HIV Infection

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HIV-1 (human immunodeficiency virus type 1) is one of the most dangerous and widespread infectious viruses and causes the deaths of millions of people. The global spread of this virus, which has taken on the character of a pandemic, has made HIV a central health problem worldwide. Currently, thanks to the active development of innovative forms of antiretroviral drugs and increased access to effective means of prevention, HIV infection has become a non-fatal, and in many cases, chronic disease. Thus, the life expectancy of people living with HIV (PLWH) has significantly increased. At the same time, in the population of PLWH, in addition to the consistenly observed higher rates of morbidity and mortality from cardiovascular diseases, various metabolic complications, and non-AIDS-related malignancies, there is a clear trend towards the spread of neurocognitive disorders.

HIV-1 CNS CNS cells neurocognitive disorders (HAND)

1. Mental Disorders Associated with HIV Infection

The relationship between HIV infection and mental illness is rather complex and largely unexplored to date. It has been shown that people with severe mental disorders have a significantly increased risk of HIV infection [1][2]. It was also found that the percentage of HIV infection in patients with a mental pathology is, on average, seven times higher than that among mentally healthy people [1][2]. It is believed that this is due to the distortion of the processes of perception and thinking in persons suffering from mental disorders, their use of psychoactive substances, their risky sexual behavior, and sexual victimization [1][2]. Thus, it has been found that an increased risk of HIV infection is directly associated with hypersexuality during an exacerbation of mental illness. It was noted that the frequency of sexual activity in the acute phase of schizophrenia increased in 38.6% of individuals and in 44.8% of individuals with bipolar disorders, the frequency of sexual activity in individuals with mental illnesses under the influence of heroin increased in 43.4% [3]. Such patients had sexual behavior associated with an increased risk of sexual transmission of HIV: 39–42.7% had intercourse with several sexual partners at the same time; 24% had sex with prostitutes, and in doing so, 65% had unprotected sexual intercourse (of which 12.5% had unprotected sexual intercourse in order to earn money), [3][4]. Additionally, as a result of impaired cognitive abilities, evaluation, and judgment, people with mental disorders are much more likely to be at risk of coerced sex [3][4][5][6][7][8]. The frequency of forced sexual intercourse among this group of individuals is 10–38% [4][9][10]. Many patients with mental illnesses such as schizophrenia and bipolar disorder have been found to have experienced sexual abuse in childhood [7][9][11]. The traumatic experience is later reproduced in life and such persons repeatedly become victims of sexual violence; they are characterized by sexually promiscuous and risky sexual behavior in adulthood [7][12].

In turn, over the more than thirty years of the HIV epidemic, many materials have been accumulated indicating that HIV infection predisposes one to the development of a mental pathology such as anxiety disorders, bipolar disorders, schizophrenia, and cognitive disorders. It has been observed that the early stages of HIV infection are most often accompanied by a depressive state [13][14]. The progression of HIV infection is then characterized by the development of psychosis, adjustment disorder, and bipolar disorder [1][15][16]. In the African continent, where the burden of HIV infection is particularly high, the prevalence of HIV infection among adults with severe mental disorders ranges from 11 to 48.6% [17][18][19][20][21][22]. The results of a multisite study conducted in the United States showed that 36% of people living with HIV (PLWH) suffered from severe depression, 15.8% suffered from generalized anxiety disorder (GAD), and 10.5% suffered from panic disorder (PD)—three times higher than similar indicators among the general population [23][24][25]. At the same time, a combination of GAD and PD was diagnosed in 5% of PLWH [24]. Thus, it can be stated that HIV infection is a serious predictor of the development of severe forms of depression, GAD, and PD [26]. It should be noted that early initiation of antiretroviral therapy (ART) does not reduce the risk of any of these mental disorders. In India, the number of HIV-infected people with severe forms of depression is 59%, and in China, this number ranges from 32.9 to 85.6% [13][27][28][29]. It is found that depressive conditions in PLWH significantly increase the risk of death [30][31]. An analysis of the case histories of 5927 HIV-infected people showed that mild and short-term (1–4 days) depression and/or mild but more persistent depressive conditions can negatively affect the process of HIV treatment and the survival of PLWH [14].

It was revealed that psychosis is more often diagnosed in patients with severe immunodeficiency (CD4 ≤ 200–350 cells/mm^3), which usually occurs in the late stages of HIV infection. The frequency of the first psychotic episodes in HIV-positive individuals ranges from 1 to 15% [32][33]. For psychoses arising in HIV-infected patients, hallucinations, affective disorders, cognitive impairments, and dementia are common [34][35]. Moreover, the risk of schizophrenia and acute psychosis in people infected with HIV during the first year after infection is quite high, with an incidence rate of 8.24 and 12.7, respectively [32]. Moreover, an increased risk of developing schizophrenia persists for more than 5 years after the diagnosis of an HIV infection, at which point the majority of PLWH receive antiretroviral therapy (ART), leading to suppression of viral replication and of opportunistic infections [32]. It was found that the comorbidity of HIV infection and schizophrenia among such patients significantly correlates with a high risk of lethal cases [16][32]. The results of two large-scale studies showed that among patients with schizophrenia, there was a higher mortality rate in the group of HIV-positive individuals compared to the group of HIV-negative patients [16][32]. A six-year follow-up of such patients revealed that the mortality among HIV-positive patients diagnosed with schizophrenia was 25.5%, while that among HIV-negative patients with the same diagnosis was only 17.8% [16]. Another more long-term (12-year) study found that the mortality rate in the group of patients with HIV and schizophrenia was 25.8, while in those with schizophrenia but not infected with HIV, this indicator was 6.24 [32].

