

CYTOKINES AND HIV ASSOCIATED NEUROLOGICAL MANIFESTATIONS: A SYSTEMATIC REVIEW

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Abstract. *Background.* Cytokines are key players in the immune system's reaction to HIV and play a crucial role in HIV pathogenesis. Dysregulation of cytokines can contribute to the disease's pathogenesis and associated complications, making a comprehensive understanding of their roles crucial for developing efficacious therapeutic interventions against HIV/AIDS. Therefore, the aim of this systematic review is to examine the role of cytokines in HIV associated neurological manifestations and related complications. *Materials and methods.* Databases such as PubMed, Scopus, Web of Science, and Embase were explored for original English literature until September 10, 2022. Eligible articles for data extraction were screened and selected in two steps using some inclusion/ exclusion criteria. This study conforms to the PRISMA checklist and Newcastle-Ottawa Scale (NOS). *Results.* This review included a total of 15 studies. It was identified that cytokines were associated with sleep problems and numerous neurological manifestations. The most common neurological conditions include dementia, seizure, meningitis, cerebral toxoplasmosis, microcephalus, encephalitis, and gliosis. Commonly used cytokines detection methods included PCR, ELISA, Luminex xMAP multiplex platform, and PUREGene DNA Isolation System. Cytokine samples were mostly taken from blood and tissue. *Conclusion.* There is an interconnecting pathway of cytokines, neurological function (mainly dementia), and sleep habits in people living with HIV. Despite this, the mechanism of cytokines influencing sleep problems and neuropathological disorders remains unclear. Further research is warranted to determine the potential mechanisms and impact of cytokines associations in HIV progression.

Key words: HIV, AIDS, cytokines, infection, HIV infection, neuropathological disorder.

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ЦИТОКИНЫ И ВИЧ-АССОЦИИРОВАННЫЕ НЕВРОЛОГИЧЕСКИЕ ПРОЯВЛЕНИЯ: СИСТЕМАТИЧЕСКИЙ ОБЗОР

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Резюме. Цитокины играют ключевую роль в реакции иммунной системы на ВИЧ и в патогенезе ВИЧ-инфекции. Нарушение регуляции цитокинов сопровождается развитием заболевания и связанных с ним осложнений, что делает решающим понимание их роли в патогенезе ВИЧ для разработки эффективных терапевтических вмешательств против ВИЧ/СПИДа. В этой связи целью настоящего систематического обзора является изучение роли цитокинов в развитии неврологических проявлений, связанных с ВИЧ-инфекцией, и ее осложнений. *Материалы и методы.* Для изучения оригинальной англоязычной литературы, опубликованной до 10 сентября 2022 г., были использованы базы данных PubMed, Scopus, Web of Science и Embase. Подходящие статьи для оценки данных были проверены и отобраны в два этапа с использованием некоторых критериев включения/исключения, в соответствии с контрольным списком PRISMA и шкалой Ньюкасл–Оттава (NOS). *Результаты.* В обзор были включены 15 исследований. Было выявлено, что цитокины ассоциированы с нарушением сна и многочисленными неврологическими проявлениями. Наиболее распространенными неврологическими состояниями являются деменция, судороги, менингит, церебральный токсоплазмоз, микроцефалия, энцефалит и глиоз. Обычно используемые методы обнаружения цитокинов включают ПЦР, ИФА, мультиплексную платформу Luminex xMAP и систему выделения ДНК PUREGene. Содержание цитокинов главным образом оценивалось в образцах крови и тканей. *Заключение.* Существует взаимосвязанная ассоциация между цитокинами, неврологической функцией (в основном деменции) и режимом сна у людей, живущих с ВИЧ. Несмотря на это, механизм влияния цитокинов на сон и развитие нейрпатологических расстройств остается неясным. Необходимы дальнейшие исследования для определения потенциальных механизмов и влияния ассоциаций цитокинов на прогрессирование ВИЧ-инфекции.

Ключевые слова: ВИЧ, СПИД, цитокины, инфекция, ВИЧ-инфекция, нейрпатологическое расстройство.

Introduction

An estimated 38 million individuals worldwide are living with HIV, making it a major public health burden [24, 46]. The implementation of Highly Active Antiretroviral Therapy (HAART) has drastically improved survival rates [26, 41], however, people living with HIV (PLHIV) face ongoing challenges including immune system dysfunction, heightened vulnerability to opportunistic infections and malignancies, and complications involving both physical and mental health [25, 39].

Understanding the complex interactions between HIV and the immune system is crucial for optimizing treatment strategies [42]. Cytokines, which are signaling molecules released by immune cells, play a central role in modulating immune responses and are key players in the pathogenesis of HIV infection [30]. These cytokines mediate various immune responses that are central to the host's defense against HIV, including the activation and regulation

of T cells. A disturbance in this regulation often leads to immune system dysfunction, driving HIV progression [18].

HIV infection gradually decreases the quantity and ability of CD4⁺ T cells, which are essential for effectively responding to viral infections [27]. The dysregulation of cytokine production, including a reduction in Th1 cytokines (e.g., IFN γ and IL-2) and a rise in Th2 cytokines (e.g., IL-4 and IL-10), significantly contributes to the disease progression. Cytokine signaling aberrations contribute to chronic inflammation, tissue injury, and HIV-associated comorbidities [19]. Proinflammatory cytokines such as IL-6 and TNF further exacerbate immune dysfunction, contributing to chronic inflammation, tissue damage, and comorbid conditions like cardiovascular and neurocognitive disorders [51]. Moreover, even in the presence of ongoing antiretroviral therapy (ART), cytokine signaling abnormalities may sustain viral replication in lymphoid tissues, thereby preserving HIV reservoirs.

Table 1. Risk of bias assessment for the included studies

Reference	Selection Out of 4	Comparability Out of 2	Outcome Out of 3	Total Out of 9
[34]	3	1	2	6
[11]	4	1	2	7
[2]	3	2	3	8
[44]	3	2	3	8
[33]	3	0	3	6
[47]	3	2	2	7
[5]	3	2	3	8
[21]	3	2	2	7
[14]	2	2	3	7
[16]	3	2	3	8
[48]	4	1	3	8
[32]	4	0	2	6
[45]	3	2	2	7
[13]	4	1	3	8
[3]	4	1	3	8

Given the crucial role of cytokines in modulating the immune response in PLHIV, recent research has focused on their potential to serve as therapeutic targets [41]. Cytokines such as IL-10 and TGF- β , which have anti-inflammatory properties, can mitigate HIV-related inflammation and viral replication [18]. However, excessive production of these cytokines can also inhibit the immune system's ability to fight off the virus, thus allowing it to persist in the body despite treatment [18].

In addition to their role in immune regulation, cytokines are also implicated in HIV-associated neurological complications, including mental health disorders and neurocognitive decline [40]. HIV infection has been shown to affect cognitive function and mental health, leading to complications such as dementia, sleep disturbances, and other neurological deficits [48]. These issues arise in part from the interaction between proinflammatory cytokines and the central nervous system (CNS), as well as their contribution to chronic inflammation, which exacerbates neurocognitive impairments [40]. Despite recent attention to the role of cytokines on HIV, there is still a lack of a comprehensive study that thoroughly focuses on the interplay of cytokine systems and HIV-related neurological comorbidities in English or Russian. This systematic review, therefore, addresses this gap by exploring the linkage between cytokine dysregulation and HIV-related neurological conditions.

