 10.15789/2220-7619-CAH-17533

CYTOKINES AND HIV ASSOCIATED NEUROLOGICAL MANIFESTATIONS: A SYSTEMATIC REVIEW

SeyedAlinaghi S.[a],

Afsahi A.M.[b],

Mirzapour P [a],

Alikarami S. [c],

Afzalian A [c],

Matini P.[d],

Mahrokhi S.[a],

Ali Z.[a],

Pashaei A. [a, e],

Eslami S.[c],

Vahedi F.[c],

Paranjkhoo P [f],

Habibi M. A. [g],

Molla A.[h],

Dadjou A.[h],

Parikhani S.N [c],

Mehraeen E. [i],

Hackett D., [j]

[a] Iranian Institute for Reduction of High Risk Behaviors, Tehran University of Medical Sciences, Tehran, Iran.

[b] University of California, San Diego (UCSD), California, USA.

[c] Tehran University of Medical Sciences, Tehran, Iran.

[d] Iran University of Medical Sciences, Tehran, Iran.

[e] University of British Columbia, Vancouver, Canada.

[f] American University of Armenia, Yerevan 0019, Armenia.

[g] Qom University of Medical Sciences, Qom, Iran.

 ISSN 2220-7619 (Print)
ISSN 2313-7398 (Online)

 10.15789/2220-7619-CAH-17533

[h] Bushehr University of Medical Sciences, Bushehr, Iran.

[i] Khalkhal University of Medical Sciences, Khalkhal, Iran.

[j] The University of Sydney, Sydney, New South Wales, Australia.

 ISSN 2220-7619 (Print)
ISSN 2313-7398 (Online)

 10.15789/2220-7619-CAH-17533

ЦИТОКИНЫ И ВИЧ-АССОЦИИРОВАННЫЕ НЕВРОЛОГИЧЕСКИЕ ПРОЯВЛЕНИЯ: СИСТЕМАТИЧЕСКИЙ ОБЗОР

Сейед Алинаги С.[1],

Афсахи А.М.[2],

Мирзапур П. [1],

Аликарами С. [3],

Афзалян А. [3],

Матини П.[4],

Махрохи С.[1],

Али З.[1],

Пашаи А.[1,5],

Эслами С.[3],

Вахеди Ф.[3],

Паранджху П. [6],

Хабиби М.А. [7],

Молла А.[8],

Даджу А.[8],

Парихани С.Н. [3],

Мехраин Э. [9],

Хакетт Д., [10]

[1] Иранский институт по снижению рискованного поведения, Тегеранский университет медицинских наук, Тегеран, Иран.

[2] Калифорнийский университет, Сан-Диего (UCSD), Калифорния, США.

[3] Тегеранский университет медицинских наук, Тегеран, Иран.

[4] Иранский университет медицинских наук, Тегеран, Иран.

[5] Университет Британской Колумбии, Ванкувер, Канада.

[6] Американский университет Армении, Ереван 0019, Армения.

[7] Университет медицинских наук Кум, Кум, Иран.

 ISSN 2220-7619 (Print)
ISSN 2313-7398 (Online)

 10.15789/2220-7619-CAH-17533

[8] Университет медицинских наук Бушер, Бушер, Иран.

[9] Университет медицинских наук Халхал, Халхал , Иран.

[10] Сиднейский университет, Сидней, Новый Южный Уэльс, Австралия.

 ISSN 2220-7619 (Print)
ISSN 2313-7398 (Online)

 10.15789/2220-7619-CAH-17533

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.

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.

Keywords: HIV, AIDS, Cytokines, Infection, HIV infection, Neuropathological disorder

 ISSN 2220-7619 (Print)
ISSN 2313-7398 (Online)

 10.15789/2220-7619-CAH-17533

Резюме

История вопроса: Цитокины играют ключевую роль в реакции иммунной системы на ВИЧ и в патогенезе ВИЧ-инфекции. Нарушение регуляции цитокинов может способствовать патогенезу заболевания и связанным с ним осложнениям, что делает решающим всестороннее понимание их роли для разработки эффективных терапевтических вмешательств против ВИЧ/СПИДа. В этой связи, целью настоящего систематического обзора является изучение роли цитокинов в неврологических проявлениях, связанных с ВИЧ-инфекцией, и связанных с ними осложнениями.

Методы: Базы данных PubMed, Scopus, Web of Science и Embase были использованы для изучения оригинальной англоязычной литературы, опубликованной до 10 сентября 2022 года. 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 распространенные неврологические состояния включают деменцию, судороги, менингит, церебральный токсоплазмоз, микроцефалию, 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 нейропатологические расстройства остается неясным. Необходимы

 ISSN 2220-7619 (Print)
ISSN 2313-7398 (Online)

 10.15789/2220-7619-CAH-17533

дальнейшие исследования для определения потенциальных механизмов и влияния ассоциаций цитокинов на прогрессирование ВИЧ-инфекции.

Ключевые слова: ВИЧ, СПИД, цитокины, инфекция, ВИЧ-инфекция, нейропатологическое расстройство

 ISSN 2220-7619 (Print)
ISSN 2313-7398 (Online)

 10.15789/2220-7619-CAH-17533

1. 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 (43).

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

 ISSN 2220-7619 (Print)
ISSN 2313-7398 (Online)

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.

1. 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)**.

2.1. 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]

2.2. 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.

1.3. 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.

2.4. 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.

