Inflamación y Trastornos Cognitivos en la Infección por VIH

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Fundació Lluita contra les Infeccions
Servei de Malalties Infeccioses
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- - -
Universitat Oberta de Catalunya (UOC)

1. Trastornos Cognitivos en la Infección por VIH

2. VIH e Inflamación

3. Inflamación y Cerebro en la Infección por VIH

1. Trastornos Cognitivos en la Infección por VIH

Un Poco de Historia...

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Annals of NEUROLOGY
An Official Journal of the American Neurological Association and the Child Neurology Society
ANA AMERICAN NEUROLOGICAL ASSOCIATION

Original Article

The AIDS dementia complex: I. Clinical features

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> J Neuropsychiatry Clin Neurosci. 1989 Summer;1(3):296-302. doi: 10.1176/jnp.1.3.296.

Neuropsychological function in physically asymptomatic, HIV-seropositive men

S Perry [1], D Belsky-Barr, W B Barr, L Jacobsberg

above the cut-off (p = .02). The data suggest that a subpopulation of HIV-infected adults may exhibit subtle neuropsychological impairment before they develop clinical signs of cognitive deficit or immunosuppression.

> J Neuropsychiatry Clin Neurosci. 1991 Fall;3(4):422-8. doi: 10.1176/jnp.3.4.422.

Neuropsychological abnormalities in asymptomatic HIV seropositive military personnel

L E Klusman [1], J M Moulton, L K Hornbostel, J J Picano, M T Beattie

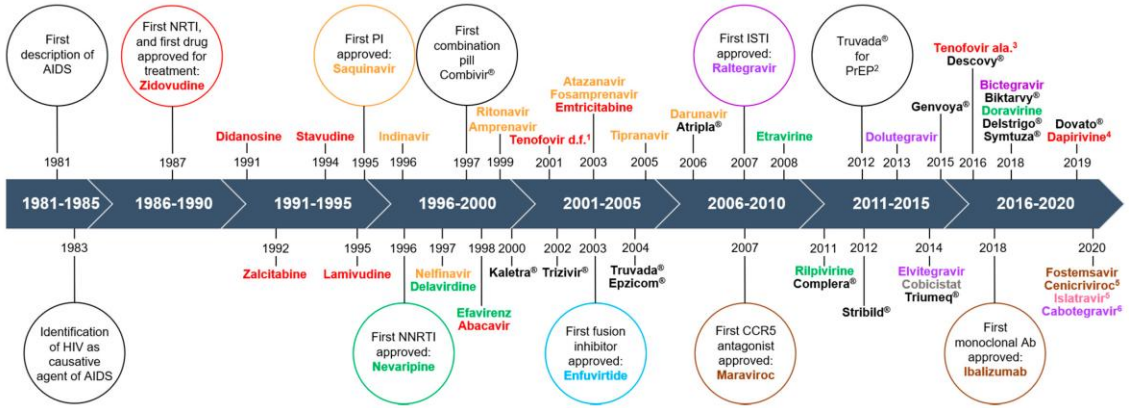
Review > J Int Neuropsychol Soc. 1995 May;1(3):304-15. doi: 10.1017/s1355617700000308.

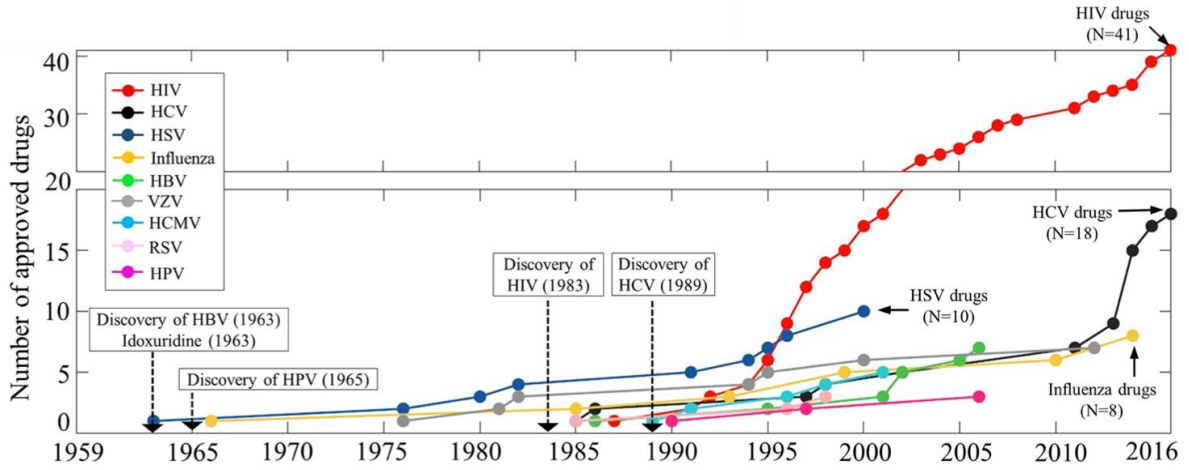
Neuropsychological studies of asymptomatic human immunodeficiency virus-type-1 infected individuals. The HNRC Group. HIV Neurobehavioral Research Center

D A White [1], R K Heaton, A U Monsch

seropositive asymptomatic and seronegative individuals. Overall, the differences observed between median rates of impairment for asymptomatic (35%) and seronegative (12%) groups provided the clearest indication of deficits in asymptomatics. In addition, five variables were

Actualidad: Año 2025





Medicalising normality? Using a simulated dataset to assess the performance of different diagnostic criteria of HIV-associated cognitive impairment

