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# ASSERTION OF A DIDACTIC ILLUSTRATION SCHEME OF THE IMMUNOLOGICAL RELATIONSHIP BETWEEN THE INDUCTION OF THE CCL5-CCR5 AXIS BY HIV-1 INFECTION AND NEUROAIDS

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**Abstract:** The occurrence of neurological illness in an HIV-positive individual can be result of the host immune response. C-C Chemokine Receptor 5 (CCR5) is the primary receptor for HIV-1 entry, and it orientates the functions of chemokines from the C-C class, including C-C Motif Chemokine Ligand 5 (CCL5/RANTES). This research sought to review and build a didactic model about the immunopathological relationship between the CCL5-CCR5 axis and neuroAIDS progression. This is a systematic review, according to PRISMA 2020, using articles between January 1990 and June 2023 in PUBMED, LILACS, MEDLINE, and SCIELO databases. The scheme construction was performed in Adobe Photoshop CS6 software. Regarding the data found, through the release of gp120 mediated by CCR5 activation in Central Nervous System-CNS cells, there is an increased secretion of CCL5/RANTES mRNA, which can oligomerize on the cell surface and act as a powerful modulator of neuroinflammation. The release of viral proteins, such as Tat, induced by the CCL5-CCR5 pathway causes reactivity in astrocytes, altering the porosity of the blood-brain barrier (BBB). Oligodendrocytes and neurons are directly affected by Tat, resulting in increased neuronal injury and mortality. Reactive oxygen species (ROS), reactive nitrogen species (RNS), neurotoxins, and proinflammatory mediators are all increased by chronic stimulation of activated microglia and these elements in macrophages cause apoptosis and damage to neuronal cells. Therefore, when high concentrations of CCL5/RANTES are present in HIV-1 infected ones, there is more intense inflammatory responses, such as, in neuroAIDS.

**Keywords:** HIV; neurological manifestations; CCR5; CCL5; immunity.

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## 1. Introduction

Acute, chronic, and AIDS are the three phases of HIV infection [1]. The progression of AIDS depends on complex interactions between host and virus, linked, above all, to viral load and immunodeficiency. In this sense, the most important characteristics for disease progression are immune activation and apoptosis. The virus searches for CD4

receptors and the gp120/gp41 Env glycoprotein after entering the host's body to penetrate immune cells and interfere with the body's immunological response [2].

HIV interacts with C-C chemokine receptor type 5 (CCR5) or C-X-C chemokine receptor type 4 (CXCR4), which serve as viral co-receptors, after employing CD4 cells as the main receptor. X4 viruses are isolates (usually M-tropic) that preferentially utilize CXCR4, R5 isolates are isolates (often M-tropic) that preferentially use CCR5, and R5X4 isolates are dual-tropic isolates that preferentially use both CCR5 and CXCR4. Co-receptor signaling may also contribute to ongoing neuroinflammation and indirect neurotoxicity, both of which may aid in the development of neuroAIDS [3,4].

CCR5 is the primary receptor for HIV-1 entry in cells when combined with the viral glycoprotein 120 (gp120). It orientates the functions of chemokines from the C-C class, including C-C Motif Chemokine Ligand 5 (CCL5/RANTES), which participates in defense against HIV-1 [5]. This research sought to review and build a didactic model about the immunopathological relationship between the CCL5-CCR5 axis and neuroAIDS progression.

## 2. Methods

This is a systematic review, according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020, using articles and reviews published in Portuguese, Spanish or English between January 1990 and June 2023 in PUBMED, LILACS, MEDLINE, and SCIELO databases through the descriptors: "HIV-1"; "CCR5"; "CCL5" and "Neurological Manifestations" [6]. To create the guiding question: "Which immunopathological features induced by CCL5-CCR5 immune axis in HIV-1 infected people provokes neuroAIDS progression?", the PICO strategy was used with the following anagrams: population, intervention, comparison, and outcome [7]. For Population, it was people infected with HIV-1; for Intervention, it was considered induction of the CCL5-CCR5 axis by this infection; for Comparation, it was immune response in these individuals; and Outcome was neuroAIDS progression.

Data were organized in Microsoft Office Excel 365, collecting the following information: (1) title, author, and year of publication; (2) database; (3) kind of study; (4) results relevant to the research topic. The extracted data were displayed in the study in tabular form. The methodological quality assessment was done through Joanna Briggs Institute (JBI) Checklists [8]. The scheme construction was performed in Adobe Photoshop CS6 software.

## 3. Results and Discussion

The sampling resulted in 36 articles. The major number of papers included was international, of English language, from the PUBMED database. Methodological quality was considered high for the included studies based on the observed JBI score.