Result

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 excluded. In the full-text evaluation of the 790 studies, 775 articles did not meet the inclusion criteria. Ultimately, 15 articles were included (**Figure 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 TNFα linked to sleep disturbances.

Neuroinflammatory cytokines, such as TNF-α, iNOS, MIP-1α, and MIP-1β, 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.

Recurrence of IL-1β, 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).

 10.15789/2220-7619-CAH-17533

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 (AS), 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 IL1-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-g and TNF-a 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

 ISSN 2220-7619 (Print)
ISSN 2313-7398 (Online)

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, IL-2, and TNFα 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 TNFα 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 therapeutically 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.

 10.15789/2220-7619-CAH-17533

ТАБЛИЦЫ

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

 ISSN 2220-7619 (Print)
ISSN 2313-7398 (Online)

 10.15789/2220-7619-CAH-17533

Table 2. Summary of findings

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
(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-la, MIP-113 mRNA. Mostly microglial cells/macrophages or astrocytes, and occasionally neurons also expressed iNOS, MIP-la and MIP-1β.	N/A	Cytokine transcription was not found in the patients who did not have CNS-related presentations. TNF-α, iNOS, MIP-1α, MIP-1β 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 (±2.5) HIV- controls 13 (±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.

 ISSN 2220-7619 (Print)
ISSN 2313-7398 (Online)

 10.15789/2220-7619-CAH-17533

(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.
(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-1a, 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

 ISSN 2220-7619 (Print)
ISSN 2313-7398 (Online)

 10.15789/2220-7619-CAH-17533

										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-12β, MCP-1, CCL5, SDF-1α, IFN-γ, IL-1α, IL-1β, IL-1R1, IL-1RA, and TGF-β1 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 IL4, IL4R, IL6, IL10, CCL5, and CXCL12 (SDF1) loci. The homozygous IL4 –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 IL4 and IL10 may be involved in the progression of HIV infection.
(5)	USA	Cross-sectional	257 HIV+ adults	44.8 ± 8.6	Daytime napping	Luminex xMAP multiplex platform PUREGene DNA Isolation System	Blood	IFN-γ, IFN-γ R1, IL1B, IL1R, IL1R2, IL2, IL4, IL6, IL8, IL10, NFKB1, NFKB2, and TNFα	Higher IL-1β 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) IL1B with rs1143642, rs1143627, and rs16944; 3) IL2 rs2069763; 4) IL6 with rs4719714, rs1554606, and rs2069845; 5) IL17A with rs3819024 and rs8193036; 6) NFKB1 rs4648110; and 7) NFKB2 rs1056890.
(21)	USA	Cross-sectional	289 adults with HIV/AIDS including 193 men, 73 women, and 23 transgenders	44.9 ±8.4	Poor sleep maintenance	Luminex xMAP multiplex platform PUREGene DNA Isolation System	Blood	IL-1β, 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 ≥ 200 cells/mm³, and with undetectable viral loads. Similar reductions were observed for IL-1β and the IL-6/IL-10 ratio among	The most significant associations between inflammatory markers and WASO were observed with CRP and TNFα. A higher WASO% was linked to the SNPs IL1R2 rs11674595 and TNFα rs1041981, whereas a lower WASO% was associated with IL2 rs2069776. Both IL1R2 rs11674595 and TNFα rs1041981 were found to be associated with shorter sleep duration.

 ISSN 2220-7619 (Print)
ISSN 2313-7398 (Online)

 10.15789/2220-7619-CAH-17533

									participants with undetectable viral loads.	
(14)	USA	Cross-sectional	307 adults with HIV/ AIDS including: 212 men, 72 women, and 23 transgenders	44.9 ±8.3	Sleep onset insomnia	Luminex xMAP multiplex platform PUREGene DNA Isolation System	Blood	IL-1β, 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-1β, IL-2, IL-6, and TNF-α, did not differ substantially between sleep groups.	After adjustment, four SNPs were significantly associated with SOI: IL1B rs1143642, IL6 rs4719714, NFKB1 rs4648110, TNFα rs2857602.
(16)	USA	Cohort	74 medically stable HIV+ adults	45 ± 9.66	N/A	multiplex bead array immunoassay (Luminex)	Blood	IFN-γ, IL-1β, IL-6, IL-8, IL-10, IL-16, IL-18, IP-10, MCP-1, MIP-1β, SDF-1α, 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-1β, IL-6, IL-16, IL-18, IP-10, MIP-1β, and SDF-1α, 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-a, 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	IL1β, IL6, IL18, CCL2, CXCL8, CXCL9, and CXCL10	N/A	In both healthy and under cART doners, dopamine treatment of human macrophages enhances the production of cytokines including IL-1β, IL-6, IL-18, CCL2, CXCL8, CXCL9, and CXCL10. This suggests that Dopamine modulates cytokines, promoting inflammation in both chronic HIV infected

 ISSN 2220-7619 (Print)
ISSN 2313-7398 (Online)

 10.15789/2220-7619-CAH-17533

										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	IL1α, S100β	N/A	Elevated levels of IL-1α and S100β 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	IL1β, IL2, IL6, TNFα	N/A	IL6 was frequently correlated with IL1β and sIL2R in CSF, and with the synthesis of intrathecal IgG. IL1β and IL6 were often found respectively in the CSF of 58% and 42% of HIV-1 patients, including those who were asymptomatic. TNFα and IL2 were not detectable in the CSF.
(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	TNFα, IL1α, IL4 and IL6	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