According to the materials of the short international neuropsychiatric questionnaire (MINI), cases of bipolar disorder among PLWH in economically developed countries are 5.6–8.1%, which is 3–4 times higher than the same indicators among the general populations of these countries (2.1%) [36][37][38]. In developing countries, this figure reaches 30% [39]. Manic disorder in HIV-positive individuals during later stages of the infection often occurs as a phase of bipolar disorder and is likely associated with the direct effect of HIV on the cells of the central nervous system (CNS). Manic disorder can also result from a secondary infection or be influenced by ART. It was found that

severe cognitive impairment occurred in 54.8% of people with HIV-associated mania, while in HIV-negative people with the initial stage of that same mental pathology, such disorders occurred in only 15.9% [29]. It was also shown that HIV-associated manic disorder represents the initial stage of HIV-associated dementia [49–51], which occurs in 10% of HIV-positive individuals during the late stages of HIV infection [40].

2. Biological Mechanisms of HIV-1—Effect on CNS Functions

It has now been proven that neurocognitive changes in HIV-positive individuals are the result of the direct effect of HIV on the central nervous system (CNS). It was found that following the first days after infection with human immunodeficiency virus type 1 (HIV-1), this viral agent penetrates into the tissues of the CNS [41] and localizes in the various parts of the brain [42][43]. Viral RNA was found in the caudate nucleus, the cortex of the frontal lobe of the brain, and the cerebrospinal fluid. HIV-1 localized in the basal ganglia of the CNS causes progressive neurodegenerative changes, as well as impaired neuromotor and neurocognitive functions. A number of studies have shown that the development of HIV infection is accompanied by a decrease in the volume of the caudate nucleus and white matter, as well as the cortical and subcortical gray matter of the brain [56–58], which is directly related to bipolar disorders [44]. Dysregulation in the metabolic activity of the basal ganglia was also identified. These phenomena were shown to be expressed in the form of hypermetabolism in the early stages of HIV infection and hypometabolism in the later stages of the infectious process [45].

It is believed that HIV-1 enters the CNS via the migration of virus-infected mononuclear blood cells/monocytes using the “Trojan horse mechanism”, which allows the virus to cross the blood–brain barrier (BBB) and infect the astrocytes, oligodendrocytes, and progenitor cells [46][47][48]. It has been shown that HIV-1 can change BBB permeability by modifying the expression of proteins involved in the maintenance of a dense barrier epithelium through the action of the viral *tat* protein [49][50]. Free viral particles can also penetrate the BBB via transcytosis, which is mediated by the viral protein *gp120* [51] or by productive infection of the endothelial cells [52][53]. Some researchers believe that the freely circulating proteins *gp120*, *tat*, and *nef* can bind to the microvascular endothelial cells and cause changes in the BBB without direct involvement of the virus [54]. However, the main targets of HIV-1 invasion are the macrophages and microglia cells upon whose surfaces the co-receptors CXCR4 and CCR5 are expressed, which are necessary for the virus to enter cells [55][56][57] and which become cellular reservoirs for the long-term persistence of the virus in the CNS, thus playing an important role in the development of HIV-induced dementia [47][58][59]. The cerebrospinal fluid can also serve as a reservoir for the virus, which was confirmed by the results of the studies showing a high level of HIV-1 RNA in the cerebrosinal fluid of AIDS patients [60][61].

By penetrating into the CNS, HIV-1 induces an increase in the expression of chemokine receptors, the production of inflammatory mediators, the production of enzymes that destroy the extracellular matrix, and excitotoxicity mediated by glutamate receptors, which, in turn, initiates the activation of numerous downstream signaling pathways and disrupts neuronal and glial functions [47][62].

It has been shown that the viral protein *tat* can cause activation of the effector pyrine domain of the Nod-like receptor (NLR) containing the NLRP3 of the inflammasome in microglia, which leads to an increase in the levels of

caspase-1 and IL-1β; this, in turn, induces the production of TNF-α and IL-6, thereby enhancing inflammatory processes [63]. In addition, HIV-1 infection of the microglial cells and macrophages induces the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS), which disrupts the functions of the signaling pathways associated with apoptosis and leads to cell cycle arrest, causing serious DNA damage and protein damage [64][65].

In astrocytes, in contrast to microglia and macrophages, the full replication of HIV-1 is limited [66][67]. These cells cannot produce full-fledged viral particles, but, at the same time, they contribute to the damage of brain cells by generating astrogliosis [68]. Virus-infected astrocytes can produce a number of viral regulatory proteins, such as *tat*, *nef*, and *rev*, which are involved in the development of inflammation and, therefore, neuronal damage [69]. It is known that *tat* activates HIV-1 transcription and enhances the process of the infection of primary astrocytes [70]. On the other hand, *nef* can induce the production of ROS by astrocytes, which leads to the rapid death of neurons, thereby causing the development of HIV-1-associated neurocognitive disorders and explaining the reason for the rapid development of dementia in patients not receiving ART or with low adherence to treatment [71].