Jonathan Underwood [1], Davide De Francesco [2], Robert Leech [3], Caroline A Sabin [2], Alan Winston [1]; Pharmacokinetic and Clinical Observations in PeoPle Over fiftY (POPPY) study

> PLoS One. 2018 Apr 11;13(4)

Moving on From HAND: Why We Need New Criteria for Cognitive Impairment in Persons Living With Human Immunodeficiency Virus and a Proposed Way Forward

Sam Nightingale,[1] Anna J. Dreyer,[1] Deanna Saylor,[2,3] Magnus Gisslén,[4,5] Alan Winston,[6,7] and John A. Joska[1]

> Clin Infect Dis. 2021 Sep 15;73(6):1113-1118.

nature reviews neurology

2024 Feb;20(2):127-128.

Cognitive criteria in HIV: greater consensus is needed

Lucette A Cysique [1 2 3 4 5], Bruce J Brew [6 7], Jane Bruning [8], Desiree Byrd [9 10], Jane Costello [11], Kirstie Daken [12], Ronald J Ellis [13], Pariya L Fazeli [14], Karl Goodkin [15], Hetta Gouse [16], Robert K Heaton [13], Scott Letendre [13], Jules Levin [17], Htein Linn Aung [18], Monica Rivera Mindt [9 19], David Moore [13], Amy B Mullens [12], Sérgio Monteiro de Almeida [20], Jose A Muñoz-Moreno [21], Chrispher Power [22], Reuben N Robbins [23], John Rule [24], Reena Rajasuriar [25], Micah J Savin [26], Jeff Taylor [27], Mattia Trunfio [13 28], David E Vance [14], Pui Li Wong [25], Steven P Woods [29], Edwina J Wright [30 31 32 33], Sean B Rourke [34 35]

Guías Clínicas Actuales

Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents With HIV

Developed by the HHS Panel on Antiretroviral Guidelines for Adults and Adolescents—A Working Group of the NIH Office of AIDS Research Advisory Council (OARAC)

September 2024

Neurological Symptoms in People With HIV on Antiretroviral Therapy

Evidence is currently not available to support empiric intensification or switch of ARV regimens in people on systemically suppressive ART with mild neurological and/or cognitive symptoms who do not have documented CSF escape. Such individuals should be referred for neurological evaluation to

Adherence Concerns

Suboptimal adherence to ART is the most common cause of treatment failure. Although most older people with HIV are able to achieve viral suppression with a single-tablet regimen, some people who have a long history of ART may have acquired drug resistance, thus requiring more complex multiple-pill regimens. Complex dosing requirements, high pill burden, polypharmacy, inability to access medications because of cost or availability, limited health literacy (including misunderstanding of instructions), depression, substance use, frailty, and neurocognitive impairment

Cerebrospinal Fluid Viral Escape

Presentation with new-onset central nervous system (CNS) signs and symptoms has been reported as a rare form of "compartmentalized" virologic failure. People experiencing this present with new,

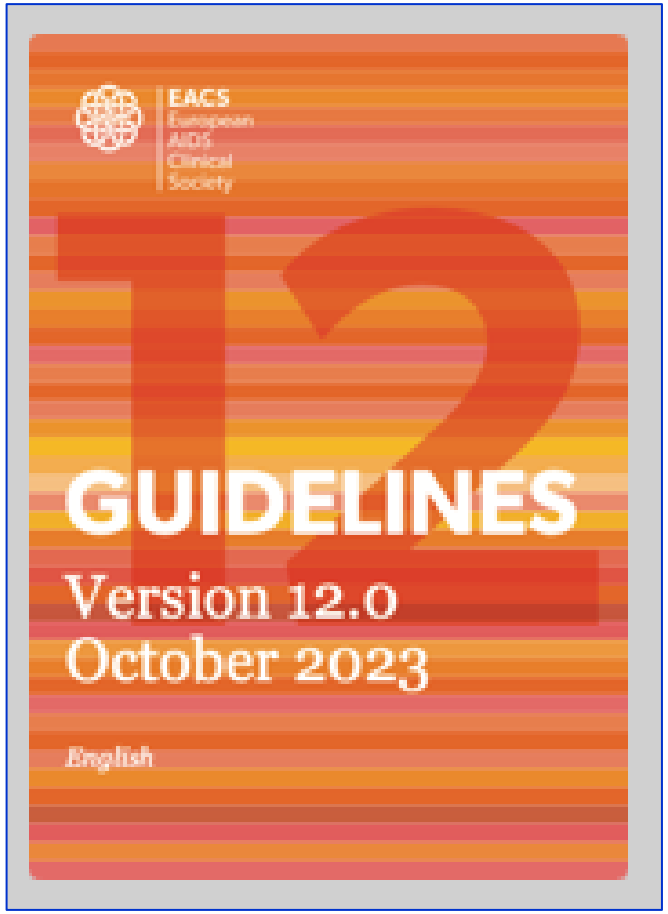
Neurocognitive Impairment in the Older Person With HIV

Cognitive impairment in people with HIV can manifest as difficulty with memory, attention, speed of information processing, and executive and motor functions. Studies that use neuropsychological testing to define categories of impaired cognition—termed HIV-associated neurocognitive disorder (HAND)—find that up to 30% of people with HIV on virally suppressive ART meet these research-based criteria[144], although these categories have not been validated for use in clinical practice. Research studies also demonstrate a steeper decline in performance on neuropsychological