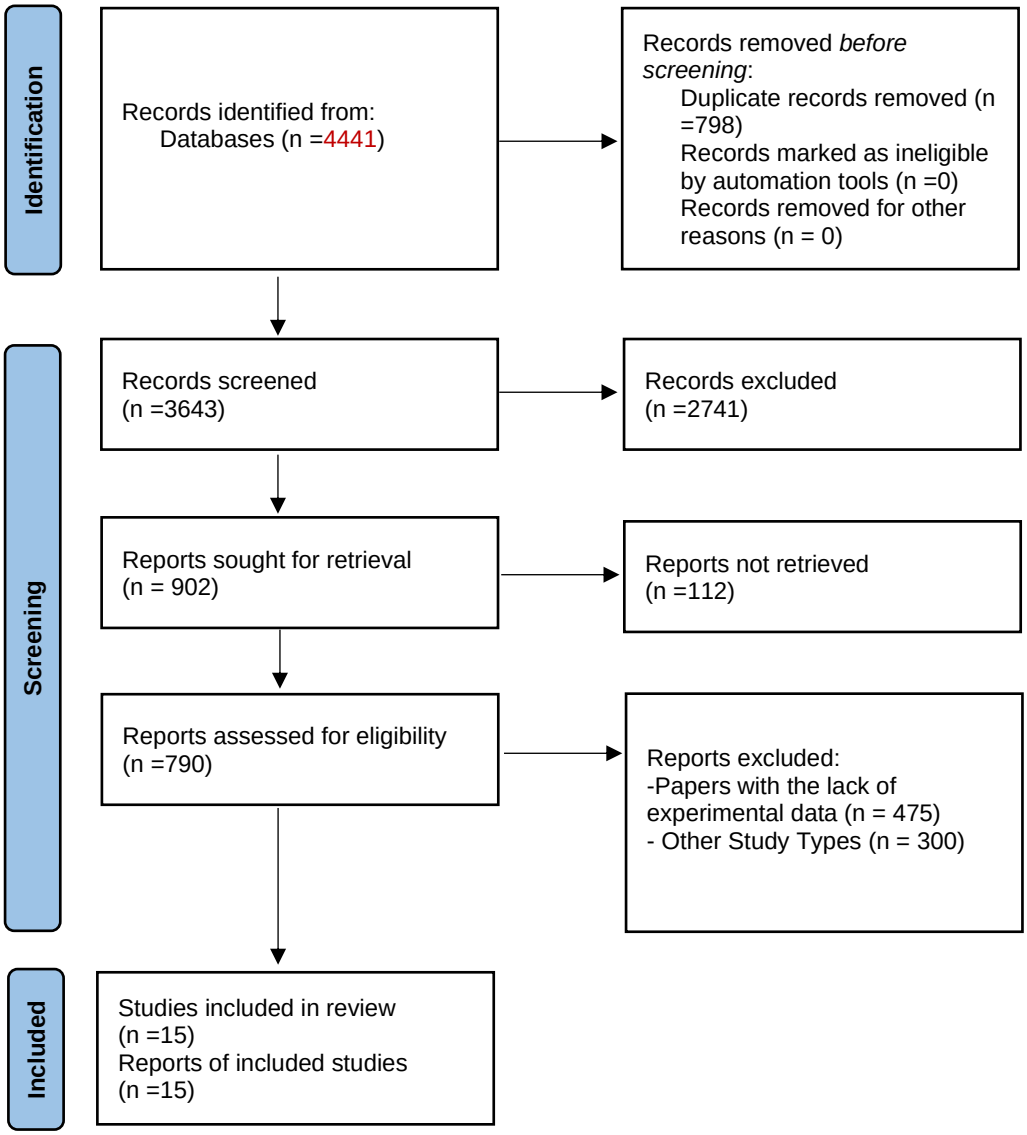
Abbreviations: ALS: Amyotrophic Lateral Sclerosis, ANI: Asymptomatic Neurocognitive Impairment, ALCAM: Activated Leukocyte Cell Adhesion Molecule, APP: Amyloid Precursor Protein, ART: Antiretroviral Therapy, cART: Combination Antiretroviral Therapy, CM: Cryptococcal Meningitis, CNS: Central Nervous System, 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.

 ISSN 2220-7619 (Print)
ISSN 2313-7398 (Online)

 10.15789/2220-7619-CAH-17533

РИСУНКИ

Figure 1 -PRISMA flow diagram of study retrieval process



 ISSN 2220-7619 (Print)
ISSN 2313-7398 (Online)

 10.15789/2220-7619-CAH-17533

ТИТУЛЬНЫЙ ЛИСТ_МЕТАДАННЫЕ

Блок 1. Информация об авторе ответственном за переписку

Esmaeil Mehraeen, PhD, Assistant Professor, Department of Health Information Technology, Khalkhal University of Medical Sciences, Khalkhal, Iran;
postal code: 5681761351;
telephone: +98-45-32426801;
fax: +98-45-32422305;
e-mail: es.mehraeen@gmail.com

Исмаил Мехраин, доктор философии, доцент кафедры информационных технологий здравоохранения, Университет медицинских наук Халхал, Халхал, Иран;
почтовый индекс: 5681761351;
телефон: +98-45-32426801;
факс: +98-45-32422305;
электронная почта: es.mehraeen@gmail.com