Despite the fact that some oligodendrocytes express the CXCR4 co-receptor (one of the key receptors involved in the infection of HIV-1 cells) [72], it is believed that the most profound damage to oligodendrocytes is caused by the release of viral proteins from other cells infected with the virus [73]. It has been found that the viral *tat* protein promotes the death of oligodendrocytes or leads to their incomplete maturation, as well as the dysregulation of myelin protein expression, which reduces the ability of oligodendrocytes to create myelin sheaths [74][75]. *Tat*-induced damage to oligodendrocytes is associated with a change in the balance between the protein kinase CaMKIIβ and tyrosine kinase 3β (Gsk3β), leading to oligodendrocyte apoptosis and the development of a neuropathology [75].

Neurons cannot be infected with HIV-1, because they do not express the virus-specific receptors necessary for the virus to enter these cells. However, the viral proteins *tat*, *nef*, and *gp120*, which have high neurotoxic potential, can disrupt interneuronal connections and even cause neuronal death [76]. The *tat* protein interacting with the markers of the phagosomes in neurons changes the morphology of these formations, thereby preventing their fusion with lysosomes [77]. The *nef* protein has a similar effect, disrupting the autophagy process and causing neurodegenerative disorders [78].

References

1. Blank, M.B.; Himelhoch, S.; Walkup, J.; Eisenberg, M.M. Treatment Considerations for HIV-Infected Individuals with Severe Mental Illness. Curr. HIV AIDS Rep. 2013, 10, 371–379, doi:10.1007/s11904-013-0179-3.
2. Hobkirk, A.L.; Towe, S.L.; Lion, R.; Meade, C.S. Primary and secondary HIV prevention among persons with severe mental illness: Recent findings. Curr. Hiv Aids Rep. 2015, 12, 406–412,

doi:10.1007/s11904-015-0294-4.

3. Hariri, A.G.; Karadag, F.; Gokalp, P.; Essizoglu, A. Risky Sexual Behavior among Patients in Turkey with Bipolar Disorder, Schizophrenia, and Heroin Addiction. J. Sex. Med. 2011, 8, 2284–2291, doi:10.1111/j.1743-6109.2011.02282.x.
4. Meade, C.S.; Graff, F.S.; Griffin, M.L.; Weiss, R.D. HIV risk behavior among patients with co-occurring bipolar and substance use disorders: Associations with mania and drug abuse. Drug Alcohol Depend. 2008, 92, 296–300, doi:10.1016/j.drugalcdep.2007.07.013.
5. Chandra, P.S.; Carey, M.P.; Carey, K.B.; Prasada Rao, P.S.; Jairam, K.R.; Thomas, T. HIV risk behaviour among psychiatric inpatients: Results from a hospital-wide screening study in Southern India. Int. J. STD AIDS 2003, 14, 532–538, doi:10.1258/095646203767869147.
6. Carey, M.P.; Carey, K.B.; Maisto, S.A.; Schroder, K.E.; Vanable, P.A.; Gordon, C.M. HIV risk behavior among outpatient: Association with psychiatric disorder, substance use disorder, and gender. J. Nerv. Ment. Dis. 2004, 192, 289–296, doi:10.1097/01.nmd.0000120888.45094.38.
7. Meade, C.S.; Kershaw, T.S.; Hansen, N.B.; Sikkema, K.J. Long-term correlates of childhood abuse among adults with severe mental illness: Adult victimization, substance abuse, and HIV sexual risk behavior. AIDS Behav. 2009, 13, 207–216, doi:10.1007/s10461-007-9326-4.
8. Varshney, M.; Mahapatra, A.; Krishnan, V.; Gupta, R.; Deb, K.S. Violence and mental illness: What is the true story? J. Epi-demiol. Community Health 2016, 70, 223–225, doi:10.1136/jech-2015-205546.
9. Chandra, P.S.; Carey, M.P.; Carey, K.B.; Shalinianant, A.; Thomas, T. Sexual coercion and abuse among women with a se-vere mental illness in India: An exploratory investigation. Compr. Psychiatry 2003, 44, 205–212, doi:10.1016/S0010-440X(03)00004-X.
10. Wang, Q.W.; Hou, C.L.; Wang, S.B.; Huang, Z.H.; Huang, Y.H.; Zhang, J.J.; Jia, F.J. Frequency and correlates of violence against patients with schizophrenia living in rural China. BMC Psychiatry 2020, 20, 286, doi:10.1186/s12888-020-02696-9.
11. Newman, J.M.; Turnbull, A.; Berman, B.A.; Rodrigues, S.; Serper, M.R. Impact of traumatic and violent victimization expe-riences in individuals with schizophrenia and schizoaffective disorder. J. Nerv. Ment. Dis. 2010, 198, 708–714, doi:10.1097/NMD.0b013e3181f49bf1.
12. Markowitz, S.M.; O'Cleirigh, C.; Hendriksen, E.S.; Bullis, J.R.; Stein, M.; Safren, S.A. Childhood sexual abuse and health risk behaviors in patients with HIV and a history of injection drug use. AIDS Behav. 2011, 15, 1554–1560, doi:10.1007/s10461-010-9857-y.
13. Wang, T.; Fu, H.; Kaminga, A.C.; Li, Z.; Guo, G.; Chen, L.; Li, Q. Prevalence of depression or depressive symptoms among people living with HIV/AIDS in China: A systematic review and meta-analysis. BMC Psychiatry 2018, 18, 160, doi:10.1186/s12888-018-1741-8.