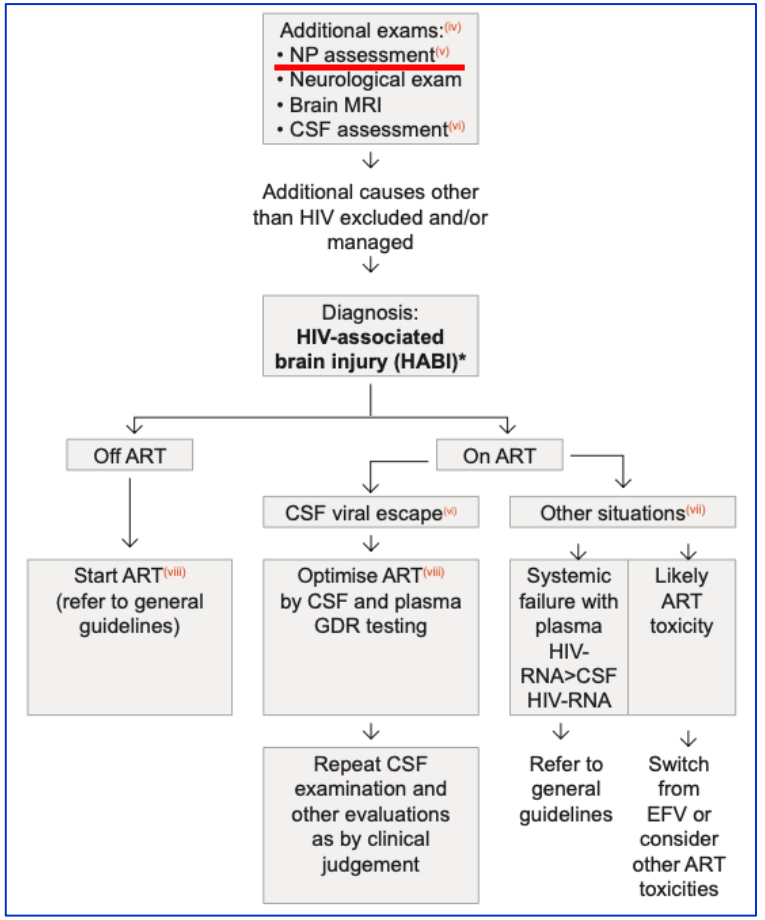
Polypharmacy in Older People With HIV

In people aging with HIV, the effects of polypharmacy, including the use of drugs that affect neurocognitive function, can contribute to serious adverse outcomes, such as serious falls and fractures, delirium, hospitalization (including intensive care unit admissions), and death.[52-57]

Guías Clínicas Actuales



Algorithm for Diagnosis and Management of Cognitive and Central Nervous System Neurological Symptoms



Guías Clínicas Actuales

GeSIDA
GRUPO DE ESTUDIO DEL SIDA-SEIMC

GOBIERNO DE ESPAÑA · MINISTERIO DE SANIDAD, CONSUMO Y BIENESTAR SOCIAL

DOCUMENTO DE CONSENSO SOBRE EL MANEJO CLÍNICO DE LA COMORBILIDAD NEUROPSIQUIÁTRICA Y COGNITIVA ASOCIADA A LA INFECCIÓN POR VIH-1

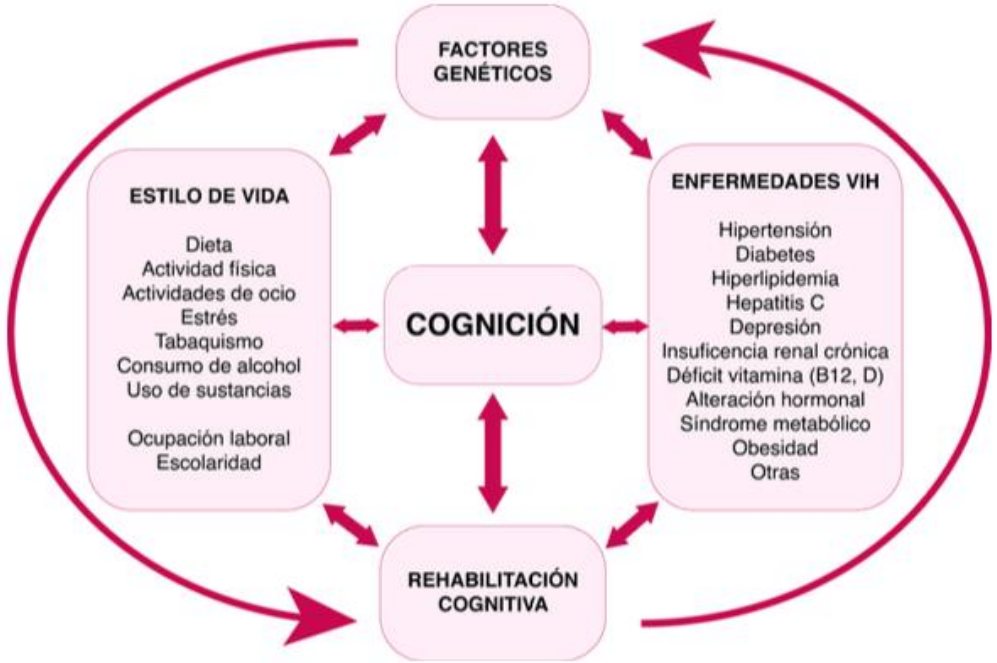
Versión 1.0. – junio de 2020.

5.5.2. DIAGNÓSTICO NEUROPSICOLÓGICO

El diagnóstico neuropsicológico de los TNAV comprende la evaluación tanto del funcionamiento cognitivo como del grado de afectación funcional que puedan presentar los pacientes diagnosticados de deterioro cognitivo, a nivel profesional, en el hogar y/o a nivel social.