When high concentrations of CCL5/RANTES are present in the body of those infected with the HIV virus, it presents more intense inflammatory responses in certain body regions, such as the onset of dementia in patients with HIV and adhesion of endothelial cells [9].

RANTES/CCL5 selectively activates the 3-kinase phosphatidylinositol (PI3K). In addition to being crucial to T-cell activation, the PI3K pathway also contributes to RANTES-induced chemotaxis and cell polarization. Besides that, various biochemical signals are induced by RANTES/CCL5, some of which are not activated by other chemokines. In particular, RANTES/CCL5 stimulates T cells in a manner akin to that of a mitogen (RANTES-activated human T lymphocytes) despite not being a T-cell mitogen phosphoinositide 3-kinase's function [10]. Additionally, through gp120-mediated rises in CCL5/RANTES mRNA, RANTES/CCL5 can oligomerize on the cell surface and act as a powerful modulator of inflammation, particularly neuroinflammation, and a contributor to neuroAIDS [11].

In this sense, Figure 1 explains the progression of neuroAIDS by the view of CCL5-CCR5 axis induction. The chronological stages of the image were represented by letters (A-Z) and it is described below.

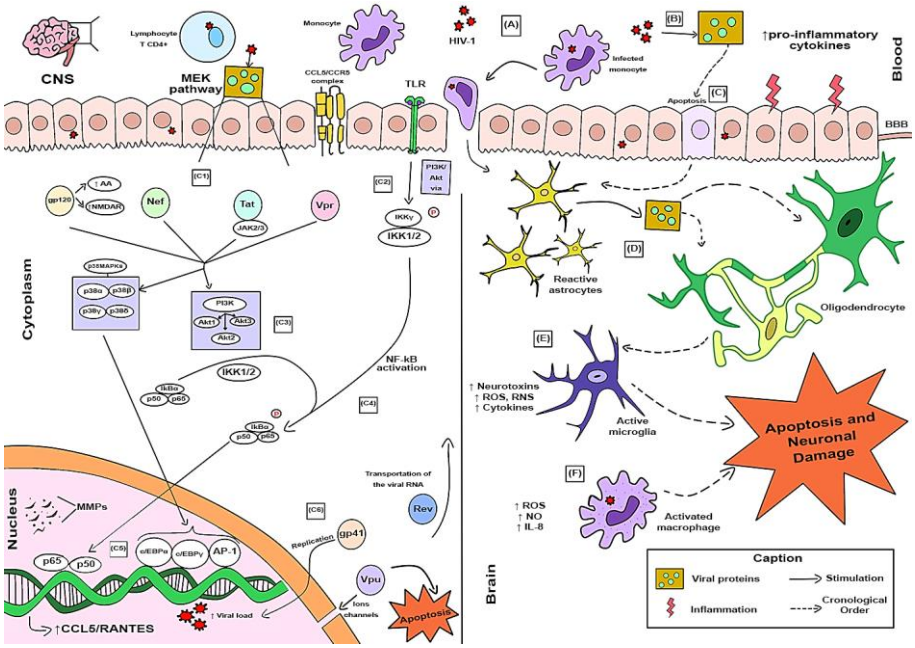


**Figure 1.** Illustrative scheme of CCL5-CCR5 axis induction by HIV-1 infection and HIV-1 neurotoxicity effects in molecular and cellular levels of the central nervous system (CNS).

It initiates with viral entry into host CNS cells, such as CD4+ T cells (by CCL5-CCR5 axis) and monocytes from the bloodstream, as well as blood-brain barrier (BBB) epithelial cells through pattern recognition and pathogen-associated molecular damage (PAMPs/DAMPs) in pattern recognition receptors (PRRs), such as Toll-like Receptors (TLRs) (A) [12]. Next, the viral replication process releases viral proteins that exacerbate the inflammatory process by increasing levels of inflammatory mediators (B) [13]. The BBB epithelial cell ends up undergoing apoptosis through molecular mechanisms of the inflammatory pathways involved, especially, NF-kB (C) [14].