14. Pence, B.W.; Mills, J.C.; Bengtson, A.M.; Gaynes, B.N.; Breger, T.L.; Cook, R.L.; Moore, R.D.; Grelotti, D.J.; O'Cleirigh, C.; Mugavero, M.J. Association of increased chronicity of depression with HIV appointment attendance, treatment failure, and mortality among HIV-infected adults in the United States. JAMA Psychiatry 2018, 75, 379–385, doi:10.1001/jamapsychiatry.2017.4726.
15. Helleberg, M.; Pedersen, M.G.; Pedersen, C.B.; Mortensen, P.B.; Obel, N. Associations between HIV and schizophrenia and their effect on HIV treatment outcomes: A nationwide population-based cohort study in Denmark. Lancet HIV 2015, 2, e344–e350, doi:10.1016/S2352-3018(15)00089-2.
16. Closson, K.; McLinden, T.; Patterson, T.L.; Eyawo, O.; Kibel, M.; Card, K.G.; Salters, K.; Chau, W.; Ye, M.; Hull, M.W.; et al. HIV, schizophrenia, and all-cause mortality: A population-based cohort study of individuals accessing universal medical care from 1998 to 2012 in British Columbia, Canada. Schizophr. Res. 2019, 209, 198–205, doi:10.1016/j.schres.2019.04.020.
17. Lundberg, P.; Nakasujja, N.; Musisi, S.; Thorson, A.E.; Cantor-Graae, E.; Allebeck, P. HIV prevalence in persons with severe mental illness in Uganda: A cross-sectional hospital-based study. Int. J. Ment. Health Syst. 2013, 7, 20, doi:10.1186/1752-4458-7-20.
18. Maling, S.; Todd, J.; Van der Paal, L.; Grosskurth, H.; Kinyanda, E. HIV-1 seroprevalence and risk factors for HIV infection among first-time psychiatric admissions in Uganda. AIDS Care 2011, 23, 171–178, doi:10.1080/09540121.2010.498939.
19. Camara, A.; Sow, M.S.; Touré, A.; Sako, F.B.; Camara, I.; Soumaoro, K.; Delamou, A.; Doukouré, M. Anxiety and depression among HIV patients of the infectious disease department of Conakry University Hospital in 2018. Epidemiol. Infect. 2020, 148, e8, doi:10.1017/S095026881900222X.
20. Kim, M.H.; Mazenga, A.C.; Yu, X.; Devandra, A.; Nguyen, C.; Ahmed, S.; Kazembe, P.N.; Sharp, C. Factors associated with depression among adolescents living with HIV in Malawi. BMC Psychiatry 2015, 15, 264, doi:10.1186/s12888-015-0649-9.
21. Ngum, P.A.; De Fon, P.N.; Ngu, R.C.; Verla, V.S.; Luma, H.N. Depression among HIV/aids patients on highly active an-tiretroviral therapy in the southwest regional hospitals of Cameroon: A cross-sectional study. Neurol. Ther. 2017, 6, 103–114, doi:10.1007/s40120-017-0065-9.
22. Abebe, H.; Shumet, S.; Nassir, Z.; Agidew, M.; Abebaw, D. Prevalence of Depressive Symptoms and Associated Factors among HIV-Positive Youth Attending ART Follow-Up in Addis Ababa, Ethiopia. AIDS Res. Treat. 2019, 1–7, doi:10.1155/2019/4610458.
23. Simoni, J.M.; Safren, S.A.; Manhart, L.E.; Lyda, K.; Grossman, C.I.; Rao, D.; Mimiaga, M.J.; Wong, F.Y.; Catz, S.L.; Blank, M.B.; et al. Challenges in addressing depression in HIV research: Assessment, cultural context, and methods. AIDS Behav. 2011, 15, 376–388, doi:10.1007/s10461-010-9836-3.

24. Bing, E.G.; Burnam, M.A.; Longshore, D.; Fleishman, J.A.; Sherbourne, C.D.; London, A.S.; Turner, B.J.; Eggan, F.; Beckman, R.; Vitiello, B.; et al. Psychiatric disorders and drug use among human immunodeficiency virus-infected adults in the United States. Arch. Gen. Psychiatry 2001, 58, 721–728, doi:10.1001/archpsyc.58.8.721.

25. Kessler, R.C.; Birnbaum, H.; Bromet, E.; Hwang, I.; Sampson, N.; Shahly, V. Age differences in major depression: Results from the National Comorbidity Survey Replication (NCS-R). Psychol. Med. 2010, 40, 225–237, doi:10.1017/S0033291709990213.

26. Tsao, J.C.; Dobalian, A.; Moreau, C.; Dobalian, K. Stability of anxiety and depression in a national sample of adults with hu-man immunodeficiency virus. J. Nerv. Ment. Dis. 2004, 192, 111–118, doi:10.1097/01.nmd.0000110282.61088.cc.

27. Bhatia, M.S.; Munjal, S. Prevalence of Depression in People Living with HIV/AIDS Undergoing ART and Factors Associated with it. J. Clin. Diagn. Res. 2014, 8, WC01–WC04, doi:10.7860/JCDR/2014/7725.4927.

28. Huang, X.; Meyers, K.; Liu, X.; Li, X.; Zhang, T.; Xia, W.; Hou, J.; Song, A.; He, H.; Li, C.; et al. The Double Burdens of Men-tal Health Among AIDS Patients with Fully Successful Immune Restoration: A Cross-Sectional Study of Anxiety and Depres-sion in China. Front. Psychiatry 2018, 24, 384, doi:10.3389/fpsyt.2018.00384.