Evaluación del funcionamiento neurocognitivo

5. TRASTORNOS NEUROCOGNITIVOS ASOCIADOS AL VIH



2. VIH e Inflamación

Inflamación Crónica en el VIH

viruses

MDPI

Review

Chronic HIV Transcription, Translation, and Persistent Inflammation

Jonathan M. Kilroy [1,†], Andrew A. Leal [1,†] and Andrew J. Henderson [1,2,*]

Viruses **2024**, *16*, 751

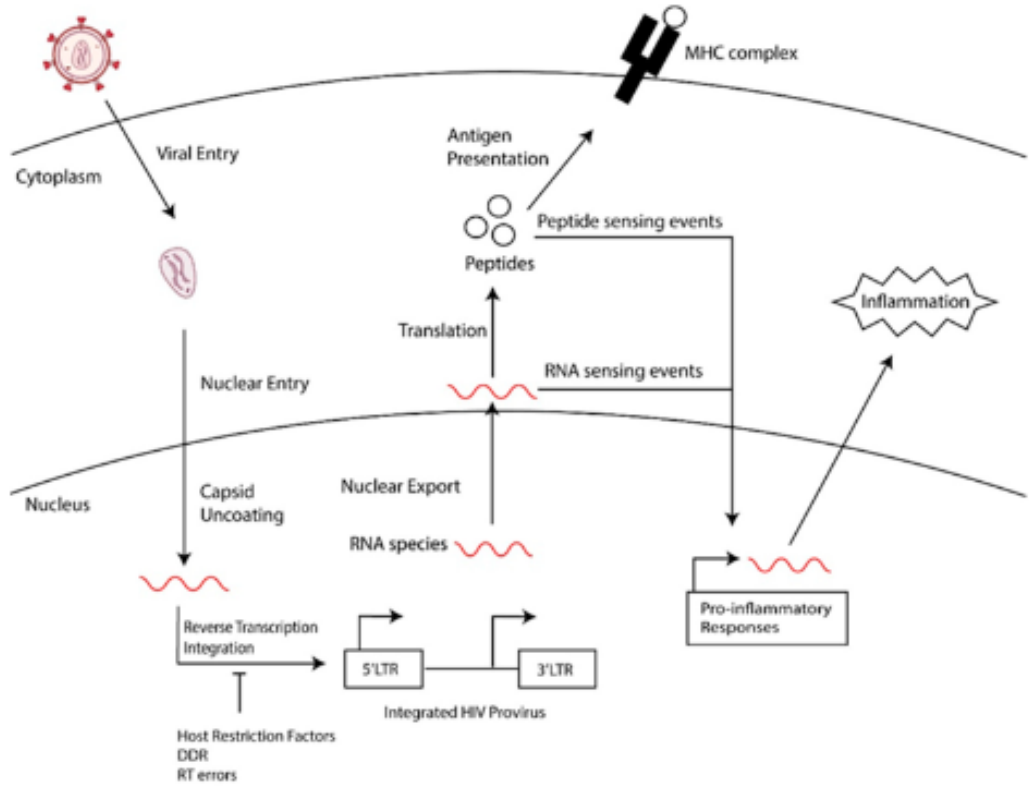


Figure 1. General overview of the generation of defective HIV proviruses and how they may contribute to chronic inflammation.

Enfermedad Cardiovascular y Microbioma

HIV and cardiovascular disease: the role of inflammation

Dirajlal-Fargo, Sahera[a,b]; Funderburg, Nicholas[c]

Current Opinion in HIV and AIDS 17(5):p 286-292, September 2022.

Inflammation in HIV and Its Impact on Atherosclerotic Cardiovascular Disease

Laventa M. Obare, Tecla Temu, Simon A. Mallal, Celestine N. Wanjalla

May 24, 2024

HIV and Comorbidities – the importance of Gut Inflammation and the Kynurenine Pathway

R MacCann[a,b], A.L. Landay[c], Paddy W.G. Mallon[a,b]

Curr Opin HIV AIDS. 2023

Deciphering HIV-associated inflammation: microbiome's influence and experimental insights

Ricky A. Lippincott[a], John O'Connor[b], Charles P. Neff[a], Catherine Lozupone[b] and Brent E. Palmer[a]

September 2024

3. Inflamación y Cerebro en la Infección por VIH

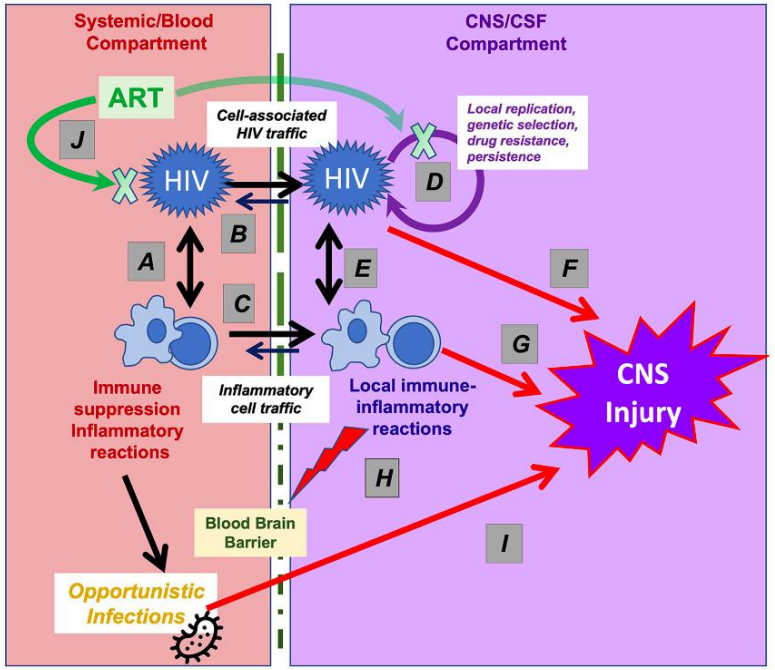
VIH, Inflamación y SNC

Neuroimmunology of CNS HIV Infection: A Narrative Review

*Ana-Claire Meyer[1], Alfred Kongnyu Njamnshi[2], Magnus Gisslen[3,4] and Richard W. Price[5]**

