

PEARLS

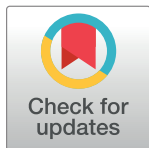
# "APP"reciating the complexity of HIV-induced neurodegenerative diseases

Mojgan H. Naghavi \*

Department of Microbiology-Immunology, Northwestern University Feinberg School of Medicine, Chicago, Illinois, United States of America

\* [Mojgan.naghavi@northwestern.edu](mailto:Mojgan.naghavi@northwestern.edu)

Since the beginning of the epidemic in the 1980s, human immunodeficiency virus type 1 (HIV-1) has infected more than 70 million and killed approximately 35 million people globally. Although widespread use of combination antiretroviral therapy (cART) has effectively increased the life span of many infected individuals in the Western world, HIV-1 continues to be a major public health issue in both developed and resource-poor settings [1]. In addition to causing acquired immunodeficiency syndrome (AIDS), HIV-1 infection also causes serious neuropathology. Like all other retroviruses, upon entry into the host cell, HIV-1 converts its single-stranded RNA genome into double-stranded DNA that integrates into the host genome. To produce new viral particles or virions, HIV-1 proteins—together with the viral RNA—assemble at the plasma membrane, where a new immature virus forms. Virions then mature through processing of precursor group-specific antigen (Gag) polyprotein by HIV-1 protease at or after budding from the cell surface [2].



## Effects of HIV-1 infection on the central nervous system

In many infected individuals, HIV-1 enters the central nervous system (CNS) leading to a broad spectrum of HIV-1-associated neurocognitive disorders (HANDs) ranging from mild impairments to severe HIV-associated dementia (HAD) [1]. Although HAD is rare in patients on cART, milder forms of HAND are still prevalent in these patients, likely due to irreversible injury prior to starting therapy, the persistence of virus in the CNS, and toxic effects of therapy itself [1, 3]. To enter the CNS, HIV-1 must cross the blood-brain barrier (BBB). This is believed to occur through a “Trojan horse” mechanism as a passenger in CD4+ cells, e.g., T cells or monocytes [4]. Indeed, HIV-1-mediated disruption of the integrity and function of the BBB plays an important role in AIDS neuropathogenesis [5]. Inside the CNS, HIV-1 establishes infection primarily in perivascular macrophages and microglia (Fig 1A) based on animal studies (in nonhuman primates or humanized mice) or acquired material during autopsy of HIV-1-positive individuals [4]. HIV-1 is also proposed to infect astrocytes to cause neuropathology, although this remains less well understood. Cell-free mature HIV-1 does not efficiently infect astrocytes but other routes of transmission, e.g., cell-to-cell transmission of immature HIV-1 virions from lymphocytes or engulfment of HIV-1-infected macrophage material has been linked to productive infection as well as functional changes during nonproductive infection of astrocytes that contribute to HAD [6, 7]. Because HIV-1 does not directly infect neurons, secretion of a mixture of host (inflammatory cytokines and chemokines) and viral proteins from these brain-resident infected cells is believed to induce localized inflammation resulting in HIV-1-induced neuronal dysfunction and death [4]. Neurotoxic HIV-1 proteins include envelope glycoprotein (Gp120), transactivator of transcription (Tat), the accessory viral protein R (Vpr), negative regulatory factor (Nef), and matrix p17 [8–12].

### OPEN ACCESS

**Citation:** Naghavi MH (2018) "APP"reciating the complexity of HIV-induced neurodegenerative diseases. *PLoS Pathog* 14(10): e1007309. <https://doi.org/10.1371/journal.ppat.1007309>