This review aims to systematically assess the roles of various cytokines in the pathogenesis of HIV infection, including their impact on immune function and mental health. By reviewing the available literature, this study aims to identify potential therapeutic

targets for the management of HIV-related complications, with a focus on neurocognitive and mental health disorders.

Materials and methods

A thorough examination of the current literature regarding the roles of various cytokines in HIV infection was conducted. To ensure reliable and authentic results The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist was followed. Additionally, the Newcastle-Ottawa Scale (NOS) was used to assess risk of bias (Table 1).

Data sources. Four online databases were explored including PubMed, Scopus, Web of Science, and Embase up until September 10, 2022 using keywords and their combinations. The search strategy employed is as follows:

A. “Cytokines” OR “cytokine” OR “Cytokine” [Title/Abstract]

B. “HIV” OR “Human immunodeficiency virus” [Title/Abstract]

C. [A] AND [B]

Study selection. Study screening and selection was completed through a two-step process. The initial step consisted of screening of articles based on title and abstract, which was complete by four research members. In the second step, five investigators reviewed and evaluated the full texts of the articles. Inclusion criteria were original articles in English that investigated cytokines in PLHIV. Studies involving non-human data (e.g., animals and/or *in vitro* investigations), unpublished, lacking accessible full texts, case series and reports, conference papers, and editorial letters were excluded.

Data extraction. Data extraction was conducted for studies that fulfilled the inclusion criteria. Five researchers extracted the essential data from the full texts. Other researchers checked duplications and other irrelevant data in the selected articles. Data extraction consisted of neurological manifestations associated with cytokines, detection methods and samples origin of cytokines, name of cytokine and cell source of cytokines production, and serum level of cytokines.

Quality assessment. The Newcastle–Ottawa Scale (NOS) was used to evaluate the selected studies' risk of bias. This assessment tool consists of three aspects with the maximum possible scores of 4, 2, and 3 for selection, comparability, and exposure/outcome, respectively. The maximum obtainable score for each study is 9.

Results

Study characteristics. The online database search retrieved 4441 articles. Following the screening of the obtained studies, 798 duplicates were eliminated. Subsequently, the titles and abstracts of the remained 3643 articles were examined and 2853 records were

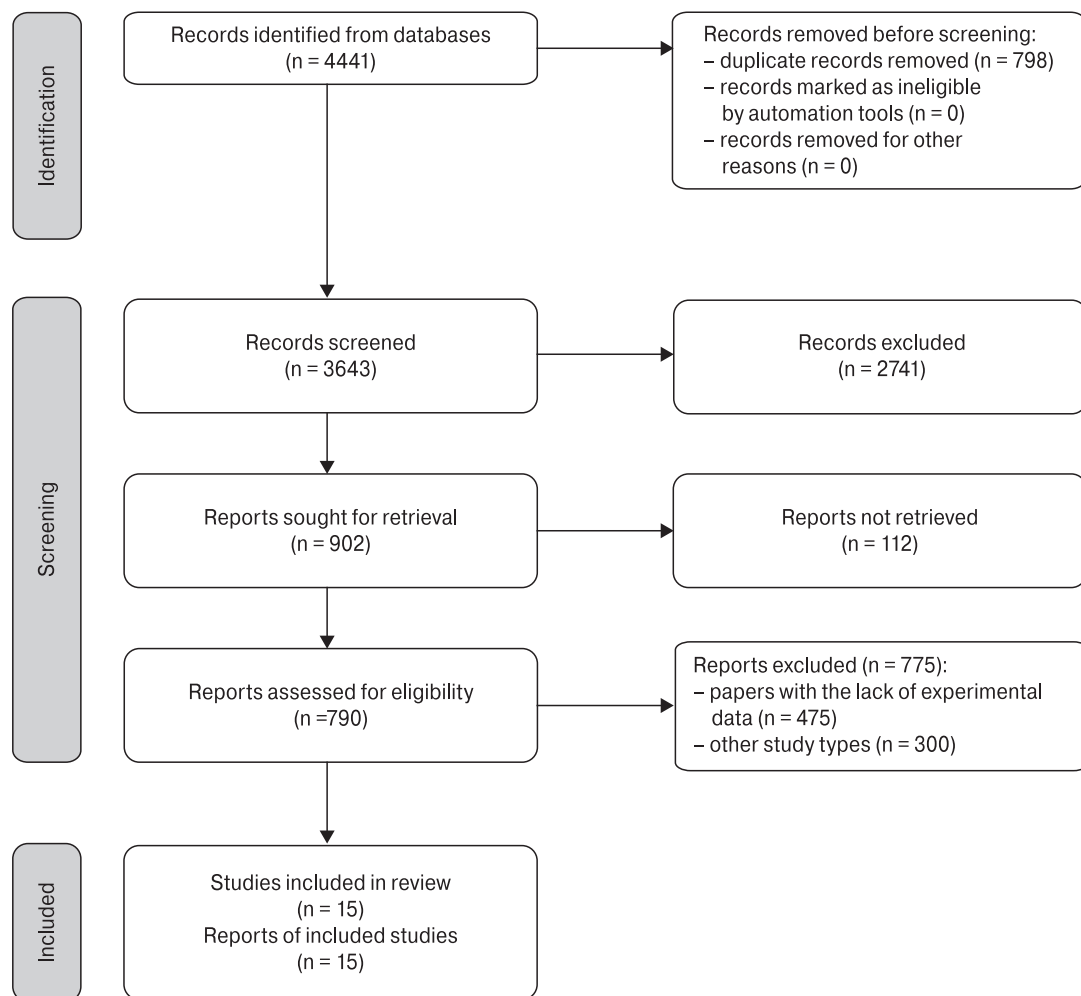


Figure 1. PRISMA flow diagram of study retrieval process

excluded. In the full-text evaluation of the 790 studies, 775 articles did not meet the inclusion criteria. Ultimately, 15 articles were included (Fig. 1).

Quality assessment. The details of the quality assessment of the selected studies are shown in Table 1. All the included studies had scores ranging from 6 to 9 in the NOS scale, demonstrating moderate to high quality of evidence.

The included studies were carried out in five countries, including the USA (n = 12), Germany (n = 1), Switzerland (n = 1), and Italy (n = 1). The year of publication for the included studies ranged from 1989 to 2018. The types of studies included were case-control (n = 5), cross-sectional (n = 5), cohort (n = 4), and interventional (n = 1).

This systematic review included studies regarding cytokine involvement in HIV-associated neurological complications. The findings demonstrate the major role of cytokines in neuroinflammation and HIV neuropathogenesis across varied populations and methodologies and serves cytokines as both diagnostic markers and therapeutic targets in addressing HIV-associated neurological complications.