frontiers | Frontiers in Neurology

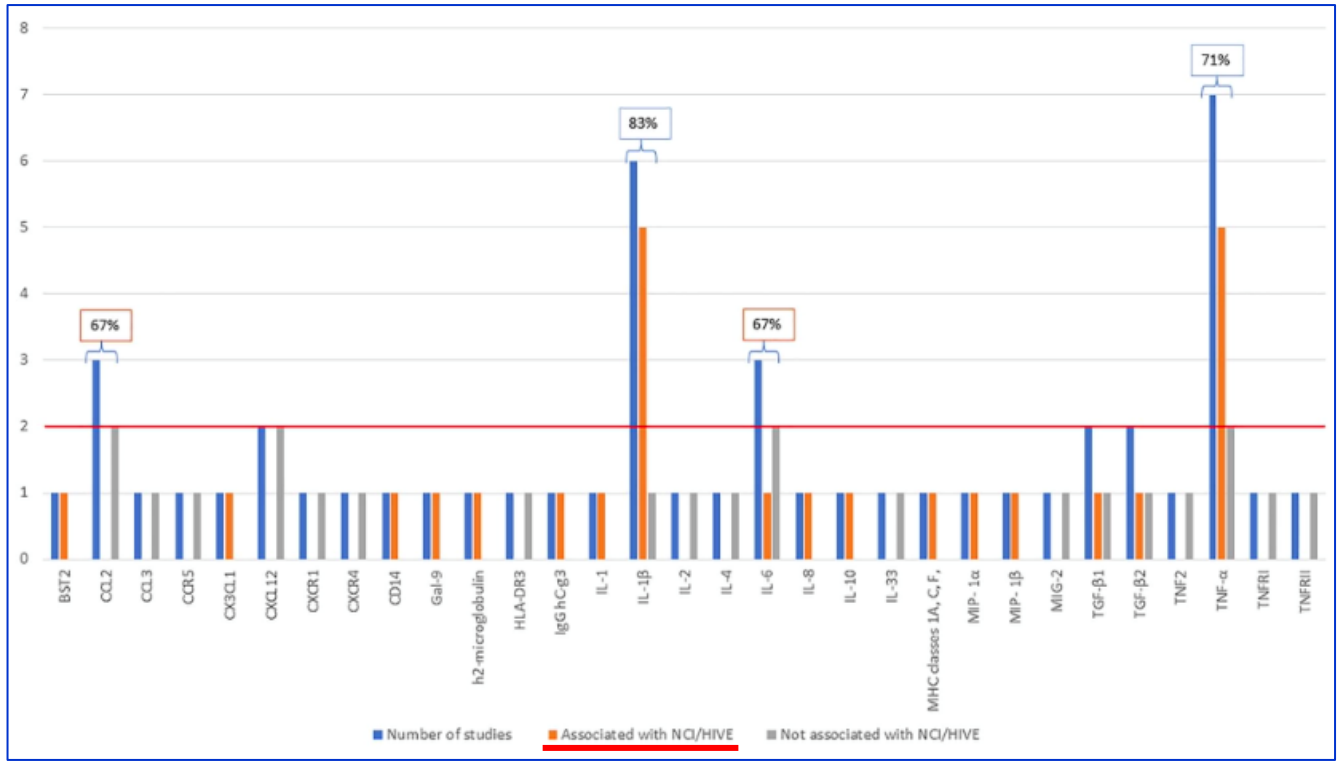
June 2022 | Volume 13



The relationship between HIV-1 neuroinflammation, neurocognitive impairment and encephalitis pathology: A systematic review of studies investigating post-mortem brain tissue

Monray Edward Williams[1] | Petrus J. W. Naudé[2,3]

Rev Med Virol. 2024;e2519.