29. Charlson, F.J.; Baxter, A.J.; Hui, G.C.; Shidhaye, R.; Whiteford, H.A. The burden of mental, neurological, and substance use disorders in China and India: A systematic analysis of community representative epidemiological studies. Lancet 2016, 388, 376–389, doi:10.1016/S0140-6736(16)30590-6.

30. Todd, J.V.; Cole, S.R.; Pence, B.W.; Lesko, C.R.; Bacchetti, P.; Cohen, M.H.; Feaster, D.J.; Gange, S.; Griswold, M.E.; Mack, W.; et al. Effects of antiretroviral therapy and depressive symptoms on all-cause mortality among HIV-infected women. Am. J. Epidemiol. 2017, 185, 869–878, doi:10.1093/aje/kww192.

31. Antelman, G.; Kaaya, S.; Wei, R.; Mbwambo, J.; Msamanga, G.I.; Fawzi, W.W.; Fawzi, M.C. Depressive symptoms increase risk of HIV disease progression and mortality among women in Tanzania. J. Acquir. Immune Defic. Syndr. 2007, 44, 470–477, doi:10.1097/QAI.0b013e31802f1318.

32. Helleberg, M.; Kronborg, G.; Larsen, C.S.; Pedersen, G.; Pedersen, C.; Gerstoft, J.; Obel, N. Causes of death among Danish HIV patients compared with population controls in the period 1995–2008. Infection 2012, 40, 627–634, doi:10.1007/s15010-012-0293-y.

33. Adewuya, A.O.; Afolabi, M.O.; Ola, B.A.; Ogundele, O.; Ajibare, A.O.; Oladipo, B.F. Psychatric disorders among the HIV-positive population in Nigeria: A control study. J. Psychosom. Res. 2007, 63, 203–206, doi:10.1016/j.jpsychores.2007.03.006.

34. Dolder, C.R.; Patterson, T.L.; Dilip, V.J. HIV, psychosis and aging: Past, present and future. AIDS 2004, 18, S35–S42, PMID:15075496.

35. Harris, M.J.; Jeste, D.V.; Gleghorn, A.; Sewell, D.D. New-onset psychosis in HIV infected patients. J. Clin. Psychiatry 1991, 52, 369–376, PMID:1894589.

36. De Sousa, G.W.; Da Silva, C.A.H.; Barreto, R.D.; Negreiros de Matos, K.J.; Do Menino, J.S.L.T.; De Matos e Souza, F.G. Prev-alence of bipolar disorder in a HIV-infected outpatient population. AIDS Care 2013, 25, 1499–1503, doi:10.1080/09540121.2013.779625.

37. Atkinson, J.H.; Higgins, J.A.; Vigil, O.; Dubrow, R.; Remien, R.H.; Steward, W.T.; Casey, C.Y.; Sikkema, K.J.; Correale, J.; Ake, C.; et al. Psychiatric context of acute/early HIV infection. The NIMH multisite acute HIV infection study: IV. AIDS Be-hav. 2009, 13, 1061–1067, doi:10.1007/s10461-009-9585-3.

38. Merikangas, K.R.; Akiskal, H.S.; Angst, J.; Greenberg, P.E.; Hirschfeld, R.M.; Petukhova, M.; Kessler, R.C. Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. Arch. Gen. Psychiatry 2007, 64, 543–552, doi:10.1001/archpsyc.64.5.543.

39. Nakimuli-Mpungu, E.; Musisi, S.; Katabira, E.; Nachega, J.; Bass, J. Prevalence and factors associated with depressive disor-ders in an HIV+ patient population in southern Uganda. J. Affect. Disord. 2011, 135, 160–167, doi:10.1016/j.jad.2011.07.009.

40. Dougherty, R.H.; Skolasky, R.L., Jr.; McArthur, J.C. Progression of HIV-associated dementia treated with HAART. AIDS Read. 2002, 12, 69–74, PMID:11905143.

41. Valcour, V.; Chalermchai, T.; Sailasuta, N.; Marovich, M.; Lerdlum, S.; Suttichom, D.; Suwanwela, N.C.; Jagodzinski, L.; Michael, N.; Spudich, S.; et al. RV254/SEARCH 010 Study Group. Central nervous system viral invasion and inflammation during acute HIV infection. Int. J. Infect. Dis. 2012, 206, 275–282, doi:10.1093/infdis/jis326.

42. Kumar, A.M.; Borodowsky, I.; Fernandez, B.; Gonzalez, L.; Kumar, M. Human immunodeficiency virus type 1 RNA levels in different regions of human brain: Quantification using real-time reverse transcriptase-polymerase chain reaction. J. Neuro-virol. 2007, 13, 210–224, doi:10.1080/13550280701327038.

43. Lawrence, D.M.; Durham, L.C.; Scwartz, L.; Seth, P.; Maric, D.; Major, E.O. Human immunodeficiency virus type 1 infection of human brain-derived progenitor cells. J. Virol. 2004, 78, 7319–7328, doi:10.1128/JVI.78.14.7319-7328.2004.

44. Vita, A.; De Peri, L.; Deste, G.; Sacchetti, E. Progressive loss of cortical gray matter in schizophrenia: A meta-analysis and meta-regression of longitudinal MRI studies. Transl. Psychiatry 2012, 2, e190, doi:10.1038/tp.2012.116.