Key neurological manifestations and cytokine associations. In the review of studies, it was found that cytokines are related to conditions such as sleep problems, dementia, seizures, meningitis, cerebral toxoplasmosis, microcephaly, encephalitis and gliosis, of which sleep problems are the most common. For example, Foster et al. demonstrated associations between higher levels of pro-inflammatory cytokines (e.g., IFN γ , IL-12, and TNF α) and altered sleep patterns, such as increased sleep duration and efficiency, yet poorer neurocognitive test performance. Byun et al. and Lee et al. discussed SNPs in cytokine-related genes e.g., IL1B, IL2, IL17A, IL1R2, and TNF α linked to sleep disturbances.

Neuroinflammatory cytokines, such as TNF α , iNOS, MIP-1 α , and MIP-1 β , were found to predominate in brain regions of individuals with HIV-associated dementia, as reported by Nuovo et al. Elevated IL-6 and IL-16 levels, noted in Gongvatana et al., correlated with brain structural abnormalities. Other findings emphasized that cytokines (e.g., IL-8 and MCP-1) remain elevated in monocyte cultures, even after cognitive improvement through cART.

Table 2. Summary of findings

Reference	Country	Type of study	Population	Mean age $\pm$ SD	Neurological manifestation	Detection methods of cytokines	Sample of cytokines detection	Evaluated cytokines and their cell sources	Serum level of cytokines	Main findings
[34]	USA	Case-Control	7 HIV+ and 5 HIV- controls	N/A	4 of 7 cases had symptoms: 2 had long-standing dementia 1 had severe motor and developmental skills retardation 1 had a 2-year history of seizure	RT in situ PCR from CNS biopsy of deceased participants	Cerebrum, cerebellum, and brain stem	TNF α , iNOS, MIP-1 α , MIP-1 β . Mostly microglial cells/macrophages or astrocytes, and occasionally neurons also expressed iNOS, MIP-1 α and MIP-1 β	N/A	Cytokine transcription was not found in the patients who did not have CNS-related presentations. TNF α , iNOS, MIP-1 α , MIP-1 β predominantly found in regions with a high density of virus-infected cells and less predominant in the cerebellum and midbrain of individuals with AIDS- associated dementia where viral-infected cells were less frequent. The primary contributors to AIDS dementia were extensive viral infection affecting microglia, neurons, and astrocytes, along with cytokine secretion by proximate uninfected cells
[11]	USA	Cohort	38 HIV+ and 35 HIV- controls	HIV+ cases: 13 ($\pm$ 2.5) HIV- controls: 13 ($\pm$ 3.2)	HIV-infected cases had worse working memory, higher mental fatigue scores, more self-reported issues with socio-emotional, behavioral, and executive function, higher total sleep time at night, daytime sleep, and sleep efficacy	Flow cytometry for both plasma and intracellular cytokine levels	Blood; plasma and intracellular cytokines	IL-10, IL-12, TNF α , and IFN γ Lymphocytes	Lower TNF α production and CD69 activation marker expression in stimulated CD4+ and CD8+ T cells. Higher levels of unstimulated IFN γ and TNF α in both CD4+ and CD8+ T cells	Elevated levels of pro-inflammatory cytokines (IFN γ , IL-12, and TNF α) were linked to variations in sleep duration, which in turn correlated with reduced performance on neurodevelopmental and neurocognitive assessments in HIV-infected patients
[2]	USA	Cohort	61 HIV+ cases including: 28 with HAND and 33 with NC	HAND: 34.0 years NC: 35.3 years	N/A	Multiplex assay (Luminex)	Blood	Fractalkine (CX3CL1), IFN γ , IL-2, IL-4, IL-6, IL-8, IL-10, IP-10, MCP-1, and TNF α . Cultured mononuclear cells	At baseline and even after one year of cART, cultured cells from HAND individuals exhibited significantly increased levels of IL-8 and MCP-1 compared to NC patients	During the one-year cART treatment, the cognitive status of 18 individuals transitioned from HAND to NC; however, the levels of IL-8 and MCP-1 produced by their monocytes remained elevated compared to those with NC. The levels of IL-8 and MCP-1 in CD14+ cultured cells did not show a correlation with the levels found in plasma or CSF. This research highlights a connection between monocyte-related neuropathogenesis in HIV patients

Reference	Country	Type of study	Population	Mean age±SD	Neurological manifestation	Detection methods of cytokines	Sample of cytokines detection	Evaluated cytokines and their cell sources	Serum level of cytokines	Main findings
[44]	USA	Case-Control	5 HIV+ with ANI, 9 HIV+ with MND/ HAD 5 HIV- with ALS 9 HIV- normal controls	Ranged between 31 to 57	N/A	Double-label immunochemistry	Occipital lobe brain cells	OPN Mainly expressed by resident macrophages/microglia, also by astrocytes, and unexpectedly by neurons	N/A	Levels of OPN in microglial cells from individuals with HIV+ANI and MND/HAD were higher than those in HIV-negative controls and similar to the expression observed in ALS. Within neurons, the HIV+ANI group exhibited the highest levels of OPN expression indicating that although HIV-infected macrophages are the primary source of OPN, resident CNS cells also produce this inflammatory cytokine at notable levels. In addition, astrocytes from individuals with HIV+ MND/HAD showed significantly elevated OPN levels compared to those observed in ALS samples. The persistent elevation of OPN levels, which correlates with the severity of impairment and is higher than in uninfected individuals, suggests that OPN remains consistently present in the brain parenchyma of patients with HAND
[33]	Germany	Cohort	33 HIV+ males	43.6±10.8	Neuropsychological Performance	Solid-phase protein array	Blood and CSF	IFN γ , IL-1 α , IL-2, IL-4, IL-5, IL-7, IL-12, CCL16, CXCL2, TGF- β , TIMP-1, ALCAM/CD166, CCL28, CNTF, and MMP-2	N/A	Most cytokines demonstrated a positive correlation with the duration of HIV infection, regardless of the type of received ART or whether having AIDS or non-AIDS conditions. In the Digit-Symbol Test, HIV patients were able to decode fewer symbols in 90 seconds when primarily inflammatory cytokines were present. Regarding basal ganglia movement control, contraction time analysis, a quicker contraction was observed with the neuroprotective and anti-inflammatory cytokines CNTF and IL-4, while a slower contraction was associated with MMP-2 and ALCAM. Additionally, MMP-2 correlated with diminished performance in the Grooved-Pegboard test (psychomotor speed). Rey-Osterrieth figure test (constructive apraxia), IL-12 was linked to decreased performance, indicating constructive apraxia in the CSF
[47]	USA	Cross-sectional	579 North Americans with high risk of HIV-1 including: 319 HIV+, 258 HIV-	N/A	N/A	PCR-based SNP Genotyping	Blood	IL-2, IL-4, IL-4R, IL-6, IL-10, IL-12 β , MCP-1, CCL5, SDF-1 α , IFN γ , IL-1 α , IL-1 β , IL-1R1, IL-1RA, and TGF- β 1 genes. Peripheral blood mononuclear cells	N/A	HIV-1-positive individuals showed significant differences compared to ethnically matched HIV-1-negative controls regarding several SNPs located at the IL-4, IL-4R, IL-6, IL-10, CCL5, and CXCL12 (SDF1) loci. The homozygous IL-4 -590T/T genotype was linked to greater CD4+ counts in adolescents infected with HIV-1 who were not undergoing ART and were free of AIDS. These findings suggest that genetic variations in IL-4 and IL-10 may be involved in the progression of HIV infection