Блок 2. Информация об авторах

SeyedAhmad SeyedAlinaghi, MD, MPhil, PhD, Clinical Epidemiologist, Associate Professor, Research Deputy of Iranian Research Center for HIV/AIDS (IRCHA), Tehran University of Medical Sciences, Tehran, Iran;
СейедАхмад СейедАлинаги, к.м.н., магистр философии, клинический эпидемиолог, доцент, научный сотрудник Иранского исследовательского центра ВИЧ/СПИДа (IRCHA), Тегеранский университет медицинских наук, Тегеран, Иран;
Сиднейский университет, Сидней, Новый Южный Уэльс, Австралия;

Amir Masoud Afsahi, PhD, Assistant Professor, Department of Radiology, School of Medicine, University of California, San Diego (UCSD), California, USA;

 ISSN 2220-7619 (Print)
ISSN 2313-7398 (Online)

Амир Масуд Афсахи, доктор философии, доцент кафедры радиологии медицинского факультета Калифорнийского университета, Сан-Диего (UCSD), Калифорния, США;

Pegah Mirzapour, Postdoc Student, Research Deputy of Iranian Research Center for HIV/AIDS (IRCHA), Tehran University of Medical Sciences, Tehran, Iran;

Пега Мирзапур, аспирант, научный сотрудник Иранского исследовательского центра по ВИЧ/СПИДу (IRCHA), Тегеранский университет медицинских наук, Тегеран, Иран;

Sogol Alikarami, MD, Student, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran;

Согол Аликарами, студент, Медицинская школа, Тегеранский университет медицинских наук, Тегеран, Иран ;

Arian Afzalian, MD, Student, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran;

Ариан Афзалиан, студент, Медицинский факультет, Тегеранский университет медицинских наук, Тегеран, Иран;

Parisa Matini, MD, Student, School of Medicine, Iran University of Medical Sciences, Tehran, Iran

Париса Матини, студент, Медицинский факультет, Иранский университет медицинских наук, Тегеран, Иран

Sona Mahrokhi, MD, Student, Research Deputy of Iranian Research Center for HIV/AIDS (IRCHA), Tehran University of Medical Sciences, Tehran, Iran;

Сона Махрохи, заместитель по научной работе Иранского исследовательского центра по ВИЧ/СПИДу (IRCHA), Тегеранский медицинский университет, Тегеран, Иран;

Zoha Ali, MD, Student, Research Deputy of Iranian Research Center for HIV/AIDS (IRCHA), Tehran University of Medical Sciences, Tehran, Iran;
Зоха Али, заместитель по научной работе Иранского исследовательского центра по ВИЧ/СПИДу (IRCHA), Тегеранский медицинский университет Науки, Тегеран, Иран;

Ava Pashaei, PhD student, School of Nursing, University of British Columbia, Vancouver, Canada;
Ава Пашаи, аспирантка, Школа сестринского дела, Университет Британской Колумбии, Ванкувер, Канада;

Sepehr Eslami, MD, Student, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran;
Сепер Эслами, студент, Школа медицины, Тегеранский университет медицинских наук, Тегеран, Иран;

Farzin Vahedi, MD, Student, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran;
Фарзин Вахеди, студент, Школа медицины , Тегеранский университет медицинских наук, Тегеран, Иран;

Parinaz Paranjkhoo, MD, MPH, Student, Research Assistant, Turpanjian College of Health Sciences, American University of Armenia, Yerevan, Armenia;
Париназ Паранджху, магистр общественного здравоохранения, студент, научный сотрудник, Колледж медицинских наук Турпанджяна, Американский университет Армении, Ереван, Армения;

Mohammad Amin Habibi, MD, Student, Clinical Research Development Center, Qom University of Medical Sciences, Qom, Iran

Мохаммад Амин Хабиби, студент, Центр развития клинических исследований , Университет медицинских наук Кума, Кум, Иран

Ayoob Molla, Student, School of Medicine, Bushehr University of Medical Sciences, Bushehr, Iran;
Аюб Молла, студент, Медицинский факультет, Бушерский университет медицинских наук, Бушер, Иран;

Ali Dadjou, Student, School of Medicine, Bushehr University of Medical Sciences, Bushehr, Iran;
Али Даджоу, студент, Медицинский факультет, Бушерский университет медицинских наук, Бушер, Иран;

Sahar Nooralioghli Parikhani, BS in Nursing, Expert, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran;
Сахар Нооралиогли Парихани, бакалавр сестринского дела, эксперт медицинского факультета Тегеранского университета медицинских наук, Тегеран, Иран;

Daniel Hackett, PhD, Assistant Professor, Physical Activity, Lifestyle, Ageing and Wellbeing Faculty Research Group, School of Health Sciences, Faculty of Medicine and Health, The University of Sydney, Sydney, New South Wales, Australia;
Дэниел Хакетт, доктор философии, доцент, исследовательская группа факультета физической активности, образа жизни, старения и благополучия, Школа медицинских наук, факультет медицины и здравоохранения,

Блок 3. Метаданные статьи

CYTOKINES AND HIV ASSOCIATED NEUROLOGICAL MANIFESTATIONS: A SYSTEMATIC REVIEW

 10.15789/2220-7619-CAH-17533

ЦИТОКИНЫ И ВИЧ-АССОЦИИРОВАННЫЕ НЕВРОЛОГИЧЕСКИЕ ПРОЯВЛЕНИЯ: СИСТЕМАТИЧЕСКИЙ ОБЗОР

Сокращенное название статьи для верхнего колонтитула:

CYTOKINES IN NEUROLOGICAL MANIFESTATIONS

ЦИТОКИНЫ ПРИ НЕВРОЛОГИЧЕСКИХ ПРОЯВЛЕНИЯХ

Keywords: HIV, AIDS, Cytokines, Infection, HIV infection, Neuropathological disorder

Ключевые слова: ВИЧ, СПИД, цитокины, инфекция, ВИЧ-инфекция, нейропатологическое расстройство

Обзоры.