45. Capuron, L.; Pagnoni, G.; Demetrashvili, M.; Lawson, D.H.; Fornwalt, F.B.; Woolwine, B.; Berns, G.S.; Nemeroff, C.B.; Miller, A.H. Basal Ganglia Hypermetabolism and Symptoms of Fatigue during Interferon-α Therapy. Neuropsychopharmacology 2007, 32, 2384–2392, doi:10.1038/sj.npp.1301362.

46. Spudich, S.; Gonzalez-Scarano, F. HIV-1-related central nervous system disease: Current issues in pathogenesis, diagnosis, and treatment. Cold Spring Harb. Perspect. Med. 2012, 2, a007120, doi:10.1101/cshperspect.a007120.

47. Kaul, M.; Lipton, S.A. Mechanisms of neuroimmunity and neurodegeneration associated with HIV-1 infection and AIDS. J. Neuroimmune Pharm. 2006, 1, 138–151, doi:10.1007/s11481-006-9011-9.

48. Persidsky, Y.; Gendelman, H.E. Mononuclear phagocyte immunity and the neuropathogenesis of HIV-1 infection. J. Leukoc. Biol. 2003, 74, 691–701, doi:10.1189/jlb.0503205.

49. Xu, R.; Feng, X.; Xie, X.; Zhang, J.; Wu, D.; Xu, L. HIV-1 Tat protein increases the permeability of brain endothelial cells by both inhibiting occludin expression and cleaving occludin via matrix metalloproteinase-9. Brain Res. 2012, 1436, 13–19, doi:10.1016/j.brainres.2011.11.052.

50. Woollard, S.M.; Bhargavan, B.; Yu, F.; Kanmogne, G.D. Differential effects of Tat proteins derived from HIV-1 subtypes B and recombinant CRF02_AG on human brain microvascular endothelial cells: Implications for blood–brain barrier dysfunc-tion. J. Cereb. Blood Flow Metab. 2014, 34, 1047–1059, doi:10.1038/jcbfm.2014.54.

51. Banks, W.A.; Freed, E.O.; Wolf, K.M.; Robinson, S.M.; Franko, M.; Kumar, V.B. Transport of human immunodeficiency virus type 1 pseudoviruses across the blood–brain barrier: Role of envelope proteins and adsorptive endocytosis. J. Virol. 2001, 75, 4681–4691, doi:10.1128/JVI.75.10.4681-4691.2001.

52. Banks, W.A.; Robinson, S.M.; Wolf, K.M.; Bess, J.W., Jr.; Arthur, L.O. Binding, internalization, and membrane incorporation of human immunodeficiency virus-1 at the blood–brain barrier is differentially regulated. Neuroscience 2004, 128, 143–153, doi:10.1016/j.neuroscience.2004.06.021.

53. Maslin, C.L.V.; Kedzierska, K.; Webseter, N.; Muller, W.; Crowe, S. Transendothelial migration of monocytes: The underlying molecular mechanisms and consequences of HIV-1 infection. Curr. HIV Res. 2005, 3, 303–317, doi:10.2174/157016205774370401.

54. Annunziata, P. Blood–brain barrier changes during invasion of the central nervous system by HIV-1. J. Neurol. 2003, 250, 901–906, doi:10.1007/s00415-003-1159-0.

55. Feng, Y.; Broder, C.C.; Kennedy, P.E.; Berger, E.A. HIV-1 Entry Cofactor: Functional cDNA Cloning of a Sev-en-Transmembrane, G Protein-Coupled Receptor. Science 1996, 272, 872–877, doi:10.1126/science.272.5263.872.

56. Deng, H.; Liu, R.; Ellmeier, W.; Choe, S.; Unutmaz, D.; Burkhart, M.; Di Marzio, P.; Marmon, S.; Sutton, R.E.; Hill, C.M.; et al. Identification of a major co-receptor for primary isolates of HIV-1. Nature 1996, 381, 661–666, doi:10.1038/381661a0.

57. Dragic, T.; Litwin, V.; Allaway, G.P.; Martin, S.R.; Huang, Y.; Nagashima, K.A.; Cayanan, C.; Maddon, P.J.; Koup, R.A.; Moore, J.P.; et al. HIV-1 entry into CD4+ cells is mediated by the chemokine receptor CC-CKR-5. Nature 1996, 381, 667–673, doi:10.1038/381667a0.

58. Crowe, S.; Zhu, T.; Muller, W.A. The contribution of monocyte infection and trafficking to viral persistence, and maintenance of the viral reservoir in HIV infection. J. Leukoc. Biol. 2003, 74, 635–641, doi:10.1189/jlb.0503204.

59. Pierson, T.; McArthur, J.; Siliciano, R.S. Reservoirs for HIV-1: Mechanisms for viral persistence in the presence of antiviral immune responses and antiretroviral therapy. Ann. Rev. Immunol. 2002, 18, 665–708, doi:10.1146/annurev.immunol.18.1.665.

60. Rosadas, C.; Puccioni-Sohler, M. Relevance of retrovirus quantification in cerebrospinal fluid for neurologic diagnosis. J. Bio-med. Sci. 2015, 22, 66, doi:10.1186/s12929-015-0170-y.

61. Christo, P.P.; Greco, D.B.; Aleixo, A.W.; Livramento, J.A. Factors influencing cerebrospinal fluid and plasma HIV-1 RNA detection rate in patients with and without opportunistic neurological disease during the HAART era. BMC Infect. Dis. 2007, 7, 147, doi:10.1186/1471-2334-7-147.