Table 2. Summary of findings (continued)

Reference	Country	Type of study	Population	Mean age $\pm$ SD	Neurological manifestation	Detection methods of cytokines	Sample of cytokines detection	Evaluated cytokines and their cell sources	Serum level of cytokines	Main findings
[5]	USA	Cross-sectional	257 HIV+ adults	44.8 $\pm$ 8.6	Daytime napping	Luminex xMAP multiplex platform PUREGene DNA Isolation System	Blood	IFN γ , IFN γ R1, IL-1 β , IL-1R, IL-1R2, IL-2, IL-4, IL-6, IL-8, IL-10, NF- κ B1, NF- κ B2, and TNF α	Higher IL-1 β and IL-2 were observed in participants with longer daytime napping	Prolonged daytime napping was linked to 12 single nucleotide polymorphisms (SNPs) across seven genes: 1) IFN γ rs2069728; 2) IL-1 β with rs1143642, rs1143627, and rs16944; 3) IL-2 rs2069763; 4) IL-6 with rs4719714, rs1554606, and rs2069845; 5) IL-17A with rs3819024 and rs193036; 6) NF- κ B1 rs4648110; and 7) NF- κ B2 rs1056890
[21]	USA	Cross-sectional	289 adults with HIV/AIDS including 193 men, 73 women, and 23 transgenders	44.9 $\pm$ 8.4	Poor sleep maintenance	Luminex xMAP multiplex platform PUREGene DNA Isolation System	Blood	IL-1 β , IL-2, IL-6, IL-10, IL-13, and TNF α	TNF α plasma levels were lower in participants on ART, with CD4+ T-cell counts $\geq$ 200 cells/mm ³ , and with undetectable viral loads. Similar reductions were observed for IL-1 β and the IL-6/IL-10 ratio among participants with undetectable viral loads.	The most significant associations between inflammatory markers and WASO were observed with CRP and TNF α . A higher WASO% was linked to the SNPs IL-1R2 rs11674595 and TNF α rs1041981, whereas a lower WASO% was associated with IL-2 rs2069776. Both IL-1R2 rs11674595 and TNF α rs1041981 were found to be associated with shorter sleep duration
[14]	USA	Cross-sectional	307 adults with HIV/AIDS including: 212 men, 72 women, and 23 transgenders	44.9 $\pm$ 8.3	Sleep onset insomnia	Luminex xMAP multiplex platform PUREGene DNA Isolation System	Blood	IL-1 β , IL-2, IL-6, IL-10, IL-13, and TNF α	Plasma levels of IL-13 were significantly associated with SOI after adjustment. Other cytokine levels of IL-1 β , IL-2, IL-6, and TNF α , did not differ substantially between sleep groups.	After adjustment, four SNPs were significantly associated with SOI: IL-1 β rs1143642, IL-6 rs4719714, NF- κ B1 rs4648110, TNF α rs2857602

Reference	Country	Type of study	Population	Mean age±SD	Neurological manifestation	Detection methods of cytokines	Sample of cytokines detection	Evaluated cytokines and their cell sources	Serum level of cytokines	Main findings
[16]	USA	Cohort	74 medically stable HIV+ adults	45±9.66	N/A	multiplex bead array immunoassay (Luminex)	Blood	IFN γ , IL-1 β , IL-6, IL-8, IL-10, IL-16, IL-18, IP-10, MCP-1, MIP-1 β , SDF-1 α , TNF α , and TRAIL.		Higher levels of IFN γ , MCP-1, and TNF α were associated with increased volumes of the amygdala, putamen, WM, and GM, and pallidum. Elevated levels of IL-1 β , IL-6, IL-16, IL-18, IP-10, MIP-1 β , and SDF-1 α were correlated with reduced volumes in the hippocampus, pallidum, thalamus, putamen, WM, and GM, and amygdala as well as an increase in ventricular volume. IL-6 and IL-16 exhibited a strong linkage with brain volume metrics after controlling for other variables
[48]	USA	Interventional	Human astrocytes (primary and A172 cell line)	N/A	N/A	ELISA, Western Blot, RT-PCR	Brain	CXCL10 from A172 astrocytes Protein from both primary human astrocytes and A172 astrocytes	The combination of HIV-1 and the cytokine mix resulted in a notable increase in CXCL10 RNA in the treated cells	Astrocytes may be synergistically induced to produce CXCL10 at the RNA and protein levels by HIV-1, IFN γ , and TNF α , which can worsen the pathophysiology of HIV-associated dementia. Possible causes of this induction include signaling pathways such as JAK/STAT, MAPK, and PI3-K
[32]	USA	Case-Control	12 cART-treated donors and 35 healthy donors	47±8.68 (cART) 34.9±13.8 (healthy)	Neuroinflammation	AlphaLISA for cytokine production from Supernatant and lysates	Peripheral blood mononuclear cells	IL-1 β , IL-6, IL-18, CCL2, CXCL8, CXCL9, and CXCL10	N/A	In both healthy and under cART donors, dopamine treatment of human macrophages enhances the production of cytokines including IL-1 β , IL-6, IL-18, CCL2, CXCL8, CXCL9, and CXCL10. This suggests that Dopamine modulates cytokines, promoting inflammation in both chronic HIV infected individuals under viral suppression by cART and in healthy ones
[45]	USA	Case-control	7 HIV +, 11 HIV- controls	Controls ranged between 22–66	SAH, meningitis, dementia	IHC	Brain	IL-1 β , S100 β	N/A	Elevated levels of IL-1 α and S100 β plays a crucial role in neuropathogenesis of AIDS-related dementia by glial activation
[13]	Switzerland	Cross sectional	38 HIV-1 seropositive patients	N/A	5 had AIDS dementia complex, 9 CM, 6 CT, 1 AS, 1 progressive diffuse leukoencephalopathy, 1 microcephalus	Elisa, bioassay, and immunoassay	CSF and Serum	IL-1 β , IL-2, IL-6, TNF α	N/A	IL-6 was frequently correlated with IL-1 β and sIL2R in CSF, and with the synthesis of intrathecal IgG. IL-1 β and IL-6 were often found respectively in the CSF of 58% and 42% of HIV-1 patients, including those who were asymptomatic. TNF α and IL-2 were not detectable in the CSF

Table 2. Summary of findings (continued)