Microbioma, Inflamación y Alteración Cognitiva en el VIH

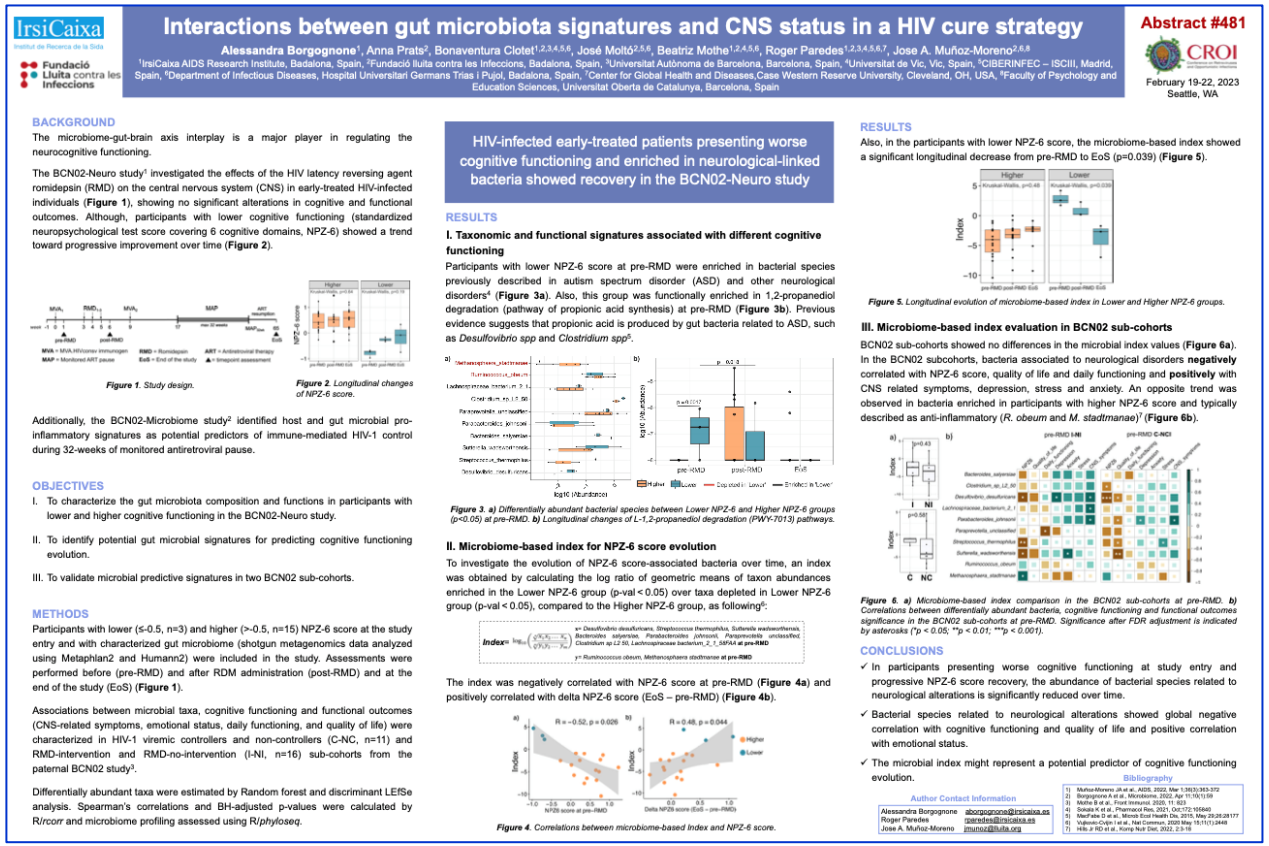
IrsiCaixa
Institut de Recerca de la Sida
Fundació Lluita contra les Infeccions

Interactions between gut microbiota signatures and CNS status in a HIV cure strategy

Alessandra Borgognone[1], Anna Prats[2], Bonaventura Clotet[1,2,3,4,5,6], José Moltó[2,5,6], Beatriz Mothe[1,2,4,5,6], Roger Paredes[1,2,3,4,5,6,7], Jose A. Muñoz-Moreno[2,6,8]

[1]IrsiCaixa AIDS Research Institute, Badalona, Spain, [2]Fundació lluita contra les Infeccions, Badalona, Spain, [3]Universitat Autònoma de Barcelona, Barcelona, Spain, [4]Universitat de Vic, Vic, Spain, [5]CIBERINFEC – ISCIII, Madrid, Spain, [6]Department of Infectious Diseases, Hospital Universitari Germans Trias i Pujol, Badalona, Spain, [7]Center for Global Health and Diseases,Case Western Reserve University, Cleveland, OH, USA, [8]Faculty of Psychology and Education Sciences, Universitat Oberta de Catalunya, Barcelona, Spain

Abstract #481
CROI
February 19-22, 2023
Seattle, WA



IrsiCaixa
Interactions between gut microbiota signatures and CNS status in a HIV cure strategy
Abstract #481 CROI February 19-22, 2023 Seattle, WA

BACKGROUND

The microbiome-gut-brain axis interplay is a major player in regulating the neurocognitive functioning.

The BCN02-Neuro study[1] investigated the effects of the HIV latency reversing agent romidepsin (RMD) on the central nervous system (CNS) in early-treated HIV-infected individuals (**Figure 1**), showing no significant alterations in cognitive and functional outcomes. Although, participants with lower cognitive functioning (standardized neuropsychological test score covering 6 cognitive domains, NPZ-6) showed a trend toward progressive improvement over time (**Figure 2**).

Figure 1. Study design.

Figure 2. Longitudinal changes of NPZ-6 score.

Additionally, the BCN02-Microbiome study[2] identified host and gut microbial pro-inflammatory signatures as potential predictors of immune-mediated HIV-1 control during 32-weeks of monitored antiretroviral pause.

OBJECTIVES

I. To characterize the gut microbiota composition and functions in participants with lower and higher cognitive functioning in the BCN02-Neuro study.

II. To identify potential gut microbial signatures for predicting cognitive functioning evolution.

III. To validate microbial predictive signatures in two BCN02 sub-cohorts.

METHODS

Participants with lower (≤-0.5, n=3) and higher (>-0.5, n=15) NPZ-6 score at the study entry and with characterized gut microbiome (shotgun metagenomics data analyzed using Metaphlan2 and Humann2) were included in the study. Assessments were performed before (pre-RMD) and after RDM administration (post-RMD) and at the end of the study (EoS) (**Figure 1**).

Associations between microbial taxa, cognitive functioning and functional outcomes (CNS-related symptoms, emotional status, daily functioning, and quality of life) were characterized in HIV-1 viremic controllers and non-controllers (C-NC, n=11) and RMD-intervention and RMD-no-intervention (I-NI, n=16) sub-cohorts from the paternal BCN02 study[3].