Количество страниц текста – 7, количество таблиц – 2, количество рисунков – 1.

14.11.2023.

 ISSN 2220-7619 (Print)
ISSN 2313-7398 (Online)

REFERENCES

No.	Authors, Title	Title of publication	DOI/URL
1	Adinolfi LE, Nevola R, Lus G, et al. Chronic hepatitis C virus infection and neurological and psychiatric disorders: an overview. World J Gastroenterol. 2015;21(8):2269-2280. doi:10.3748/wjg.v21.i8.2269. PMID: 25741133; PMCID: PMC4342902	World Journal of Gastroenterology	https://pubmed.ncbi.nlm.nih.gov/25741133/
2	Agsalda-Garcia MA, Sithinamsuwan P, Valcour VG, Chalermchai T, Tipsuk S, Kuroda J, Nakamura C, Ananworanich J, Zhang G, Schuetz A, Slike BM, 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 Apr 1;74(4):454-458. doi: 10.1097/QAI.0000000000001259. PMID: 28225719; PMCID: PMC5325111.	Journal of Acquired Immune Deficiency Syndromes	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5325111/
3	An SF, 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;91(5):494-503. doi: 10.1007/s004010050457. PMID: 8740230.	Acta Neuropathol	https://pubmed.ncbi.nlm.nih.gov/8740230/
4	Benameur K, Agarwal A, Auld SC, et al. Encephalopathy and Encephalitis Associated with Cerebrospinal Fluid Cytokine Alterations and Coronavirus Disease, Atlanta, Georgia, USA, 2020. Emerg Infect Dis. 2020;26(9):2016-2021. doi:10.3201/eid2609.202122. PMID: 32487282; PMCID: PMC7454059	Emerging Infectius Diseases	https://pubmed.ncbi.nlm.nih.gov/32487282/
5	Byun E, Gay CL, Portillo CJ, Pullinger CR, Aouizerat BE, Lee KA. Cytokine polymorphisms are associated with daytime napping in adults living with HIV. Sleep Med. 2017 Apr;32:162-170. doi: 10.1016/j.sleep.2016.12.021. Epub 2017 Jan 20. PMID: 28366330; PMCID: PMC5628054.	Sleep Medicine	https://pubmed.ncbi.nlm.nih.gov/28366330/
6	Catalfamo M, Le Saout C, Lane HC. The role of cytokines in the pathogenesis and treatment of HIV infection. Cytokine Growth Factor Rev. 2012 Aug-Oct;23(4-5):207-14. doi: 10.1016/j.cytogfr.2012.05.007. Epub 2012 Jun 26. PMID: 22738931; PMCID: PMC3726258.	Cytokine & Growth Factor Reviews	https://pubmed.ncbi.nlm.nih.gov/22738931/

7	Cohen S, Ter Stege JA, Geurtsen GJ, Scherpbier HJ, Kuijpers TW, Reiss P, Schmand B, Pajkrt D. Poorer cognitive performance in perinatally HIV-infected children versus healthy socioeconomically matched controls. Clin Infect Dis. 2015 Apr 1;60(7):1111-9. doi: 10.1093/cid/ciu1144. Epub 2014 Dec 16. PMID: 25516183.	Clinical Infectious Diseases	https://pubmed.ncbi.nlm.nih.gov/25516183/
8	Deeks SG, Tracy R, Douek DC. Systemic effects of inflammation on health during chronic HIV infection. Immunity. 2013 Oct 17;39(4):633-45. doi: 10.1016/j.immuni.2013.10.001. PMID: 24138880; PMCID: PMC4012895.	Immunity	https://pubmed.ncbi.nlm.nih.gov/24138880/
9	Espíndola OM, Gomes YCP, Brandão CO, et al. Inflammatory Cytokine Patterns Associated with Neurological Diseases in Coronavirus Disease 2019. Ann Neurol. 2021;89(5):1041-1045. doi:10.1002/ana.26041. PMID: 33547819; PMCID: PMC8014707	Annals of neurology	https://pubmed.ncbi.nlm.nih.gov/33547819/
10	Farhadian S, Glick LR, Vogels CBF, et al. Acute encephalopathy with elevated CSF inflammatory markers as the initial presentation of COVID-19. BMC Neurol. 2020;20(1):248. Published 2020 Jun 18. doi:10.1186/s12883-020-01812-2. PMID: 32552792; PMCID: PMC7301053	BMC Neurology	https://pubmed.ncbi.nlm.nih.gov/32552792/
11	Foster SB, Lu M, Glaze DG, Reuben JM, Harris LL, Cohen EN, Lee BN, Zhao E, Paul ME, Schwarzwald H, McMullen-Jackson C, Clark C, Armstrong FD, Brouwers PY, Miller TL, Colin AA, Scott GB, Shahzeidi S, Willen EJ, Asthana D, Lipshultz SE, Thompson BW, Shearer WT. Associations of cytokines, sleep patterns, and neurocognitive function in youth with HIV infection. Clin Immunol. 2012 Jul;144(1):13-23. doi: 10.1016/j.clim.2012.04.004. Epub 2012 May 2. PMID: 22659030; PMCID: PMC3377781.	Clinical Immunology	https://pubmed.ncbi.nlm.nih.gov/22659030/
12	Gallo P, Sivieri S, Rinaldi L, Yan XB, 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 Oct;126(1):49-53. doi: 10.1016/0022-510x(94)90093-0. PMID: 7836946.	The Journal of the Neurological Sciences	https://pubmed.ncbi.nlm.nih.gov/7836946/
13	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	Journal of Neuroimmunology	https://pubmed.ncbi.nlm.nih.gov/2656753/