Reference	Country	Type of study	Population	Mean age $\pm$ SD	Neurological manifestation	Detection methods of cytokines	Sample of cytokines detection	Evaluated cytokines and their cell sources	Serum level of cytokines	Main findings
[3]	Italy	Case-control	59 participants including, 36 asymptomatic HIV-1 Positive, 8 AIDS patients with HIV-encephalitis, 10 AIDS patients without neuropathological changes, 5 normal controls	N/A	meningitis, microglia infiltrate, gliosis hypoxic changes	IHC and PCR	Brain	TNF α , IL-1 α , IL-4 and IL-6	N/A	Cytokines were predominantly identified within WM even at an early stage, indicating that their presence may already initiate a series of events resulting in brain injury

Note. Abbreviations: ALS: Amyotrophic Lateral Sclerosis, ANI: Asymptomatic Neurocognitive Impairment, ALCAM: Activated Leukocyte Cell Adhesion Molecule, APP: Amyloid Precursor Protein, ART: Antiretroviral Therapy, cART: Combination Antiretroviral Therapy, CM: Cryptococcal Meningitis, CNS: Central Nervous System, CNTF: Ciliary Neurotrophic Factor, CSF: Cerebrospinal Fluid, CT: Cerebral Toxoplasmosis, CXCL10: C-X-C Motif Chemokine Ligand 10, ELISA: Enzyme-Linked Immunosorbent Assay, GM: Gray Matter, HAND: HIV-Associated Neurocognitive Disorders, IFN γ : Interferon Gamma, IL: Interleukin, iNOS: Inducible Nitric Oxide Synthase, IP-10: Interferon Gamma-Induced Protein 10, MIP: Macrophage Inflammatory Protein, MMP: Matrix Metalloproteinase, NC: Neurocognitively Normal, NFKB: Nuclear Factor Kappa B, OPN: Osteopontin, PCR: Polymerase Chain Reaction, PLHIV: People Living with HIV, SNP: Single Nucleotide Polymorphism, SOI: Sleep Onset Insomnia, TNF α : Tumor Necrosis Factor Alpha, WASO: Wake After Sleep Onset, WM: White Matter.

Recurrence of IL-1 β , IL-6, and TNF α in blood, cerebrospinal fluid (CSF), and brain tissues linked these markers to disease severity. From other results obtained from the review of studies, basal ganglia movement control showed better performance in the presence of neuroprotective cytokines (CNTF and IL-4) and in the presence of inflammatory cytokines Matrix metalloproteinase-2 (MMP-2) while ALCAM got worse. Slow psychomotor speed was also observed in the presence of MMP-2. Nolan et al. explored dopamine's role in cytokine modulation, presenting pathways for chronic neuroinflammation management. Elevated CXCL10 signified HIV's effects on neuronal functionality through inflammation exacerbation demonstrated by Williams et al.

Detection methods and sample sources. The most commonly used detection methods were PCR, ELISA, Luminex xMAP multiplex platforms, and the PUREGene DNA Isolation System. Cytokines were primarily detected in blood, cerebrospinal fluid (CSF), and brain tissues. In addition, specific cytokines like CXCL10 were highly expressed in astrocytes in HIV dementia. Full details of the included studies are provided in Table 2.

Discussion

Since HIV-1 is a neurotropic virus, it can enter the CNS early in the infection process, resulting in neurologic disease as the only clinical manifestation of infection. The major findings of this study were that expression of cytokines including IFN γ , IL-1, IL-2, IL-4, IL-6, IL-10, IL-12, TNF α , and MMP-2 was correlated with HIV-related neurological issues, particularly dementia and sleep duration problems. Viral activation, inflammation, and tissue damage were found to be modulated by cytokine production in HIV pathophysiology.

1. First of all, the most imperative factor, Interleukin (IL), plays a vital role in the sleep pattern of PLHIV. Like other articles, this review confirmed that higher levels of the pro-inflammatory cytokines (IFN γ , IL-12, and TNF α) were linked to changes in sleep duration with a trend of higher total sleep time at night, daytime sleep, daytime napping, and sleep efficacy. For instance, Foster and colleagues reported a substantial direct and indirect connection between the production of intracellular cytokine and sleep duration and efficiency in HIV infected children [11]. Sleep disturbance was mostly related with short sleep duration and sleep onset insomnia; in agreement with studies, such as Gutierrez et al., where 73% of patients reported suffering from poor sleep quality and more than half experienced insomnia diagnosis criteria [17].

2. This study also shows that cytokines were responsible for poorer performance of HIV-infected individuals on neurodevelopment and neurocognitive tests. HIV-infected cases had worse working memory-mental (fatigue test scores) and had more

self-reported problems with socio-emotional, behavioral, and executive function; which was mentioned in other studies like, Cohen's comparison between HIV-infected children versus healthy controls matched with socioeconomic status [7].

3. In addition, these cytokines played a crucial role in a number of brain infections, such as SAH and Meningitis, HIV encephalitis, cryptococcal meningitis (CM), cerebral toxoplasmosis (CT), aseptic meningitis (AM), progressive diffuse leukoencephalopathy, and microcephalus (Gallo et al., 1989). In a study by Wolf et al., the importance of IL-12 activity and its interaction with other cytokines, such as IL-4 and IL-10, has illuminated to use for AIDS vaccine adjuvants to make direct immune response [22]. Moreover, other findings also recommend that IL-10 participates in different immunomodulatory roles in CNS diseases [37].

4. Additionally, the presence of cytokines may induce the sequence of events resulting in brain injury. For example, glial activation with elevated expression of IL-1 α and β -APP may be important in the neuropathogenesis of HIV-related dementia. A study by Mustafa et al. describes pathogenetic hypotheses for dementia in HIV patients [28]. Another study in the US, also proclaimed that higher levels of some cytokines lead to indirect mechanisms of brain dysfunction, such as HIV dementia [15].

Various inflammatory cytokines can cause or worsen HIV-related dementia. Massive viral replication in infected cells and cytokine secretion are the main causes of this phenomenon [34]. Also, it is mentioned that HIV-1 in collaboration with the cytokines IFN γ and TNF α can synergistically promote CXCL10 in human astrocytes aggravating AIDS dementia [49]. On the other hand, dopamine treatment in healthy and cART-treated donors promotes the production of inflammatory cytokines such as CXCL10 [32] which may worsen the situation. TNF is also associated with a series of events leading to brain injury in meningitis [40], and higher volumes of the putamen, amygdala, pallidum, GM, and WM [16]. Glial activation with elevated expression of IL1- α and β -APP may contribute to AIDS dementia [45]. The presence of neuroprotective cytokines IL-4 and CNTF helped basal ganglia movement, whereas slow contraction speed was observed in the presence of inflammatory cytokines ALCAM and MMP-2 [33]. Higher levels of the pro-inflammatory cytokines (IFN γ , IL-12, and TNF α) were associated with changes in sleep duration which itself was linked to poorer performance on neurodevelopment and neurocognitive tests in HIV-infected individuals [11]. Twelve SNPs from IFNG, IL1B, IL2, IL6, IL17A, NFKB1, and NFKB2 genes are related to long daytime napping [5]. Also, a positive feedback loop of NFKB2 production with IL-1 β , IL-6, and TNF α may cause extended cytokine production by peripheral blood monocytes, human fetal astrocytes, and THP-1 and U373 cells [29]. SNPs in IL1R2, TNF,

and IL2 are related to poor sleep maintenance and shifted WASO. Different TNF SNPs have unprincipled influences on WASO [21]. OPN is released by infiltrating macrophages and resident astrocytes and rises with HAND intensity. A high level of INFG is directly related to changes in sleep duration and poor performance in neurocognitive tests [11], lower marks in digit-symbol decoding tests [33], higher volumes of the putamen, pallidum, amygdala, gray matter, and white matter [3].