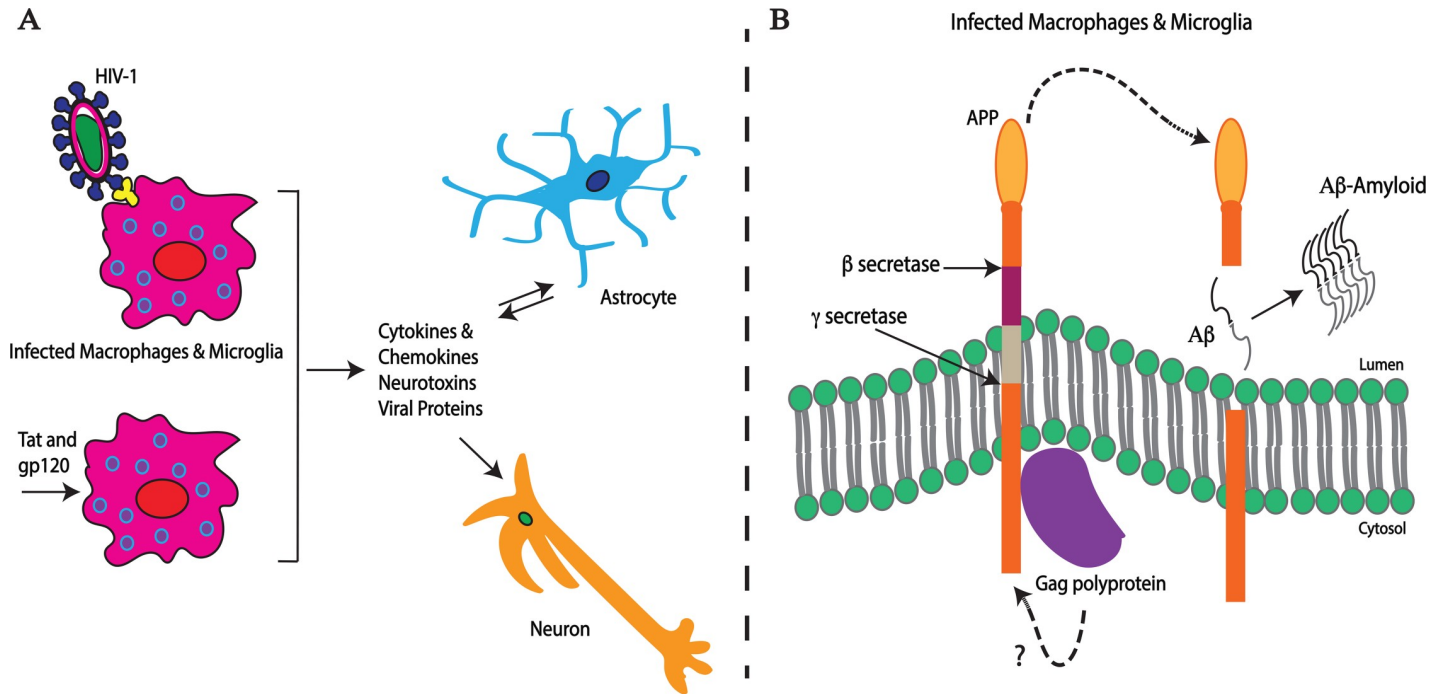
**Editor:** Matthew J. Evans, Mount Sinai School of Medicine, UNITED STATES

**Published:** October 25, 2018

**Copyright:** © 2018 Mojgan H. Naghavi. This is an open access article distributed under the terms of the [Creative Commons Attribution License](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

**Funding:** This work was supported by grants from the National Institutes of Health to M.H.N. (R01NS099064). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

**Competing interests:** The author has declared that no competing interests exist.



**Fig 1. HIV-1 infection in the brain results in neurodegeneration.** (A) Effects of HIV-1 on target cells in the CNS. Microglia and macrophages infected with HIV-1 and/or exposed to viral proteins (such as Tat and gp120) along with infected astrocytes secrete a mix of host and viral factors. This induces a toxic and inflammatory environment that contributes to the complex process of neuronal dysfunction and death in infected individuals that develop HAND. (B) HIV-1 Gag counteracts an innate restriction imposed by APP resulting in overproduction of neurotoxic A $\beta$ . APP traps HIV-1 Gag polyprotein in cell membrane regions enriched in secretases during late-stage viral assembly and/or production in microglia or macrophages. To counteract this, Gag promotes secretase-dependent APP processing resulting in overproduction of toxic A $\beta$  isoforms. A $\beta$ ,  $\beta$ -amyloid; APP, amyloid precursor protein; CNS, central nervous system; Gag, group-specific antigen; gp120, envelope glycoprotein 120; HAND, HIV-1 associated neurocognitive disorders; HIV-1, human immunodeficiency virus type 1; Tat, transactivator of transcription.