Differentially abundant taxa were estimated by Random forest and discriminant LEfSe analysis. Spearman's correlations and BH-adjusted p-values were calculated by R/*rcorr* and microbiome profiling assessed using R/*phyloseq*.

HIV-infected early-treated patients presenting worse cognitive functioning and enriched in neurological-linked bacteria showed recovery in the BCN02-Neuro study

RESULTS

I. Taxonomic and functional signatures associated with different cognitive functioning

Participants with lower NPZ-6 score at pre-RMD were enriched in bacterial species previously described in autism spectrum disorder (ASD) and other neurological disorders[4] (**Figure 3a**). Also, this group was functionally enriched in 1,2-propanediol degradation (pathway of propionic acid synthesis) at pre-RMD (**Figure 3b**). Previous evidence suggests that propionic acid is produced by gut bacteria related to ASD, such as *Desulfovibrio spp* and *Clostridium spp*[5].

Figure 3. a) Differentially abundant bacterial species between Lower NPZ-6 and Higher NPZ-6 groups (p<0.05) at pre-RMD. b) Longitudinal changes of L-1,2-propanediol degradation (PWY-7013) pathways.

II. Microbiome-based index for NPZ-6 score evolution

To investigate the evolution of NPZ-6 score-associated bacteria over time, an index was obtained by calculating the log ratio of geometric means of taxon abundances enriched in the Lower NPZ-6 group (p-val < 0.05) over taxa depleted in Lower NPZ-6 group (p-val < 0.05), compared to the Higher NPZ-6 group, as following[6]:

$$Index = \log_{10}\left(\frac{\sqrt[n]{x_1 x_2 \dots x_n}}{\sqrt[m]{y_1 y_2 \dots y_m}}\right)$$

x= *Desulfovibrio desulfuricans, Streptococcus thermophilus, Sutterella wadsworthensis, Bacteroides salyersiae, Parabacteroides johnsonii, Paraprevotella unclassified, Clostridium sp L2 50, Lachnospiraceae bacterium_2_1_58FAA* **at pre-RMD**

y= *Ruminococcus obeum, Methanosphaera stadtmanae* **at pre-RMD**

The index was negatively correlated with NPZ-6 score at pre-RMD (**Figure 4a**) and positively correlated with delta NPZ-6 score (EoS – pre-RMD) (**Figure 4b**).

Figure 4. Correlations between microbiome-based index and NPZ-6 score.

RESULTS

Also, in the participants with lower NPZ-6 score, the microbiome-based index showed a significant longitudinal decrease from pre-RMD to EoS (p=0.039) (**Figure 5**).

Figure 5. Longitudinal evolution of microbiome-based index in Lower and Higher NPZ-6 groups.

III. Microbiome-based index evaluation in BCN02 sub-cohorts

BCN02 sub-cohorts showed no differences in the microbial index values (**Figure 6a**). In the BCN02 subcohorts, bacteria associated to neurological disorders **negatively** correlated with NPZ-6 score, quality of life and daily functioning and **positively** with CNS related symptoms, depression, stress and anxiety. An opposite trend was observed in bacteria enriched in participants with higher NPZ-6 score and typically described as anti-inflammatory (*R. obeum* and *M. stadtmanae*)[7] (**Figure 6b**).

*Figure 6. a) Microbiome-based index comparison in the BCN02 sub-cohorts at pre-RMD. b) Correlations between differentially abundant bacteria, cognitive functioning and functional outcomes significance in the BCN02 sub-cohorts at pre-RMD. Significance after FDR adjustment is indicated by asterosiks (*p < 0.05; **p < 0.01; ***p < 0.001).*

CONCLUSIONS

- ✓ In participants presenting worse cognitive functioning at study entry and progressive NPZ-6 score recovery, the abundance of bacterial species related to neurological alterations is significantly reduced over time.
- ✓ Bacterial species related to neurological alterations showed global negative correlation with cognitive functioning and quality of life and positive correlation with emotional status.
- ✓ The microbial index might represent a potential predictor of cognitive functioning evolution.

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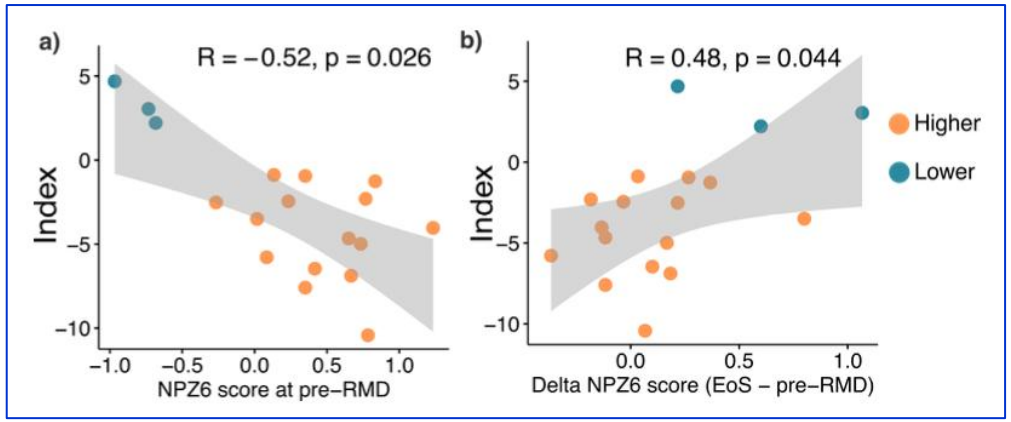
1) Muñoz-Moreno JA et al., AIDS. 2022; Mar 1;36(3):365-372
2) Borgognone A et al., Microbiome. 2022; Apr 11;10(1):59
3) Mothe B et al., Front Immunol. 2020; 11: 822
4) Sokala K et al., Pharmacol Res. 2021; Oct;172:105840
5) Hills RD et al., Int J Environ Res Public Health. 2019; May 23;16(10):1935
6) Vallejo-Cidón I et al., Nat Commun. 2020 May 15;11(1):2448
7) Hills Jr RD et al., Komp Nutr Diet. 2022; 2:5-16