62. Ramesh, G.; MacLean, A.G.; Philipp, M.T. Cytokines and chemokines at the crossroads of neuroinflammation, neurodegener-ation, and neuropathic pain. Mediat. Inflam. 2013, 480739, doi:10.1155/2013/480739.

63. Chivero, E.T.; Guo, M.; Periyasamy, P.; Liao, K.; Callen, S.E.; Buch, S. HIV Tat primes and activates microglial NLRP3 in-flammasome-mediated neuroinflammation. J. Neurosci. 2017, 37, 3599–3609, doi:10.1523/JNEUROSCI.3045-16.2017.

64. Von Bernhardi, R.; Eugenin-von Bernhardi, L.; Eugenin, J. Microglial cell dysregulation in brain aging and neurodegenera-tion. Front. Aging Neurosci. 2015, 7, 124, doi:10.3389/fnagi.2015.00124.

65. Mohanty, S.; Molin, M.D.; Ganguli, G.; Padhi, A.; Jena, P.; Selchow, P.; Sengupta, S.; Meuli, M.; Sander, P.; Sonawane, A. Mycobacterium tuberculosis EsxO (Rv2346c) promotes bacillary survival by inducing oxidative stress mediated genomic in-stability in macrophages. Tuberculosis 2016, 96, 44–57, doi:10.1016/j.tube.2015.11.006.

66. Churchill, M.; Nath, A. Where does HIV hide? A focus on the central nervous system. Curr. Opin. HIV AIDS 2013, 8, 165–169, doi:10.1097/COH.0b013e32835fc601.

67. Bissel, S.J.; Wiley, C.A. Human immunodeficiency virus infection of the brain: Pitfalls in evaluating infected/affected cell populations. Brain Pathol. 2004, 14, 97–108, doi:10.1111/j.1750-3639.2004.tb00503.x.

68. Gonzalez-Scarano, F.; Martin-Garcia, J. The neuropathogenesis of AIDS. Nat. Rev. Immunol. 2005, 5, 69–81, doi:10.1038/nri1527.

69. Pu, H.; Tian, J.; Flora, G.; Lee, Y.W.; Nath, A.; Hennig, B.; Toborek, M. HIV-1 Tat protein upregulates inflammatory media-tors and induces monocyte invasion into the brain. Mol. Cell Neurosci. 2003, 24, 224–237, doi:10.1016/S1044-7431(03)00171-4.

70. Bencheikh, M.; Bentsman, G.; Sarkissian, N.; Canki, M.; Volsky, D.J. Replication of different clones of human immunodefi-ciency virus type 1 in primary fetal human astrocytes: Enhancement of viral gene expression by Nef. J. Neurovirol. 1999, 5, 115–124, doi:10.3109/13550289909021993.

71. Calcagno, A.; Atzori, C.; Romito, A.; Vai, D.; Audagnotto, S.; Stella, M.L.; Montrucchio, C.; Imperiale. D.; Di Perri, G.; Bono-ra, S. Blood brain barrier impairment is associated with cerebrospinal fluid markers of neuronal damage in HIV-positive pa-tients. J. Neurovirol. 2016, 22, 88–92, doi:10.1007/s13365-015-0371-x.

72. Zhang, J.; Liu, J.; Katafiasz, B.; Fox, H.; Xiong, H. HIV-1 gp120-Induced Axonal Injury Detected by Accumulation of β-Amyloid Precursor Protein in Adult Rat Corpus Callosum. J. Neuroimmune Pharmacol. 2011, 6, 650–657, doi:10.1007/s11481-011-9259-6.

73. Hauser, K.F.; Hahn, Y.K.; Adjan, V.V.; Zou, S.; Buch, S.K.; Nath, A.; Bruce-Keller, A.J.; Knapp, P.E. HIV-1 Tat and morphine have interactive effects on oligodendrocyte survival and morphology. Glia 2009, 57, 194–206, doi:10.1002/glia.20746.

74. Zou, S.; Fuss, B.; Fitting, S.; Hahn, Y.K.; Hauser, K.F.; Knapp, P.E. Oligodendrocytes are targets of HIV-1 Tat: NMDA and AMPA receptor-mediated effects on survival and development. J. Neurosci. 2015, 35, 11384–11398, doi:10.1523/JNEUROSCI.4740-14.2015.

75. Zou, S.; Balinang, J.M.; Paris, J.J.; Hauser, K.F.; Fuss, B.; Knapp, P.E. Effects of HIV-1 Tat on oligodendrocyte viability are mediated by CaMKIIbeta-GSK3beta interactions. J. Neurochem. 2019, 149, 98–110, doi:10.1111/jnc.14668.

76. Nath, A.; Hauser, K.F.; Wojna, E.F.; Booze, R.M.; Maragos, W.; Predengarst, M.; Cass, W.; Turchan, J.T. Molecular Basis for Interactions of HIV and Drugs of Abuse. J. Acquir. Immune Defic. Syndr. 2002, 31, S62–S69, doi:10.1097/00126334-200210012-00006.

77. Fields, J.; Dumaop, W.; Eleuteri, S.; Campos, S.; Serger, E.; Trejo, M.; Kosberg, K.; Adame, A.; Spencer, B.; Rockenstein, E.; et al. HIV-1 Tat alters neuronal autophagy by modulating autophagosome fusion to the lysosome: Implications for HIV-associated neurocognitive disorders. J. Neurosci. 2015, 35, 1921–1938, doi:10.1523/JNEUROSCI.3207-14.2015.