<https://doi.org/10.1371/journal.ppat.1007309.g001>

Beyond the toxic effects of viral proteins, it is clear that infected macrophages also secrete host factors that contribute to the broader neurodegeneration caused by HIV-1. Although these viral and host factors are too numerous and complex to discuss here and are extensively reviewed elsewhere [4], one poorly understood, yet potentially significant, host contributor is  $\beta$ -amyloid (A $\beta$ ).

### A $\beta$ production and its role in neurodegeneration

A $\beta$  is a small peptide that is generated throughout life but whose precise physiological function and reason for production remains somewhat mysterious. In fact, the peptide is best known as the main component of amyloid plaques that are associated with neurodegenerative conditions such as Alzheimer disease (AD) and dementia in uninfected individuals [13]. Neurotoxic A $\beta$  is generated by site-specific cleavage of the amyloid precursor protein (APP). Neurons lacking APP exhibit impairments in neurite growth, intracellular trafficking, and cell-to-cell adhesion, suggesting that the precursor has important yet poorly understood biological functions in the brain. Although highly expressed in neurons, APP is a ubiquitously expressed type I membrane protein that is proteolytically processed near and within its membrane domain by four types of secretases ( $\alpha$ ,  $\beta$ ,  $\gamma$ , and  $\eta$ ) via three major pathways (amyloidogenic, nonamyloidogenic, and  $\eta$ -secretase) [14, 15] (Fig 1B). Most APP is sequentially cleaved by  $\alpha$ - and  $\gamma$ -secretases producing a large N-terminal soluble fragment (sAPP $\alpha$ ) in the extracellular space along with a short C-terminal fragment ( $\alpha$ -CTF) and nontoxic peptide (p3) released into the cytoplasm via the nonamyloidogenic pathway. Less frequently, in the amyloidogenic pathway,

APP is cleaved by  $\beta$ -secretase to generate a soluble ectodomain (sAPP $\beta$ ) and a  $\beta$ -CTF. The latter is further processed by  $\gamma$ -secretase into A $\beta$  monomers of various lengths that can self-associate to form toxic A $\beta$  oligomers. There are two main toxic A $\beta$  species, A $\beta$ 40 and A $\beta$ 42, although the smaller fraction A $\beta$ 42 is more prone to aggregation. Although the contribution of A $\beta$  species to AD has been long debated, likely due to the complexity of its role, data suggest it is a promising target for AD therapeutics.

### The question of A $\beta$ accumulation in HIV-1–infected individuals

Although A $\beta$  increases in the brain during normal aging [16], pathology studies have shown that both APP and A $\beta$  accumulation are accelerated in the brains of HIV-1–infected individuals, correlating with viral loads and the onset of HAND [17–19]. Postmortem tissue staining has also shown amyloid accumulation within the brains of simian immunodeficiency virus (SIV)-infected macaques and rats exposed to HIV-1 proteins [20, 21]. However, the question of A $\beta$  deposition in infected individuals is complex and far from certain. In vivo positron emission tomography (PET) amyloid imaging has not detected increased A $\beta$ 42 fibrillar deposition in individuals with HAND [22]. However, this may reflect limitations of imaging or unusual features of HIV-1 A $\beta$  deposition, discussed below. Elevated A $\beta$ 42 has also been reported in the cerebrospinal fluid (CSF) of HIV-1–positive patients, whereas others report no change or even decreases [23–27,28]. These kinds of conflicting observations are also evident in studies of AD and could be, among other concerns, due to the collection and handling of samples, an issue extensively reviewed elsewhere [29]. Similarly conflicting are reports of CSF levels of apolipoprotein E4 (APOE4), whose expression promotes amyloid aggregation and which is a well-established risk factor for AD [25, 30, 31]. Moreover, APOE4 appears to be more relevant in older HIV-1–positive patients [30]. Despite these uncertainties, which are also prevalent in AD research, soluble A $\beta$ 42 and APP in CSF have been suggested by many studies to serve as strong biomarkers for HAND [23, 24, 32, 33]. Moreover, suppressing A $\beta$ 42 accumulation has been proposed as a means for therapeutic intervention [34, 35]. Notably, intraneuronal A $\beta$  accumulation or perivascular diffuse A $\beta$  depositions are more prevalent in HIV-1–infected brains, whereas extracellular amyloid plaques are predominant features in AD [29, 36]. These distinct differences observed in A $\beta$  deposition patterns between HAND and AD may explain the failure of PET imaging studies to detect fibrils (discussed above) and suggest that HIV-1 specifically alters A $\beta$  metabolism in ways that may contribute to unique features of HAD and HAND. Indeed, soluble amyloid oligomers have been suggested as the primary pathological structures leading to permeabilization of cellular membranes and neuronal loss observed in AD [37].