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y= *Ruminococcus obeum, Methanosphaera stadtmanae* **at pre-RMD**

Neopterina en Sangre y Alteración Cognitiva en el VIH

PLASMA NEOPTERIN AS A POTENTIAL BIOMARKER FOR NEUROCOGNITIVE IMPAIRMENT IN AGING PEOPLE WITH HIV

Reference Number: 1405.1415.0.2562.2025

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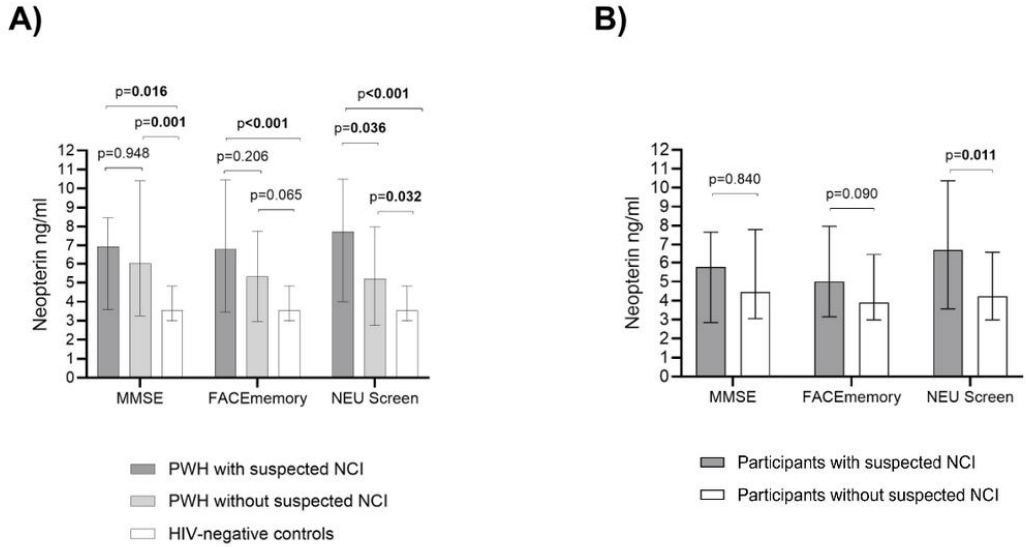

Conclusions:

The higher levels of plasma neopterin observed in aging PWH compared to HIV-negative individuals suggest persistent immune activation despite effective ART. Elevated neopterin levels were significantly associated with suspected NCI as measured by the NEU Screen. These results reinforce the NEU Screen as a useful NCI screening test in HIV infection, and, additionally, underscore the potential utility of neopterin as a plasma biomarker for cognitive decline in aging PWH.

Inflamación y Trastornos Cognitivos por VIH

HRSA CARE ACTION

JULY 2014

HIV-ASSOCIATED NEUROCOGNITIVE DISORDERS IN THE COMBINATION ANTIRETROVIRAL THERAPY ERA

U.S. Department of Health and Human Services
Health Resources and Services Administration

TABLE 2. CAUSES OF, AND POTENTIAL CONTRIBUTORS TO, NEUROLOGICAL IMPAIRMENT IN HIV PATIENTS *

HIV-RELATED	VIRAL	METABOLIC	LIFESTYLE	AGING
		INFLAMMATION		
⇩	⇩	⇩	⇩	⇩
Low CD4 cell nadir	Hepatitis C virus coinfection	History of, or risk for cardiovascular disease	Heavy, long-term use of drugs and/or alcohol	Neurodegenerative disease
Inflammatory Immune Reconstitution Syndrome	Polyomavirus JC (JC virus)	Insulin resistance/ type 2 diabetes	Injection drug use (IDU)	Polypharmacy/drug toxicity
Poor cART adherence	Cytomegalovirus	Dyslipidemia	Sedentary lifestyle	
Opportunistic infections; certain cancers, past syphillis			High BMI/unhealthy diet	
ART-associated toxicities (central nervous system toxicity, dyslipidemia, insulin resistance)			Smoking	

*Many of these factors foster neuroinflammation and can cause or worsen neurocognitive impairment.

Neuroinflamación y Comorbilidades

Neuroinflammation in HIV-associated depression: evidence and future perspectives

Arish Mudra Rakshasa-Loots [1 2], Heather C Whalley [3], Jaime H Vera [4], Simon R Cox [5]

> Mol Psychiatry. 2022 Sep;27(9):3619-3632.

Brain function abnormalities and neuroinflammation in people living with HIV-associated anxiety disorders

Yunzhu Shan [# 1], Guangqiang Sun [# 2 3], Jiahao Ji [# 1], Zhen Li [1 4], Xue Chen [1], Xin Zhang [1], Yundong Ma [2 3], Yang Zhang [1 5], Tong Zhang [1 5], Yulin Zhang [1 6]

> Front Psychiatry. 2024 Mar 18:15:1336233.

¡Gracias!

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