	cerebrospinal fluid. J Neuroimmunol. 1989 Jul;23(2):109-16. doi: 10.1016/0165-5728(89)90029-5. PMID: 2656753.		
14	Gay CL, Zak RS, Lerdal A, Pullinger CR, Aouizerat BE, Lee KA. Cytokine polymorphisms and plasma levels are associated with sleep onset insomnia in adults living with HIV/AIDS. Brain Behav Immun. 2015 Jul;47:58-65. doi: 10.1016/j.bbi.2014.11.018. Epub 2014 Dec 20. PMID: 25535857; PMCID: PMC4468032.	Brain, Behavior, and Immunity	https://pubmed.ncbi.nlm.nih.gov/25535857/
15	Glass JD, Wesselingh SL, Selnes OA, McArthur JC. Clinical-neuropathologic correlation in HIV-associated dementia. Neurology. 1993 Nov;43(11):2230-7. doi: 10.1212/wnl.43.11.2230. PMID: 8232935.	Neurology	https://pubmed.ncbi.nlm.nih.gov/8232935/
16	Gongvatana A, Correia S, Dunsiger S, Gauthier L, Devlin KN, Ross S, Navia B, Tashima KT, DeLaMonte S, Cohen RA. Plasma cytokine levels are related to brain volumes in HIV-infected individuals. J Neuroimmune Pharmacol. 2014 Dec;9(5):740-50. doi: 10.1007/s11481-014-9567-8. Epub 2014 Oct 2. PMID: 25273619; PMCID: PMC4420709.	The Journal of Neuroimmune Pharmacology	https://pubmed.ncbi.nlm.nih.gov/25273619/
17	Gutierrez J, Tedaldi EM, 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 Apr 8;7:2050312119842268. doi: 10.1177/2050312119842268. PMID: 31001423; PMCID: PMC6454647.	SAGE Open Medicine	https://pubmed.ncbi.nlm.nih.gov/31001423/
18	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 Feb 13;18(1):80. doi: 10.1186/s12879-018-2991-2. PMID: 29439673; PMCID: PMC5812185.	BMC Infectious Diseases	https://pubmed.ncbi.nlm.nih.gov/29439673/
19	Kaur R, Dhakad MS, Goyal R, Bhalla P, Dewan R. Study of TH1/TH2 Cytokine Profiles in HIV/AIDS Patients in a TertiaryCare Hospital in India. Journal of Medical Microbiology and Diagnosis. 2016;5. doi:10.4172/2161-0703.1000214	Journal of Medical Microbiology and Diagnosis	Study of TH1/TH2 Cytokine Profiles in HIV/AIDS Patients in a Tertiary Care Hospital in India
20	Kedzierska K, Crowe SM. Cytokines and HIV-1: interactions and clinical implications. Antivir Chem Chemother. 2001 May;12(3):133-50. doi: 10.1177/095632020101200301. PMID: 12959322.	Antiviral Chemistry & Chemotherapy	https://pubmed.ncbi.nlm.nih.gov/12959322/

21	Lee KA, Gay C, Pullinger CR, Hennessy MD, Zak RS, Aouizerat BE. Cytokine polymorphisms are associated with poor sleep maintenance in adults living with human immunodeficiency virus/acquired immunodeficiency syndrome. Sleep. 2014 Mar 1;37(3):453-63. doi: 10.5665/sleep.3474. PMID: 24587567; PMCID: PMC3920310.	Sleep	https://pubmed.ncbi.nlm.nih.gov/24587567/
22	Li SS, Kochar NK, Elizaga M, Hay CM, Wilson GJ, Cohen KW, De Rosa SC, Xu R, Ota-Setlik A, Morris D, Finak G, Allen M, Tieu HV, Frank I, Sobieszczyk ME, Hannaman D, Gottardo R, Gilbert PB, Tomaras GD, Corey L, Clarke DK, Egan MA, Eldridge JH, McElrath MJ, 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 Nov 6;24(11):e00263-17. doi: 10.1128/CVI.00263-17. PMID: 28931520; PMCID: PMC5674193.	Clinical and Vaccine Immunology	https://pubmed.ncbi.nlm.nih.gov/28931520/
23	Luckheeram RV, Zhou R, Verma AD, Xia B. $CD4^+$T cells: differentiation and functions. Clin Dev Immunol. 2012;2012:925135. doi: 10.1155/2012/925135. Epub 2012 Mar 14. PMID: 22474485; PMCID: PMC3312336.	Clinical & Developmental Immunology	https://pubmed.ncbi.nlm.nih.gov/22474485/
24	Mehraeen E, Safdari R, Seyedalinaghi SA, 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;248:140-147. PMID: 29726430.	Studies in Health Technology and Informatics	https://pubmed.ncbi.nlm.nih.gov/29726430/
25	Mehraeen E, Safdari R, Mohammadzadeh N, Seyedalinaghi SA, Forootan S, Mohraz M. Mobile-Based Applications and Functionalities for Self-Management of People Living with HIV. Stud Health Technol Inform. 2018;248:172-179. PMID: 29726434.	Studies in Health Technology and Informatics	https://pubmed.ncbi.nlm.nih.gov/29726434/
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;19(3):288-296. doi: 10.2174/1871526518666181022113900. PMID: 30345930.	Infectious Disorders - Drug Targets	https://pubmed.ncbi.nlm.nih.gov/30345930/
27	Mirzapour P, Motlagh F, SeyedAlinaghi S, Mehraeen E. Comparison of the effectiveness of positive thinking training	HIV & AIDS Review. International Journal of HIV-Related Problems	https://www.termedia.pl/Comparison-of-the-effectiveness-of-positive-thinking-training-and-