### Effects of HIV-1 on APP and A $\beta$ production

HIV-1 is known to alter multiple steps in A $\beta$  metabolism [29, 36]. Several HIV-1 proteins such as Tat, gp120, Vpr, Nef, and the fusion Gag-polymerase polyprotein (Gag-Pol), have been shown to affect APP or A $\beta$  levels, processing, aggregation, and/or subcellular localization [8, 10, 11, 38]. Although some of these viral proteins likely affect A $\beta$  metabolism indirectly, other viral factors appear to function more directly. For example, gp120 and Nef can cause infected microglia or astrocytes, respectively, to release pro-inflammatory cytokines that increase A $\beta$ 42, whereas Tat can directly modulate APP trafficking and processing via inhibition of the major A $\beta$ -degrading enzyme, neprilysin [29, 39, 40]. Tat is also known to reduce clearance of A $\beta$ 42 from the brain to the blood and promotes nuclear entry of A $\beta$  and inflammatory responses in human brain endothelial cells [36]. However, Tat is secretory and is highly toxic, meaning that some of its effects on A $\beta$  production may be indirect [4].

Recent findings have identified both a viral protein that induces A $\beta$  production and biological reason for why this occurs. Although APP has few known biological functions, it was recently found to act as an innate restriction to HIV-1 release from brain-resident microglia and macrophages. To evade this restriction, the HIV-1 Gag polyprotein binds and directs secretase-driven processing and degradation of APP, resulting in A $\beta$  production that can cause neurotoxicity (Fig 1B) [41]. Supporting this notion, another recent report also suggested a role for  $\beta$ -secretase BACE1 and A $\beta$  oligomer production in HIV-associated neurotoxicity [42]. Because of this, A $\beta$  production is at least in part a detrimental side effect of a viral evasion mechanism to escape a restriction to late-stage infection that is imposed by APP but that results in neurotoxic effects. Moreover, the virus-specific activities of Gag-induced APP processing along with the effects of other viral proteins on broader A $\beta$  metabolism likely contribute to the underlying differences in A $\beta$  deposition patterns in the brains of patients with HAND versus AD, discussed above. gp120 has been shown to increase APP levels [43], whereas APP can protect against gp120-induced brain damage [44]. In addition, A $\beta$  has been proposed to potentially have antimicrobial activities [45]. It is therefore tempting to speculate that these earlier reports reflect the recent discovery of APP's role in host responses to HIV-1 infection. Combined with inflammatory responses to infection and Tat cytotoxicity, Gag-mediated APP processing and A $\beta$  production are likely to be an important contributing factor to the overall complexity of HAND. Furthermore, Gag-mediated induction of APP processing does not require the protease activity of the Gag-Pol fusion polyprotein that was previously reported to cleave APP [38]. Instead, Gag binds APP and enhances its processing by host secretases [41]. Inhibiting either  $\beta$ - or  $\gamma$ -secretase suppresses Gag-mediated A $\beta$  production and protects against neurotoxicity [41]. By protecting APP from degradation, secretase inhibitors also suppress HIV-1 release and replication in microglia and macrophages, suggesting that these inhibitors may have the potential to serve dual purposes of preventing both neurodegeneration and HIV-1 replication in brain-resident target cells [41]. Although the role of APP and amyloid in HAND remains complex and somewhat controversial—similar to the situation with AD—these recent findings provide additional evidence that infected macrophage and/or microglia produce toxic amyloids and explain, at least in part, why and how infection causes this induction. However, there is undoubtedly much more to learn about the molecular basis by which this occurs, as well as the true extent to which A $\beta$  contributes to neurodegenerative disease in infected patients.