In addition to the contribution of cytokines to the neurological presentations of PLHIV, cytokine alteration patterns have also been observed in neurological complications associated with other RNA viruses. Several studies have suggested that cytokine storm is involved in the neurologic presentations of COVID-19, as higher levels of IL-2, IL-6, IL-8, IL-10, and IFN γ induced protein-10 (IP-10) have been identified in the CSF or serums of patients with virus-related encephalopathy [4, 10]. In addition, Espíndola and colleagues revealed that IL-2, IL-4, IL-6, IL-10, IL-12, chemokine (C-X-C motif) ligand 8 (CXCL8), and CXCL10 were elevated in COVID-19 patients with myelitis, encephalitis, meningoencephalitis, and acute disseminated encephalomyelitis (ADEM) [9]. Increased IL-6 levels have also been linked to disturbances in memory, cognition, and spatial learning in individuals with chronic hepatitis C virus (HCV) [1]. Identifying the cytokine cascade involved in the pathophysiology of neurological manifestations of viral infections may provide new therapeutic targets not only for HIV but also for other viral infections and improve patients' outcomes.

The results of the present review should be taken into account, with some limitations that must be considered. There was a modest number of included studies with relatively few participants and a lack of reporting of neurological changes in some studies.

Conclusion

In summary, previous studies demonstrated that polymorphisms in IL1R2, IL2, and TNF α genes were associated with changes in WASO% and sleep duration and elevated plasma levels of IL-13 along with polymorphism in IL1B, IL6, IL13, NFKB1, and TNF α genes was detected in SOI. Thus, we suggest that there is an interconnecting pathway of cytokines, neurological function (mainly dementia), and sleep habits in PLHIV. Despite this, the mechanism of cytokines influencing sleep problems and neuropathological disorders remains unclear, and further research is needed into these potential mechanisms. Further research is also needed in this area to determine whether or how these associations can affect HIV progression. The prevention of pro-inflammatory cytokine production could be achieved through better adherence to antiretroviral therapy. Yet, anti-inflammatory medications may be thera-

apeutically effective for decreasing sleep onset latency or higher sleep duration among HIV-positive adults due to their association with cytokine polymorphisms and sleeping problems.

Conflict of interest

The authors approve that they have no conflict of interest.

References

- Adinolfi L.E., Nevola R., Lus G., Restivo L., Guerrera B., Romano C., Zampino R., Rinaldi L., Sellitto A., Giordano M., Marrone A. Chronic hepatitis C virus infection and neurological and psychiatric disorders: an overview. *World J. Gastroenterol.*, 2015, vol. 21, no. 8, pp. 2269–2280. doi: 10.3748/wjg.v21.i8.2269
- Agsalda-Garcia M.A., Sithinamsuwan P., Valcour V.G., Chalermchai T., Tipsuk S., Kuroda J., Nakamura C., Ananworanich J., Zhang G., Schuetz A., Slike B.M., Shiramizu B.; SEARCH 011 Study Group. Brief report: CD14⁺ enriched peripheral cells secrete cytokines unique to HIV-associated neurocognitive disorders. *J. Acquir. Immune Defic. Syndr.*, 2017, vol. 74, no. 4, pp. 454–458. doi: 10.1097/QAI.0000000000001259
- An S.F., Ciardi A., Giometto B., Scaravilli T., Gray F., Scaravilli F. Investigation on the expression of major histocompatibility complex class II and cytokines and detection of HIV-1 DNA within brains of asymptomatic and symptomatic HIV-1-positive patients. *Acta. Neuropathol.*, 1996, vol. 91, no. 5, pp. 494–503. doi: 10.1007/s004010050457
- Benamer K., Agarwal A., Auld S.C., Butters M.P., Webster A.S., Ozturk T., Howell J.C., Bassit L.C., Velasquez A., Schinazi R.F., Mullins M.E., Hu W.T. Encephalopathy and encephalitis associated with cerebrospinal fluid cytokine alterations and coronavirus disease, Atlanta, Georgia, USA, 2020. *Emerg. Infect. Dis.*, 2020, vol. 26, no. 9, pp. 2016–2021. doi: 10.3201/eid2609.202122
- Byun E., Gay C.L., Portillo C.J., Pullinger C.R., Aouizerat B.E., Lee K.A. Cytokine polymorphisms are associated with daytime napping in adults living with HIV. *Sleep Med.*, 2017, vol. 32, pp. 162–170. doi: 10.1016/j.sleep.2016.12.021
- Catalfamo M., Le Saout C., Lane H.C. The role of cytokines in the pathogenesis and treatment of HIV infection. *Cytokine Growth Factor Rev.*, 2012, vol. 23, no. 4–5, pp. 207–214. doi: 10.1016/j.cytogfr.2012.05.007