These pathways are described in the following subtopics: (C1) in the cellular cytoplasm, viral proteins, such as Nef, Tat (together with costimulatory molecules JAK2/3), Vpr and gp120 (which releases archidonic acids - AA and quinolinic acids, such as N-methyl-d-aspartate (NMDA) receptor – NMDAR, associated with neurotoxicity in the cellular environment) act on joint pathways for secretion of molecules [15–18]; (C2) Meanwhile, TLRs activate the PI3K/Akt pathway, releasing IKK-gamma and IKK1/2 so that, simultaneously, (C3) these viral proteins activate PI3K/Akt molecules and p38MAPKs to also activate IKK1/2 [11]; Thus, (C4), there is phosphorylation of molecules related to the activation of the NF-kB pathway, which, (C5) release, in the nucleus, activated molecules, such as p65, p50, c/EBP-alpha, c/EBP-gamma and AP-1, with subsequent increased release of CCL5/RANTES and matrix metalloproteinases (MMPs) associated with neuroinflammation [19]; (C6) Other viral proteins, such as gp41, act by increasing the viral load in the cell through active replication and, consequently, generating an inflammatory cycle, in addition to the Rev protein acting by altering the splicing sites and transporting viral RNA again to the cytoplasm and the Vpu protein works by interfering with active transport ion channels (sodium and potassium pumps), which ultimately determines apoptosis [20–22].

Through the release of viral proteins like Tat, reactive astrocytes can cause epithelial cells to die, altering the porosity of the blood-brain barrier [23]. Oligodendrocytes and neurons are directly affected by the viral protein Tat, resulting in greater injury and

neuronal mortality (D) [24,25]. (E) Reactive oxygen species (ROS), reactive nitrogen species (RNS), neurotoxins, and proinflammatory mediators are all increased by chronic stimulation of activated microglia and (F) increased levels of ROS, nitric oxide (NO), interleukin (IL)-8 in macrophages that together cause apoptosis and damage to neuronal cells [26].

HIV is neurovirulent (causes illness of the nervous system), neurotrophic (can dwell in neural tissues), and neuroinvasive (can reach the CNS). The "Trojan horse" device, in which HIV-infected monocytes cross the blood-brain barrier and develop into long-lasting, persistently infected perivascular macrophages, infection of the choroid plexus, direct infection of capillary endothelial cells, and others are among the hypothesized mechanisms of CNS invasion. Capillary endothelium, microglia, monocytes, macrophages, astrocytes, and choroid plexus are some examples of HIV-infected cells. Although this is still up for debate, infections are thought to affect neurons and oligodendrocytes infrequently, if ever, and "indirect" mechanisms are thought to be responsible for most of the damage [27].

In primary infection, there is an abrupt increase of viral replication, which is followed by an aggressive immune response that gradually weakens, a protracted period of subclinical infection, the recurrence of disease, and death. Blood-brain barrier collapse, neuronal and axonal injury, neurotoxicity, and clinical symptoms are all caused by ongoing infection and inflammation; immune system damage, especially to cell-mediated immunity, makes people more susceptible to OI. White matter of the spinal cord and brain exhibits most neuropathological abnormalities of this condition, including perivascular cuffing, lymphocyte and monocyte infiltration, meningoencephalitis, glial nodules, astrocytosis, and demyelination [28].

In this context, HIV-associated neurocognitive disorders (HAND) are divided into three categories based on the decrescent seriousness of the clinical manifestations: HIV-associated dementia (HAD), mild neurocognitive disorder (MND), and asymptomatic neurocognitive impairment (ANI). HAD usually results in mortality within a year and is marked by an increase in loss of focus and concentration, noticeable motor slowing, and different behavioral characteristics. Generalized atrophy, alterations to the white matter that cause leukoencephalopathy, microglial nodules characteristic of viral encephalitis, and multinucleated giant cells that appear to be directly infected are all pathological changes in the brain that are linked to this condition [29].

Regarding pathology, the motor systems of the pyramidal and extrapyramidal lobes can be significantly impacted by HIV. Ataxia, motor slowness, incoordination, and tremor are some of the milder signs of CNS motor dysfunction. This might worsen into paraparesis, extrapyramidal movement abnormalities, crippling weakness, and stiffness. Apathy, impatience, and psychomotor retardation are some of the behavioral consequences of HAND, which can be misinterpreted for depression [30].

Given the prevalence of major depression and dysthymia in the HIV population and the possibility of HIV infection in many of the symptoms asked about in depression screening tools, such as appetite loss, this is challenging to separate. AIDS patients can have "manic" symptoms. Once more, this needs to be distinguished from an underlying bipolar disease or a pharmacological response. Patients with poorly managed illnesses, concomitant cognitive impairments, irritability, aggressiveness, and talkativeness are more likely to have so-called "secondary" or AIDS mania as well as hallucinations and paranoia [31].

## 4. Conclusion

The molecular mechanisms and cellular damages in CNS cells were described in the perspective of the CCL5-CCR5 axis induction of immune response. Therefore, when high concentrations of CCL5/RANTES are present in the body of HIV-1 infected ones, there is

production of more intense inflammatory responses in certain regions of the body, culminating, for example, in the onset of dementia in these patients.

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