78. Kyei, G.B.; Dinkins, C.; Davis, A.S.; Roberts, E.; Singh, S.B.; Dong, C.; Wu, L.; Kominami, E.; Ueno, T.; Yamamoto, A.; et al. Autophagy pathway intersects with HIV-1 biosynthesis and

regulates viral yields in macrophages. J. Cell Biol. 2009, 186, 255–268, doi:10.1083/jcb.200903070.

79. Mohanty, S.; Molin, M.D.; Ganguli, G.; Padhi, A.; Jena, P.; Selchow, P.; Sengupta, S.; Meuli, M.; Sander, P.; Sonawane, A. Mycobacterium tuberculosis EsxO (Rv2346c) promotes bacillary survival by inducing oxidative stress mediated genomic in-stability in macrophages. Tuberculosis 2016, 96, 44–57, doi:10.1016/j.tube.2015.11.006.
80. Churchill, M.; Nath, A. Where does HIV hide? A focus on the central nervous system. Curr. Opin. HIV AIDS 2013, 8, 165–169, doi:10.1097/COH.0b013e32835fc601.
81. Bissel, S.J.; Wiley, C.A. Human immunodeficiency virus infection of the brain: Pitfalls in evaluating infected/affected cell populations. Brain Pathol. 2004, 14, 97–108, doi:10.1111/j.1750-3639.2004.tb00503.x.
82. Gonzalez-Scarano, F.; Martin-Garcia, J. The neuropathogenesis of AIDS. Nat. Rev. Immunol. 2005, 5, 69–81, doi:10.1038/nri1527.
83. Pu, H.; Tian, J.; Flora, G.; Lee, Y.W.; Nath, A.; Hennig, B.; Toborek, M. HIV-1 Tat protein upregulates inflammatory media-tors and induces monocyte invasion into the brain. Mol. Cell Neurosci. 2003, 24, 224–237, doi:10.1016/S1044-7431(03)00171-4.
84. Bencheikh, M.; Bentsman, G.; Sarkissian, N.; Canki, M.; Volsky, D.J. Replication of different clones of human immunodefi-ciency virus type 1 in primary fetal human astrocytes: Enhancement of viral gene expression by Nef. J. Neurovirol. 1999, 5, 115–124, doi:10.3109/13550289909021993.
85. Calcagno, A.; Atzori, C.; Romito, A.; Vai, D.; Audagnotto, S.; Stella, M.L.; Montrucchio, C.; Imperiale. D.; Di Perri, G.; Bono-ra, S. Blood brain barrier impairment is associated with cerebrospinal fluid markers of neuronal damage in HIV-positive pa-tients. J. Neurovirol. 2016, 22, 88–92, doi:10.1007/s13365-015-0371-x.
86. Zhang, J.; Liu, J.; Katafiasz, B.; Fox, H.; Xiong, H. HIV-1 gp120-Induced Axonal Injury Detected by Accumulation of β-Amyloid Precursor Protein in Adult Rat Corpus Callosum. J. Neuroimmune Pharmacol. 2011, 6, 650–657, doi:10.1007/s11481-011-9259-6.
87. Hauser, K.F.; Hahn, Y.K.; Adjan, V.V.; Zou, S.; Buch, S.K.; Nath, A.; Bruce-Keller, A.J.; Knapp, P.E. HIV-1 Tat and morphine have interactive effects on oligodendrocyte survival and morphology. Glia 2009, 57, 194–206, doi:10.1002/glia.20746.
88. Zou, S.; Fuss, B.; Fitting, S.; Hahn, Y.K.; Hauser, K.F.; Knapp, P.E. Oligodendrocytes are targets of HIV-1 Tat: NMDA and AMPA receptor-mediated effects on survival and development. J. Neurosci. 2015, 35, 11384–11398, doi:10.1523/JNEUROSCI.4740-14.2015.
89. Zou, S.; Balinang, J.M.; Paris, J.J.; Hauser, K.F.; Fuss, B.; Knapp, P.E. Effects of HIV-1 Tat on oligodendrocyte viability are mediated by CaMKIIbeta-GSK3beta interactions. J. Neurochem.

2019, 149, 98–110, doi:10.1111/jnc.14668.

90. Nath, A.; Hauser, K.F.; Wojna, E.F.; Booze, R.M.; Maragos, W.; Predengarst, M.; Cass, W.; Turchan, J.T. Molecular Basis for Interactions of HIV and Drugs of Abuse. J. Acquir. Immune Defic. Syndr. 2002, 31, S62–S69, doi:10.1097/00126334-200210012-00006.
91. Fields, J.; Dumaop, W.; Eleuteri, S.; Campos, S.; Serger, E.; Trejo, M.; Kosberg, K.; Adame, A.; Spencer, B.; Rockenstein, E.; et al. HIV-1 Tat alters neuronal autophagy by modulating autophagosome fusion to the lysosome: Implications for HIV-associated neurocognitive disorders. J. Neurosci. 2015, 35, 1921–1938, doi:10.1523/JNEUROSCI.3207-14.2015.
92. Kyei, G.B.; Dinkins, C.; Davis, A.S.; Roberts, E.; Singh, S.B.; Dong, C.; Wu, L.; Kominami, E.; Ueno, T.; Yamamoto, A.; et al. Autophagy pathway intersects with HIV-1 biosynthesis and regulates viral yields in macrophages. J. Cell Biol. 2009, 186, 255–268, doi:10.1083/jcb.200903070.