	and acceptance and commitment therapy on quality of life and resilience of people living with HIV. HIV & AIDS Review. International Journal of HIV-Related Problems. 2022;21(1):50-57. doi:10.5114/hivar.2021.112404.		acceptance-and-commitment-therapy-on-quality-of-life-and-resilience-of-people-living-with-HIV,106,46103,0,1.html
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;25(20):11170. Published 2024 Oct 17. doi:10.3390/ijms252011170. PMID: 39456951; PMCID: PMC11508543	International Journal of Molecular Sciences	https://pubmed.ncbi.nlm.nih.gov/39456951/
29	Nath A, Conant K, Chen P, Scott C, Major EO. Transient exposure to HIV-1 Tat protein results in cytokine production in macrophages and astrocytes. A hit and run phenomenon. J Biol Chem. 1999 Jun 11;274(24):17098-102. doi: 10.1074/jbc.274.24.17098. PMID: 10358063.	Journal of Biological Chemistry	https://pubmed.ncbi.nlm.nih.gov/10358063/
30	Ngcobo S, Molatlhegi RP, Osman F, et al. Pre-infection plasma cytokines and chemokines as predictors of HIV disease progression. Sci Rep. 2022;12(1):2437. Published 2022 Feb 14. doi:10.1038/s41598-022-06532-w. PMID: 35165387; PMCID: PMC8844050	Scientific Reports	https://pubmed.ncbi.nlm.nih.gov/35165387/
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;236:319-327. PMID: 28508813.	Studies in Health Technology and Informatics	https://pubmed.ncbi.nlm.nih.gov/28508813/
32	Nolan RA, Muir R, Runner K, Haddad EK, Gaskill PJ. Role of Macrophage Dopamine Receptors in Mediating Cytokine Production: Implications for Neuroinflammation in the Context of HIV-Associated Neurocognitive Disorders. J Neuroimmune Pharmacol. 2019 Mar;14(1):134-156. doi: 10.1007/s11481-018-9825-2. Epub 2018 Dec 5. PMID: 30519866; PMCID: PMC6391172.	The Journal of Neuroimmune Pharmacology	https://pubmed.ncbi.nlm.nih.gov/30519866/
33	Nolting T, Lindecke A, Hartung HP, Koutsilieri E, Maschke M, Husstedt IW, Sopper S, Stüve O, Arendt G; German Competence Network HIV/AIDS. Cytokine levels in CSF and neuropsychological performance in HIV patients. J Neurovirol. 2012 Jun;18(3):157-61. doi: 10.1007/s13365-012-0091-4. Epub 2012 Apr 12. PMID: 22528475.	The Journal of NeuroVirology	https://pubmed.ncbi.nlm.nih.gov/22528475/

34	Nuovo GJ, Alfieri ML. AIDS dementia is associated with massive, activated HIV-1 infection and concomitant expression of several cytokines. Mol Med. 1996 May;2(3):358-66. PMID: 8784788; PMCID: PMC2230156.	Molecular Medicine	https://pubmed.ncbi.nlm.nih.gov/8784788/
35	Okoye AA, Picker LJ. CD4(+) T-cell depletion in HIV infection: mechanisms of immunological failure. Immunol Rev. 2013 Jul;254(1):54-64. doi: 10.1111/imr.12066. PMID: 23772614; PMCID: PMC3729334.	Immunological Reviews	https://pubmed.ncbi.nlm.nih.gov/23772614/
36	Pelle MT, Bazille C, Gray F. Neuropathology and HIV dementia. Handb Clin Neurol. 2008;89:807-18. doi: 10.1016/S0072-9752(07)01270-5. PMID: 18631796.	Handbook of Clinical Neurology	https://pubmed.ncbi.nlm.nih.gov/18631796/
37	Porro C, Cianciulli A, Panaro MA. The Regulatory Role of IL-10 in Neurodegenerative Diseases. Biomolecules. 2020 Jul 9;10(7):1017. doi: 10.3390/biom10071017. PMID: 32659950; PMCID: PMC7407888.	Biomolecules	https://pubmed.ncbi.nlm.nih.gov/32659950/
38	Reuter MA, Pombo C, Betts MR. Cytokine production and dysregulation in HIV pathogenesis: lessons for development of therapeutics and vaccines. Cytokine Growth Factor Rev. 2012 Aug-Oct;23(4-5):181-91. doi: 10.1016/j.cytogfr.2012.05.005. Epub 2012 Jun 27. PMID: 22743036; PMCID: PMC3582023.	Cytokine & Growth Factor Reviews	https://pubmed.ncbi.nlm.nih.gov/22743036/
39	Rubinstein PG, Aboulafia DM, Zloza A. Malignancies in HIV/AIDS: from epidemiology to therapeutic challenges. AIDS. 2014 Feb 20;28(4):453-65. doi: 10.1097/QAD.0000000000000071. PMID: 24401642; PMCID: PMC4501859.	AIDS	https://pubmed.ncbi.nlm.nih.gov/24401642/
40	Ruhanya V, Jacobs GB, Paul R, Joska J, Seedat S, Nyandoro G, Engelbrecht S, Glashoff RH. Plasma Cytokine Levels As Predictors of Global and Domain-Specific Human Immunodeficiency Virus-Associated Neurocognitive Impairment in Treatment-Naive Individuals. J Interferon Cytokine Res. 2021 Apr;41(4):153-160. doi: 10.1089/jir.2020.0251. PMID: 33885338. PMID: 33885338	J Interferon & Cytokine Research	https://pubmed.ncbi.nlm.nih.gov/33885338/
41	SeyedAlinaghi S, Karimi A, Barzegary A, Pashaei Z, Zargari G, Kianzad S et al. Prevalence and reasons of loss to follow-up in HIV clinics: a systematic review of current evidence. HIV & AIDS Review. International Journal of HIV-Related Problems. 2022;21(3):179-190. doi:10.5114/hivar.2022.117210.	HIV & AIDS Review. International Journal of HIV-Related Problems	https://www.termedia.pl/Prevalence-and-reasons-of-loss-to-follow-up-in-HIV-clinics-a-systematic-review-of-current-evidence,106,47259,1,1.html