## Acknowledgments

The author apologizes to all the colleagues whose work was not cited due to the space constraints.

## References

1. Farhadian S, Patel P, Spudich S. Neurological Complications of HIV Infection. *Curr Infect Dis Rep*. 2017; 19(12):50. Epub 2017/11/23. <https://doi.org/10.1007/s11908-017-0606-5> PMID: 29164407.
2. Goff SP. Host factors exploited by retroviruses. *Nat Rev Microbiol*. 2007; 5(4):253–63. <https://doi.org/10.1038/nrmicro1541> PMID: 17325726.
3. Soontornniyomkij V, Umlauf A, Soontornniyomkij B, Gouaux B, Ellis RJ, Levine AJ, et al. Association of antiretroviral therapy with brain aging changes among HIV-infected adults. *AIDS*. 2018. Epub 2018/06/19. <https://doi.org/10.1097/QAD.0000000000001927> PMID: 29912063.
4. Gonzalez-Scarano F, Martin-Garcia J. The neuropathogenesis of AIDS. *Nat Rev Immunol*. 2005; 5(1):69–81. <https://doi.org/10.1038/nri1527> PMID: 15630430.
5. Atluri VS, Hidalgo M, Samikkannu T, Kurapati KR, Jayant RD, Sagar V, et al. Effect of human immunodeficiency virus on blood-brain barrier integrity and function: an update. *Front Cell Neurosci*. 2015;