- Cohen S., Ter Stege J.A., Geurtsen G.J., Scherpier H.J., Kuijpers T.W., Reiss P., Schmand B., Pakr D. Poorer cognitive performance in perinatally HIV-infected children versus healthy socioeconomically matched controls. *Clin. Infect. Dis.*, 2015, vol. 60, no. 7, pp. 1111–1119. doi: 10.1093/cid/ciu1144
- Deeks S.G., Tracy R., Douek D.C. Systemic effects of inflammation on health during chronic HIV infection. *Immunity*, 2013, vol. 39, no. 4, pp. 633–645. doi: 10.1016/j.immuni.2013.10.001
- Espindola O.M., Gomes Y.C.P., Brandão C.O., Torres R.C., Siqueira M., Soares C.N., Lima M.A.S.D., Leite A.C.C.B., Venturotti C.O., Carvalho A.J.C., Torezani G., Araujo A.Q.C., Silva M.T.T. Inflammatory cytokine patterns associated with neurological diseases in coronavirus disease 2019. *Ann. Neurol.*, 2021, vol. 89, no. 5, pp. 1041–1045. doi: 10.1002/ana.26041
- Farhadian S., Glick L.R., Vogels C.B.F., Thomas J., Chiarella J., Casanovas-Massana A., Zhou J., Odio C., Vijayakumar P., Geng B., Fournier J., Bermejo S., Fauver J.R., Alpert T., Wyllie A.L., Turcotte C., Steinle M., Paczkowski P., Dela Cruz C., Wilen C., Ko A.I., MacKay S., Grubaugh N.D., Spudich S., Barakat L.A. Acute encephalopathy with elevated CSF inflammatory markers as the initial presentation of COVID-19. *BMC Neurol.*, 2020, vol. 20, no. 1: 248. doi: 10.1186/s12883-020-01812-2
- Foster S.B., Lu M., Glaze D.G., Reuben J.M., Harris L.L., Cohen E.N., Lee B.N., Zhao E., Paul M.E., Schwarzwald H., McMullen-Jackson C., Clark C., Armstrong F.D., Brouwers P.Y., Miller T.L., Colin A.A., Scott G.B., Shahzeidi S., Willen E.J., Asthana D., Lipshultz S.E., Thompson B.W., Shearer W.T. Associations of cytokines, sleep patterns, and neurocognitive function in youth with HIV infection. *Clin. Immunol.*, 2012, vol. 144, no. 1, pp. 13–23. doi: 10.1016/j.clim.2012.04.004
- Gallo P., Sivieri S., Rinaldi L., Yan X.B., Lolli F., De Rossi A., Tavolato B. Intrathecal synthesis of interleukin-10 (IL-10) in viral and inflammatory diseases of the central nervous system. *J. Neurol. Sci.*, 1994, vol. 126, no. 1, pp. 49–53. doi: 10.1016/0022-510x(94)90093-0
- Gallo P., Frei K., Rordorf C., Lazdins J., Tavolato B., Fontana A. Human immunodeficiency virus type 1 (HIV-1) infection of the central nervous system: an evaluation of cytokines in cerebrospinal fluid. *J. Neuroimmunol.*, 1989, vol. 23, no. 2, pp. 109–16. doi: 10.1016/0165-5728(89)90029-5
- Gay C.L., Zak R.S., Lerdal A., Pullinger C.R., Aouizerat B.E., Lee K.A. Cytokine polymorphisms and plasma levels are associated with sleep onset insomnia in adults living with HIV/AIDS. *Brain Behav. Immun.*, 2015, vol. 47, pp. 58–65. doi: 10.1016/j.bbi.2014.11.018
- Glass J.D., Wesselingh S.L., Selnes O.A., McArthur J.C. Clinical-neuropathologic correlation in HIV-associated dementia. *Neurology*, 1993, vol. 43, no. 11, pp. 2230–2237. doi: 10.1212/wnl.43.11.2230
- Gongvatana A., Correia S., Dunsiger S., Gauthier L., Devlin K.N., Ross S., Navia B., Tashima K.T., DeLaMonte S., Cohen R.A. Plasma cytokine levels are related to brain volumes in HIV-infected individuals. *J. Neuroimmune Pharmacol.*, 2014, vol. 9, no. 5, pp. 740–750. doi: 10.1007/s11481-014-9567-8
- Gutierrez J., Tedaldi E.M., Armon C., Patel V., Hart R., Buchacz K. Sleep disturbances in HIV-infected patients associated with depression and high risk of obstructive sleep apnea. *SAGE Open Med.*, 2019, no. 7: 2050312119842268. doi: 10.1177/2050312119842268
- Jiang Y., Yang M., Sun X., Chen X., Ma M., Yin X., Qian S., Zhang Z., Fu Y., Liu J., Han X., Xu J., Shang H. IL-10+ NK and TGF- β + NK cells play negative regulatory roles in HIV infection. *BMC Infect. Dis.*, 2018, vol. 18, no. 1: 80. doi: 10.1186/s12879-018-2991-2
- Kaur R., Dhakad M.S., Goyal R., Bhalla P., Dewan R. Study of TH1/TH2 cytokine profiles in HIV/AIDS patients in a tertiary care hospital in India. *J. Med. Microbiol. Diagn.*, 2016, vol. 5. doi: 10.4172/2161-0703.1000214
- Kedzierska K., Crowe S.M. Cytokines and HIV-1: interactions and clinical implications. *Antivir. Chem. Chemother.*, 2001, vol. 12, no. 3, pp. 133–150. doi: 10.1177/095632020101200301
- Lee K.A., Gay C., Pullinger C.R., Hennessy M.D., Zak R.S., Aouizerat B.E. Cytokine polymorphisms are associated with poor sleep maintenance in adults living with human immunodeficiency virus/acquired immunodeficiency syndrome. *Sleep*, 2014, vol. 37, no. 3, pp. 453–463. doi: 10.5665/sleep.3474

