cutler RG, Kelly J, Storie K, Pedersen WA, Tammara A, et al. (2004) Involvement of oxidative stress-induced abnormalities in ceramide and cholesterol metabolism in brain aging and Alzheimer's disease. Proc Natl Acad Sci USA 101: 2070-2075.

76. Ross AC, Leong T, Avery A, Castillo-Duran M, Bonilla H, et al. (2012) Effects of in utero antiretroviral exposure on mitochondrial DNA levels, mitochondrial function and oxidative stress. HIV Med 13: 98-106.

77. Negredo E, Romeu J, Rodríguez-Santiago B, Miró O, Garrabou G, et al. (2010) Mild improvement in mitochondrial function after a 3-year antiretroviral treatment interruption despite persistent impairment of mitochondrial DNA content. Curr HIV Res 8: 379-385.

78. Norman JP, Perry SW, Reynolds HM, Kiebala M, De Mesy Bentley KL, et al. (2008) HIV-1 Tat activates neuronal ryanodine receptors with rapid induction of the unfolded protein response and mitochondrial hyperpolarization. PLoS One 3: e3731.

79. Anandatheerthavarada HK, Biswas G, Robin MA, Avadhani NG (2003) Mitochondrial targeting and a novel transmembrane arrest of Alzheimer's amyloid precursor protein impairs mitochondrial function in neuronal cells. J Cell Biol 161: 41-54.

80. Chang S, ran Ma T, Miranda RD, Balestra ME, Mahley RW, et al. (2005) Lipid- and receptor-binding regions of apolipoprotein E4 fragments act in concert to cause mitochondrial dysfunction and neurotoxicity. Proc Natl Acad Sci USA 102: 18694-18699.

81. David DC, Hauptmann S, Scherping I, Schuessel K, Keil U, et al. (2005) Proteomic and functional analyses reveal a mitochondrial dysfunction in P301L tau transgenic mice. J Biol Chem 280: 23802-23814.

82. Devi L, Prabhu BM, Galati DF, Avadhani NG, Anandatheerthavarada HK (2006) Accumulation of amyloid precursor protein in the mitochondrial import channels of human Alzheimer's disease brain is associated with mitochondrial dysfunction. J Neurosci 26: 9057-9068.

83. Keil U, Bonert A, Marques CA, Scherping I, Weyermann J, et al. (2004) Amyloid beta-induced changes in nitric oxide production and mitochondrial activity lead to apoptosis. J Biol Chem 279: 50310-50320.

84. Osorio C, Sullivan PM, He DN, Mace BE, Ervin JF, et al. (2007) Mortalin is regulated by APOE in hippocampus of AD patients and by human APOE in TR mice. Neurobiol Aging 28: 1853-1862.

85. Schouten J, Cinque P, Gisslen M, Reiss P, Portegies P (2011) HIV-1 infection and cognitive impairment in the cART era: a review. AIDS 25: 561-575.

86. Brew BJ, Crowe SM, Landay A, Cysique LA, Guillemin G (2009) Neurodegeneration and ageing in the HAART era. J Neuroimmune Pharmacol 4: 163-174.

87. Ciccarelli N, Fabbiani M, Di Giambenedetto S, Fanti I, Baldonero E, et al. (2011) Efavirenz associated with cognitive disorders in otherwise asymptomatic HIV-infected patients. Neurology 76: 1403-1409.

88. Gutiérrez-Valencia A, Viciana P, Palacios R, Ruiz-Valderas R, Lozano F, et al. (2009) Stepped-dose versus full-dose efavirenz for HIV infection and neuropsychiatric adverse events: a randomized trial. Ann Intern Med 151: 149-156.

89. Liner KJ 2nd, Ro MJ, Robertson KR (2010) HIV, antiretroviral therapies, and the brain. Curr HIV/AIDS Rep 7: 85-91.

90. Giunta B, Ehrhart J, Obregon DF, Lam L, Le L, et al. (2011) Antiretroviral medications disrupt microglial phagocytosis of β-amyloid and increase its production by neurons: implications for HIV-associated neurocognitive disorders. Mol Brain 4: 23.

91. Robertson KR, Su Z, Margolis DM, Krambrink A, Havlir DV, et al. (2010) Neurocognitive effects of treatment interruption in stable HIV-positive patients in an observational cohort. Neurology 74: 1260-1266.

92. Winston A, Duncombe C, Li PC, Gill JM, Kerr SJ, et al. (2010) Does choice of combination antiretroviral therapy (cART) alter changes in cerebral function testing after 48 weeks in treatment-naive, HIV-1-infected individuals commencing cART? A randomized, controlled study. Clin Infect Dis 50: 920-929.

93. Bowie CR, Harvey PD (2006) Administration and interpretation of the Trail Making Test. Nat Protoc 1: 2277-2281.

94. Tross S, Price RW, Navia B, Thaler HT, Gold J, et al. (1988) Neuropsychological characterization of the AIDS dementia complex: a preliminary report. AIDS 2: 81-88.

95. Ellis RJ, Evans SR, Clifford DB, Moo LR, McArthur JC, et al. (2005) Clinical validation of the NeuroScreen. J Neurovirol 11: 503-511.

96. Kitahata MM, Gange SJ, Abraham AG, Merriman B, Saag MS, et al. (2009) Effect of early versus deferred antiretroviral therapy for HIV on survival. N Engl J Med 360: 1815-1826.

97. Anthony IC, Ramage SN, Carnie FW, Simmonds P, Bell JE (2005) Influence of HAART on HIV-related CNS disease and neuroinflammation. J Neuropathol Exp Neurol 64: 529-536.

98. Giunta B, Fernandez F, Nikolic WV, Obregon D, Rrapo E, et al. (2008) Inflammaging as a prodrome to Alzheimer's disease. J Neuroinflammation 5: 51.

99. Giunta B, Hou H, Zhu Y, Rrapo E, Tian J, et al. (2009) HIV-1 Tat contributes to Alzheimer's disease-like pathology in PSAPP mice. Int J Clin Exp Pathol 2: 433-443.

100. Rrapo E, Zhu Y, Tian J, Hou H, Smith A, et al. (2009) Green Tea-EGCG reduces GFAP associated neuronal loss in HIV-1 Tat transgenic mice. Am J Transl Res 1: 72-79.

101. Vandamme AM, Van Laethem K, De Clercq E (1999) Managing resistance to anti-HIV drugs: an important consideration for effective disease management. Drugs 57: 337-361.

This article was originally published in a special issue, **Antiretroviral Drug Development for HIV: Challenges and Perspectives** handled by Editor(s). Dr. Honglin Zhou, Hospital of the University of Pennsylvania, USA