- 9:212. <https://doi.org/10.3389/fncel.2015.00212> PMID: 26113810; PubMed Central PMCID: PMCPMC4461820.
6. Li GH, Henderson L, Nath A. Astrocytes as an HIV Reservoir: Mechanism of HIV Infection. *Curr HIV Res.* 2016; 14(5):373–81. Epub 2016/10/11. PMID: 27719663.
  7. Russell RA, Chojnacki J, Jones DM, Johnson E, Do T, Eggeling C, et al. Astrocytes Resist HIV-1 Fusion but Engulf Infected Macrophage Material. *Cell Rep.* 2017; 18(6):1473–83. Epub 2017/02/09. <https://doi.org/10.1016/j.celrep.2017.01.027> PMID: 28178524; PubMed Central PMCID: PMCPMC5316642.
  8. Nath A, Haughey NJ, Jones M, Anderson C, Bell JE, Geiger JD. Synergistic neurotoxicity by human immunodeficiency virus proteins Tat and gp120: protection by memantine. *Ann Neurol.* 2000; 47(2):186–94. PMID: 10665489.
  9. Liu Y, Jones M, Hingtgen CM, Bu G, Larabee N, Tanzi RE, et al. Uptake of HIV-1 tat protein mediated by low-density lipoprotein receptor-related protein disrupts the neuronal metabolic balance of the receptor ligands. *Nat Med.* 2000; 6(12):1380–7. <https://doi.org/10.1038/82199> PMID: 11100124.
  10. Patel CA, Mukhtar M, Pomerantz RJ. Human immunodeficiency virus type 1 Vpr induces apoptosis in human neuronal cells. *J Virol.* 2000; 74(20):9717–26. PMID: 11000244; PubMed Central PMCID: PMCPMC112404.
  11. Trillo-Pazos G, McFarlane-Abdulla E, Campbell IC, Pilkington GJ, Everall IP. Recombinant nef HIV-IIIb protein is toxic to human neurons in culture. *Brain Res.* 2000; 864(2):315–26. PMID: 10802040.
  12. Zeinolabediny Y, Caccuri F, Colombo L, Morelli F, Romeo M, Rossi A, et al. HIV-1 matrix protein p17 misfolding forms toxic amyloidogenic assemblies that induce neurocognitive disorders. *Sci Rep.* 2017; 7(1):10313. Epub 2017/09/06. <https://doi.org/10.1038/s41598-017-10875-0> PMID: 28871125; PubMed Central PMCID: PMCPMC5583282.
  13. Gouras GK, Olsson TT, Hansson O. beta-Amyloid peptides and amyloid plaques in Alzheimer's disease. *Neurotherapeutics.* 2015; 12(1):3–11. <https://doi.org/10.1007/s13311-014-0313-y> PMID: 25371168; PubMed Central PMCID: PMCPMC4322079.
  14. van der Kant R, Goldstein LS. Cellular functions of the amyloid precursor protein from development to dementia. *Dev Cell.* 2015; 32(4):502–15. <https://doi.org/10.1016/j.devcel.2015.01.022> PMID: 25710536.
  15. Willem M, Tahirovic S, Busche MA, Ovsepian SV, Chafai M, Kootar S, et al. eta-Secretase processing of APP inhibits neuronal activity in the hippocampus. *Nature.* 2015; 526(7573):443–7. <https://doi.org/10.1038/nature14864> PMID: 26322584.
  16. Price JL, Davis PB, Morris JC, White DL. The distribution of tangles, plaques and related immunohistochemical markers in healthy aging and Alzheimer's disease. *Neurobiol Aging.* 1991; 12(4):295–312. Epub 1991/07/01. PMID: 1961359.
  17. An SF, Giometto B, Groves M, Miller RF, Beckett AA, Gray F, et al. Axonal damage revealed by accumulation of beta-APP in HIV-positive individuals without AIDS. *J Neuropathol Exp Neurol.* 1997; 56(11):1262–8. Epub 1997/11/25. PMID: 9370237.
  18. Nebuloni M, Pellegrinelli A, Ferri A, Bonetto S, Boldorini R, Vago L, et al. Beta amyloid precursor protein and patterns of HIV p24 immunohistochemistry in different brain areas of AIDS patients. *AIDS.* 2001; 15(5):571–5. Epub 2001/04/24. PMID: 11316993.
  19. Achim CL, Adame A, Dumaop W, Everall IP, Masliah E, Neurobehavioral Research C. Increased accumulation of intraneuronal amyloid beta in HIV-infected patients. *J Neuroimmune Pharmacol.* 2009; 4(2):190–9. <https://doi.org/10.1007/s11481-009-9152-8> PMID: 19288297; PubMed Central PMCID: PMCPMC3055557.
  20. Mankowski JL, Queen SE, Tarwater PM, Fox KJ, Perry VH. Accumulation of beta-amyloid precursor protein in axons correlates with CNS expression of SIV gp41. *J Neuropathol Exp Neurol.* 2002; 61(1):85–90. Epub 2002/02/07. PMID: 11829347.
  21. Aksenov MY, Aksenova MV, Mactutus CF, Booze RM. HIV-1 protein-mediated amyloidogenesis in rat hippocampal cell cultures. *Neurosci Lett.* 2010; 475(3):174–8. <https://doi.org/10.1016/j.neulet.2010.03.073> PMID: 20363291; PubMed Central PMCID: PMCPMC2874942.
  22. Ances BM, Christensen JJ, Teshome M, Taylor J, Xiong C, Aldea P, et al. Cognitively unimpaired HIV-positive subjects do not have increased 11C-PiB: a case-control study. *Neurology.* 2010; 75(2):111–5. Epub 2010/06/11. <https://doi.org/10.1212/WNL.0b013e3181e7b66e> PMID: 20534887; PubMed Central PMCID: PMCPMC2905926.
  23. Clifford DB, Fagan AM, Holtzman DM, Morris JC, Teshome M, Shah AR, et al. CSF biomarkers of Alzheimer disease in HIV-associated neurologic disease. *Neurology.* 2009; 73(23):1982–7. <https://doi.org/10.1212/WNL.0b013e3181c5b445> PMID: 19907013; PubMed Central PMCID: PMCPMC2790234.