22. Li S.S., Kochar N.K., Elizaga M., Hay C.M., Wilson G.J., Cohen K.W., De Rosa S.C., Xu R., Ota-Setlik A., Morris D., Finak G., Allen M., Tieu H.V., Frank I., Sobieszczyk M.E., Hannaman D., Gottardo R., Gilbert P.B., Tomaras G.D., Corey L., Clarke D.K., Egan M.A., Eldridge J.H., McElrath M.J., Frahm N.; NIAID HIV Vaccine Trials Network. DNA priming increases frequency of T-cell responses to a vesicular stomatitis virus HIV vaccine with specific enhancement of CD8⁺ T-cell responses by interleukin-12 plasmid DNA. *Clin. Vaccine Immunol.*, 2017, vol. 24, no. 11: e00263-17. doi: 10.1128/CDVI.00263-17
23. Luckheeram R.V., Zhou R., Verma A.D., Xia B. CD4⁺T cells: differentiation and functions. *Clin. Dev. Immunol.*, 2012, no. 2012: 925135. doi: 10.1155/2012/925135
24. Mehraeen E., Safdari R., Seyedalinaghi S.A., Mohammadzadeh N., Arji G. Identifying and validating requirements of a mobile-based self-management system for people living with HIV. *Stud. Health Technol. Inform.*, 2018, vol. 248, pp. 140–147.
25. Mehraeen E., Safdari R., Mohammadzadeh N., Seyedalinaghi S.A., Forootan S., Mohraz M. Mobile-based applications and functionalities for self-management of people living with HIV. *Stud. Health Technol. Inform.*, 2018, vol. 248, pp. 172–179.
26. Mehraeen E., Safdari R., SeyedAlinaghi S., Mohammadzadeh N. Exploring and prioritization of mobile-based self-management strategies for HIV Care. *Infect. Disord. Drug. Targets*, 2019, vol. 19, no. 3, pp. 288–296. doi: 10.2174/1871526518666181022113900
27. Mirzapour P., Motlagh F., SeyedAlinaghi S., Mehraeen E. Comparison of the effectiveness of positive thinking training and acceptance and commitment therapy on quality of life and resilience of people living with HIV. *HIV & AIDS Review*. 2022, vol. 21, no. 1, pp. 50–57. doi: 10.5114/hivar.2021.112404
28. Mustafa M., Musselman D., Jayaweera D., da Fonseca Ferreira A., Marzouka G., Dong C. HIV-associated neurocognitive disorder (HAND) and Alzheimer's disease pathogenesis: future directions for diagnosis and treatment. *Int. J. Mol. Sci.*, 2024, vol. 25, no. 20: 11170. doi: 10.3390/ijms252011170
29. Nath A., Conant K., Chen P., Scott C., Major E.O. Transient exposure to HIV-1 Tat protein results in cytokine production in macrophages and astrocytes. A hit and run phenomenon. *J. Biol. Chem.*, 1999, vol. 274, no. 24, pp. 17098–17102. doi: 10.1074/jbc.274.24.17098
30. Ngcobo S., Molatlhegi R.P., Osman F., Ngcapu S., Samsunder N., Garrett N.J., Abdool Karim S.S., Abdool Karim Q., McKinnon L.R., Sivo A. Pre-infection plasma cytokines and chemokines as predictors of HIV disease progression. *Sci. Rep.*, 2022, vol. 12, no. 1: 2437. doi: 10.1038/s41598-022-06532-w
31. Niakan S., Mehraeen E., Noori T., Gozali E. Web and mobile based HIV prevention and intervention programs pros and cons — a review. *Stud. Health Technol. Inform.*, 2017, vol. 236, pp. 319–327.
32. Nolan R.A., Muir R., Runner K., Haddad E.K., Gaskill P.J. Role of macrophage dopamine receptors in mediating cytokine production: implications for neuroinflammation in the context of HIV-associated neurocognitive disorders. *J. Neuroimmune Pharmacol.*, 2019, vol. 14, no. 1, pp. 134–156. doi: 10.1007/s11481-018-9825-2
33. Nolting T., Lindecke A., Hartung H.P., Koutsilieri E., Maschke M., Husstedt I.W., Sopper S., Stüve O., Arendt G.; German Competence Network HIV/AIDS. Cytokine levels in CSF and neuropsychological performance in HIV patients. *J. Neurovirol.*, 2012, vol. 18, no. 3, pp. 157–161. doi: 10.1007/s13365-012-0091-4
34. Nuovo G.J., Alfieri M.L. AIDS dementia is associated with massive, activated HIV-1 infection and concomitant expression of several cytokines. *Mol. Med.*, 1996, vol. 2, no. 3, pp. 358–366.
35. Okoye A.A., Picker L.J. CD4(+) T-cell depletion in HIV infection: mechanisms of immunological failure. *Immunol. Rev.*, 2013, vol. 254, no. 1, pp. 54–64. doi: 10.1111/imr.12066
36. Pelle M.T., Bazille C., Gray F. Neuropathology and HIV dementia. *Handb. Clin. Neurol.*, 2008, vol. 89, pp. 807–818. doi: 10.1016/S0072-9752(07)01270-5
37. Porro C., Cianciulli A., Panaro M.A. The Regulatory Role of IL-10 in neurodegenerative diseases. *Biomolecules*, 2020, vol. 10, no. 7: 1017. doi: 10.3390/biom10071017
38. Reuter M.A., Pombo C., Betts M.R. Cytokine production and dysregulation in HIV pathogenesis: lessons for development of therapeutics and vaccines. *Cytokine Growth Factor Rev.*, 2012, vol. 23, no. 4–5, pp. 181–191. doi: 10.1016/j.cytogr.2012.05.005
39. Rubinstein P.G., Aboulafia D.M., Zloza A. Malignancies in HIV/AIDS: from epidemiology to therapeutic challenges. *AIDS*, 2014, vol. 28, no. 4, pp. 453–465. doi: 10.1097/QAD.0000000000000071
40. Ruhanya V., Jacobs G.B., Paul R., Joska J., Seedat S., Nyandoro G., Engelbrecht S., Glashoff R.H. Plasma cytokine levels as predictors of global and domain-specific human immunodeficiency virus-associated neurocognitive impairment in treatment-naïve individuals. *J. Interferon Cytokine Res.*, 2021, vol. 41, no. 4, pp. 153–160. doi: 10.1089/jir.2020.0251
41. SeyedAlinaghi S., Karimi A., Barzegary A., Pashaei Z., Zargari G., Kianzad S., MohsseniPour M., Mirzapour P., Fakhfour A., Mehraeen E., Dadras O. Prevalence and reasons of loss to follow-up in HIV clinics: a systematic review of current evidence. *HIV & AIDS Review*, 2022, vol. 21, no. 3, pp. 179–190. doi: 10.5114/hivar.2022.117210
42. Shahmohamadi E., SeyedAlinaghi S., Karimi A., Behnezhad F., Mehraeen E., Dadras O. HIV/HTLV-1 co-infection: a systematic review of current evidence. *HIV & AIDS Review*, 2021, vol. 20, no. 3, pp. 158–165. doi: 10.5114/hivar.2021.108835
43. Siliciano J.D., Siliciano R.F. Recent developments in the effort to cure HIV infection: going beyond N = 1. *J. Clin. Invest.*, 2016, vol. 126, no. 2, pp. 409–414. doi: 10.1172/JCI86047
44. Silva K., Hope-Lucas C., White T., Hairston T.K., Rameau T., Brown A. Cortical neurons are a prominent source of the proinflammatory cytokine osteopontin in HIV-associated neurocognitive disorders. *J. Neurovirol.*, 2015, vol. 21, no. 2, pp. 174–185. doi: 10.1007/s13365-015-0317-3
45. Stanley L.C., Mrak R.E., Woody R.C., Perrot L.J., Zhang S., Marshak D.R., Nelson S.J., Griffin W.S. Glial cytokines as neuropathogenic factors in HIV infection: pathogenic similarities to Alzheimer's disease. *J. Neuropathol Exp Neurol.*, 1994, vol. 53, no. 3, pp. 231–238. doi: 10.1097/00005072-199405000-00003
46. Tian X., Chen J., Wang X., Xie Y., Zhang X., Han D., Fu H., Yin W., Wu N. Global, regional, and national HIV/AIDS disease burden levels and trends in 1990–2019: A systematic analysis for the global burden of disease 2019 study. *Front. Public Health*, 2023, no. 11: 1068664. doi: 10.3389/fpubh.2023.1068664
47. Wang C., Song W., Lobashevsky E., Wilson C.M., Douglas S.D., Mytilineos J., Schoenbaum E.E., Tang J., Kaslow R.A. Cytokine and chemokine gene polymorphisms among ethnically diverse North Americans with HIV-1 infection. *J. Acquir. Immune Defic. Syndr.*, 2004, vol. 35, no. 5, pp. 446–454. doi: 10.1097/00126334-200404150-00002

48. Watkins C.C., Treisman G.J. Cognitive impairment in patients with AIDS — prevalence and severity. *HIV AIDS (Auckl.)*, 2015, vol. 7, pp. 35–47. doi: 10.2147/HIV.S39665
49. Williams R., Dhillon N.K., Hegde S.T., Yao H., Peng F., Callen S., Chebloune Y., Davis R.L., Buch S.J. Proinflammatory cytokines and HIV-1 synergistically enhance CXCL10 expression in human astrocytes. *Glia*, 2009, vol. 57, no. 7, pp. 734–743. doi: 10.1002/glia.20801
50. Wolf S.F., Sieburth D., Sypek J. Interleukin 12: a key modulator of immune function. *Stem Cells*, 1994, vol. 12, no. 2, pp. 154–168. doi: 10.1002/stem.5530120203
51. Zicari S., Sessa L., Cotugno N., Ruggiero A., Morrocchi E., Concato C., Rocca S., Zangari P., Manno E.C., Palma P. Immune activation, inflammation, and non-AIDS co-morbidities in HIV-infected patients under long-term ART. *Viruses*, 2019, vol. 11, no. 3: 200. doi: 10.3390/v11030200

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