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. International Journal of HIV-Related Problems. 2021;20(3):158-165. doi:10.5114/hivar.2021.108835.	HIV & AIDS Review. International Journal of HIV-Related Problems	https://www.termedia.pl/HIV-HTLV-1-co-infection-a-systematic-review-of-current-evidence,106,45060,1,1.html
43	Siliciano JD, Siliciano RF. Recent developments in the effort to cure HIV infection: going beyond N = 1. J Clin Invest. 2016 Feb;126(2):409-14. doi: 10.1172/JCI86047. Epub 2016 Feb 1. PMID: 26829622; PMCID: PMC4731192.	The Journal of Clinical Investigation	https://pubmed.ncbi.nlm.nih.gov/26829622/
44	Silva K, Hope-Lucas C, White T, Hairston TK, Rameau T, Brown A. Cortical neurons are a prominent source of the proinflammatory cytokine osteopontin in HIV-associated neurocognitive disorders. J Neurovirol. 2015 Apr;21(2):174-85. doi: 10.1007/s13365-015-0317-3. Epub 2015 Jan 31. PMID: 25636782; PMCID: PMC4372685.	The Journal of NeuroVirology	https://pubmed.ncbi.nlm.nih.gov/25636782/
45	Stanley LC, Mrak RE, Woody RC, Perrot LJ, Zhang S, Marshak DR, Nelson SJ, Griffin WS. Glial cytokines as neuropathogenic factors in HIV infection: pathogenic similarities to Alzheimer's disease. J Neuropathol Exp Neurol. 1994 May;53(3):231-8. doi: 10.1097/00005072-199405000-00003. PMID: 8176406.	The Journal of Neuropathology & Experimental Neurology	https://pubmed.ncbi.nlm.nih.gov/8176406/
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 Feb 15;11:1068664. doi: 10.3389/fpubh.2023.1068664. PMID: 36875364; PMCID: PMC9975742.	Frontiers in Public Health	https://pubmed.ncbi.nlm.nih.gov/36875364/
47	Wang C, Song W, Lobashevsky E, Wilson CM, Douglas SD, Mytilineos J, Schoenbaum EE, Tang J, Kaslow RA. Cytokine and chemokine gene polymorphisms among ethnically diverse North Americans with HIV-1 infection. J Acquir Immune Defic Syndr. 2004 Apr 15;35(5):446-54. doi: 10.1097/00126334-200404150-00002. PMID: 15021309.	Journal of Acquired Immune Deficiency Syndromes	https://pubmed.ncbi.nlm.nih.gov/15021309/
48	Watkins CC, Treisman GJ. Cognitive impairment in patients with AIDS - prevalence and severity. HIV AIDS (Auckl). 2015 Jan 29;7:35-47. doi: 10.2147/HIV.S39665. PMID: 25678819; PMCID: PMC4319681.	HIV/AIDS	https://pubmed.ncbi.nlm.nih.gov/25678819/
49	Williams R, Dhillon NK, Hegde ST, Yao H, Peng F, Callen S, Chebloune Y, Davis RL, Buch SJ. Proinflammatory cytokines	Glia	https://pubmed.ncbi.nlm.nih.gov/18985732/

	and HIV-1 synergistically enhance CXCL10 expression in human astrocytes. Glia. 2009 May;57(7):734-43. doi: 10.1002/glia.20801. PMID: 18985732; PMCID: PMC2667210.		
50	Wolf SF, Sieburth D, Sypek J. Interleukin 12: a key modulator of immune function. Stem Cells. 1994 Mar;12(2):154-68. doi: 10.1002/stem.5530120203. PMID: 7911046.	stem cells	https://pubmed.ncbi.nlm.nih.gov/7911046/
51	Zicari S, Sessa L, Cotugno N, Ruggiero A, Morrocchi E, Concato C, Rocca S, Zangari P, Manno EC, Palma P. Immune Activation, Inflammation, and Non-AIDS Co-Morbidities in HIV-Infected Patients under Long-Term ART. Viruses. 2019 Feb 27;11(3):200. doi: 10.3390/v11030200. PMID: 30818749; PMCID: PMC6466530.	Viruses	https://pubmed.ncbi.nlm.nih.gov/30818749/