24. Gisslen M, Krut J, Andreasson U, Blennow K, Cinque P, Brew BJ, et al. Amyloid and tau cerebrospinal fluid biomarkers in HIV infection. *BMC Neurol.* 2009; 9:63. Epub 2009/12/24. <https://doi.org/10.1186/1471-2377-9-63> PMID: 20028512; PubMed Central PMCID: PMCPMC2807422.
25. Ances BM, Benzinger TL, Christensen JJ, Thomas J, Venkat R, Teshome M, et al. 11C-PiB imaging of human immunodeficiency virus-associated neurocognitive disorder. *Arch Neurol.* 2012; 69(1):72–7. <https://doi.org/10.1001/archneurol.2011.761> PMID: 22232345; PubMed Central PMCID: PMCPMC3536500.
26. Krut JJ, Zetterberg H, Blennow K, Cinque P, Hagberg L, Price RW, et al. Cerebrospinal fluid Alzheimer's biomarker profiles in CNS infections. *J Neurol.* 2013; 260(2):620–6. Epub 2012/10/12. <https://doi.org/10.1007/s00415-012-6688-y> PMID: 23052602.
27. Peluso MJ, Meyerhoff DJ, Price RW, Peterson J, Lee E, Young AC, et al. Cerebrospinal fluid and neuroimaging biomarker abnormalities suggest early neurological injury in a subset of individuals during primary HIV infection. *J Infect Dis.* 2013; 207(11):1703–12. Epub 2013/03/06. <https://doi.org/10.1093/infdis/jit088> PMID: 23460748; PubMed Central PMCID: PMCPMC3636785.
28. Steinbrink F, Evers S, Buerke B, Young P, Arendt G, Koutsilieris E, et al. Cognitive impairment in HIV infection is associated with MRI and CSF pattern of neurodegeneration. *Eur J Neurol.* 2013; 20(3):420–8. Epub 2012/10/26. <https://doi.org/10.1111/ene.12006> PMID: 23095123.
29. Ortega M, Ances BM. Role of HIV in amyloid metabolism. *J Neuroimmune Pharmacol.* 2014; 9(4):483–91. <https://doi.org/10.1007/s11481-014-9546-0> PMID: 24816714; PubMed Central PMCID: PMCPMC4157652.
30. Valcour V, Shikuma C, Shiramizu B, Watters M, Poff P, Selnes OA, et al. Age, apolipoprotein E4, and the risk of HIV dementia: the Hawaii Aging with HIV Cohort. *J Neuroimmunol.* 2004; 157(1–2):197–202. Epub 2004/12/08. <https://doi.org/10.1016/j.jneuroim.2004.08.029> PMID: 15579298.
31. Andres MA, Feger U, Nath A, Munsaka S, Jiang CS, Chang L. APOE epsilon 4 allele and CSF APOE on cognition in HIV-infected subjects. *J Neuroimmune Pharmacol.* 2011; 6(3):389–98. Epub 2010/12/25. <https://doi.org/10.1007/s11481-010-9254-3> PMID: 21184197; PubMed Central PMCID: PMCPMC4899041.
32. Peterson J, Gisslen M, Zetterberg H, Fuchs D, Shacklett BL, Hagberg L, et al. Cerebrospinal fluid (CSF) neuronal biomarkers across the spectrum of HIV infection: hierarchy of injury and detection. *PLoS ONE.* 2014; 9(12):e116081. <https://doi.org/10.1371/journal.pone.0116081> PMID: 25541953; PubMed Central PMCID: PMCPMC4277428.
33. de Almeida SM, Ribeiro CE, Rotta I, Piovesan M, Tang B, Vaida F, et al. Biomarkers of neuronal injury and amyloid metabolism in the cerebrospinal fluid of patients infected with HIV-1 subtypes B and C. *J Neurovirol.* 2018; 24(1):28–40. Epub 2017/10/25. <https://doi.org/10.1007/s13365-017-0591-3> PMID: 29063514; PubMed Central PMCID: PMCPMC5792298.
34. Andras IE, Rha G, Huang W, Eum S, Couraud PO, Romero IA, et al. Simvastatin protects against amyloid beta and HIV-1 Tat-induced promoter activities of inflammatory genes in brain endothelial cells. *Mol Pharmacol.* 2008; 73(5):1424–33. <https://doi.org/10.1124/mol.107.042028> PMID: 18276775; PubMed Central PMCID: PMCPMC2731660.
35. Kurapati KR, Atluri VS, Samikkannu T, Nair MP. Ashwagandha (*Withania somnifera*) reverses beta-amyloid1-42 induced toxicity in human neuronal cells: implications in HIV-associated neurocognitive disorders (HAND). *PLoS ONE.* 2013; 8(10):e77624. <https://doi.org/10.1371/journal.pone.0077624> PMID: 24147038; PubMed Central PMCID: PMCPMC3797707.
36. Andras IE, Toborek M. Amyloid beta accumulation in HIV-1-infected brain: The role of the blood brain barrier. *IUBMB Life.* 2013; 65(1):43–9. <https://doi.org/10.1002/iub.1106> PMID: 23225609; PubMed Central PMCID: PMCPMC3804005.
37. Braidy N, Munoz P, Palacios AG, Castellano-Gonzalez G, Inestrosa NC, Chung RS, et al. Recent rodent models for Alzheimer's disease: clinical implications and basic research. *J Neural Transm (Vienna).* 2012; 119(2):173–95. <https://doi.org/10.1007/s00702-011-0731-5> PMID: 22086139.
38. Tomasselli AG, Hui JO, Adams L, Chosay J, Lowery D, Greenberg B, et al. Actin, troponin C, Alzheimer amyloid precursor protein and pro-interleukin 1 beta as substrates of the protease from human immunodeficiency virus. *J Biol Chem.* 1991; 266(22):14548–53. PMID: 1907279.
39. Rempel HC, Pulliam L. HIV-1 Tat inhibits neprilysin and elevates amyloid beta. *AIDS.* 2005; 19(2):127–35. PMID: 15668537.
40. Kim J, Yoon JH, Kim YS. HIV-1 Tat interacts with and regulates the localization and processing of amyloid precursor protein. *PLoS ONE.* 2013; 8(11):e77972. <https://doi.org/10.1371/journal.pone.0077972> PMID: 24312169; PubMed Central PMCID: PMCPMC3843664.
41. Chai Q, Jovasevic V, Malikov V, Sabo Y, Morham S, Walsh D, et al. HIV-1 counteracts an innate restriction by amyloid precursor protein resulting in neurodegeneration. *Nat Commun.* 2017; 8(1):1522. Epub

2017/11/17. <https://doi.org/10.1038/s41467-017-01795-8> PMID: 29142315; PubMed Central PMCID: PMC5688069.

42. Stern AL, Ghura S, Gannon PJ, Akay-Espinoza C, Phan JM, Yee AC, et al. BACE1 Mediates HIV-Associated and Excitotoxic Neuronal Damage Through an APP-Dependent Mechanism. *J Neurosci*. 2018; 38(18):4288–300. Epub 2018/04/11. <https://doi.org/10.1523/JNEUROSCI.1280-17.2018> PMID: 29632166; PubMed Central PMCID: PMC5932640.
43. Zhang J, Liu J, Katafiasz B, Fox H, Xiong H. HIV-1 gp120-induced axonal injury detected by accumulation of beta-amyloid precursor protein in adult rat corpus callosum. *J Neuroimmune Pharmacol*. 2011; 6(4):650–7. <https://doi.org/10.1007/s11481-011-9259-6> PMID: 21286834; PubMed Central PMCID: PMC3165079.
44. Mucke L, Abraham CR, Ruppe MD, Rockenstein EM, Toggas SM, Mallory M, et al. Protection against HIV-1 gp120-induced brain damage by neuronal expression of human amyloid precursor protein. *J Exp Med*. 1995; 181(4):1551–6. PMID: 7699335; PubMed Central PMCID: PMC2191956.
45. Fulop T, Witkowski JM, Bourgade K, Khalil A, Zerif E, Larbi A, et al. Can an Infection Hypothesis Explain the Beta Amyloid Hypothesis of Alzheimer's Disease? *Front Aging Neurosci*. 2018; 10:224. <https://doi.org/10.3389/fnagi.2018.00224> PMID: 30087609; PubMed Central PMCID: PMC6066504.