

1 **Title:** Central Nervous System Histoplasmosis in HIV/AIDS Patients in Endemic Region
2 of Brazil

3 Taiguara Fraga Guimarães^{1,2}, Caique Seabra Garcia de Menezes Figueiredo¹, João Paulo
4 Pires Caixeta¹, Cassia Silva de Miranda Godoy^{1,2} and Renata de Bastos Ascenço Soares^{1,2}

5 ¹ *Pontifícia Universidade Católica de Goiás, Goiânia, Brazil*

6 ² *Hospital Estadual de Doenças Tropicais Dr Anuar Auad, Goiânia, Goiânia, Brazil*

7 **Corresponding author:** Renata de Bastos A. Soares at Curso de Medicina, Escola de
8 Ciências Médicas e da Vida, Pontifícia Universidade Católica de Goiás, 74605-010,
9 Goiânia, Goiás, Brazil , phone number: +556239461485.

10 **ABSTRACT**

11 **Introduction:** Histoplasmosis is a fungal disease, caused by *Histoplasma capsulatum*.

12 **Goal:** To report 13 cases of Central nervous system of histoplasmosis in a endemic region
13 in Brazil. **Case report:** Of the 13 patients included, only 1 was on regular ART on
14 admission. The viral load was detected at high values in 9 of the 10 patients who had the
15 viral load recorded, with an average of 419,168 copies/ml. The 11 patients who had CD4
16 available had values below 150 cells/mm³ with a mean of 47.6 cells/mm³. No patient was
17 treated according to the standard recommended by the IDSA, which recommends the use
18 of AMB-L 5mg/kg (max 175mg/day) for 4-6 weeks, followed by the use of itraconazole
19 200mg 12h/12 for 1 year. Of the patients included, 8 (62%) evolved with death and the
20 other 5 (38%) evolved with discharge. **Discussion:** CNS histoplasmosis is an entity that
21 constitutes a real diagnostic challenge, especially in the context of local laboratory
22 limitations. Since we are dealing with an endemic pathogen in our region it seems certain
23 that we are underdiagnosing one of the most lethal forms of histoplasmosis. In this
24 context, routine cerebrospinal fluid collection in cases of disseminated histoplasmosis
25 becomes essential. In addition, fight for the acquisition of new diagnostic tools. In the
26 same vein, there is a need to make accessible the AMB-L to our AIDS patients.
27 Restricting access to it implies considerably reducing the chances of cure and survival. It
28 is necessary to fight for better knowledge, diagnosis and treatment of known neglected
29 diseases.

30 **Keywords:** Central Nervous system Histoplasmosis, AIDS, Fungal Infection.

31

32 INTRODUCTION

33 Recently *Histoplasmosis* appear as hyper endemic in the Brazilian territory,
34 mostly because substantial gaps exist in the Brazilian HIV program. Opportunistic
35 infections (OIs) remain frequent in Brazil due to retention in care issues, which are
36 associated to social inequities, mental diseases, drug abuse, and poor education [1]. Thus,
37 a significant proportion of patients are ‘late AIDS presenters’, being diagnosed with HIV
38 with an OI already in course, even though our country having a successful policy of free
39 antiretroviral treatment to people living with HIV (PLHIV). Individuals with advanced
40 AIDS are prone to severe disease caused by *H. capsulatum* and have high case-fatality
41 rates [1,2,3].

42 Our group participated to the largest prospective cohort study of AIDS
43 patients with disseminated histoplasmosis ever conducted [20–23]. We found a high
44 rate (21.6%) of probable/proven histoplasmosis in febrile PLWHA admitted to
45 Brazilian hospitals. These findings have tremendous impact in terms of public health
46 and disease awareness in South America, considering that Brazil is the largest country
47 and has the greatest population in this region. Despite the HIV infection being
48 widespread in the country, some opportunistic diseases still occur in a typically
49 endemic behavior. We observed a huge (>40%) prevalence of probable/proven
50 histoplasmosis among febrile PLWHA in the Central-Northeast region of Brazil,
51 especially in the states of Goiás, Ceará e Rio Grande do Norte [2].

52 Disseminated histoplasmosis ranges from mild forms such as acute
53 pulmonary to progressive disseminated form that can compromise the central nervous
54 system, a critical presentation [4,5]. The presentations in the form called
55 Neurohistoplasmosis (Histoplasmosis of the Central Nervous System) range from
56 chronic meningitis to expansive brain and/or spinal cord injuries, most often leading
57 to severe neurological impairment. Neurohistoplasmosis is present in about 5-10% of
58 those affected by the disseminated form of the disease [6,7].

59 When it comes to laboratory diagnosis, the gold standard is cerebrospinal
60 fluid (CSF) culture, which has a low yield, with fungal growth in only a quarter of
61 patients. The most sensitive method for the diagnosis of histoplasma meningitis
62 includes the use of tests to detect antibodies and antigens in the CSF that assume the
63 disease as probable. Of particular note is the investigation of the antigen, which has a

64 sensitivity ranging from 81% to 93% in immunocompromised individuals or those
65 with severe disease. [8,9,10]. CSF serology is positive in 62.2% to 70.3% of cases.
66 This method can help as long as certain criteria are met, such as documenting an H
67 band - a marker of acute disease - in the CSF or an M band, a contact marker, in a
68 patient who did not have such a marker before in the case of the immunodiffusion
69 technique. And when serological research by complement immunofixation is used, a
70 fourfold increase in titration is observed in an interval of 14 days. By associating the
71 two methodologies, a probable diagnosis is possible. [9,11].

72 The Infectious Disease Society of America (IDSA) guideline for the
73 treatment of CNS histoplasmosis recommends an initial course of liposomal
74 amphotericin (L-AMB) for 4 to 6 weeks followed by use of itraconazole for at least 1
75 year. This recommendation was based on improved survival and clinical response in
76 AIDS patients with disseminated histoplasmosis treated with AMB-L instead of
77 amphotericin deoxycholate (AMB-D). These findings, together with the
78 unsatisfactory outcome of CNS histoplasmosis, formed the basis for the IDSA
79 guideline recommendation. [10,12]. In our country, unfortunately, PLHIV/AIDS are
80 not covered by the liposomal formulation. The deoxycholate formulation is most
81 frequently used, currently not recommended due to nephrotoxicity.

82 This study represents the largest series of cases of CNS histoplasmosis
83 histoplasmosis in the country to date and carried out in a single reference unit. -
84 Hospital Estadual de Doenças Tropicais Dr Anuar Auad, Goiás state, Brazil. In fact,
85 underreporting is one of the problems currently experienced, due to laboratory
86 limitations associated with a less specific clinic, lethality, late diagnosis as well as the
87 lack of availability of AMB-L, factors that increase the prevalence of complications
88 of disseminated histoplasmosis.

89

90 **Funding**

91 This work received no specific funding.

92 **Protection of human subjects and animals in research**

93 All procedures performed in studies involving human participants were in accordance
94 with the ethical standards of the institutional and/or national research committee and
95 with the 1964 Helsinki declaration and its later amendments or comparable ethical
96 standards.

97 **Conflict of interest**

98 The Authors declare that they have no conflicts of interest to disclose.

99 **REFERENCES**

- 100 [1] Diego R. Falci, Daiane F. Dalla Lana, Alessandro C. Pasqualotto, The era of
101 histoplasmosis in Brazilian endemic mycoses, The Lancet Regional Health - Americas,
102 Volume 3, 2021, 100037, ISSN 2667-193X, <https://doi.org/10.1016/j.lana.2021.100037>.
- 103 [2] FALCI, Diego et al. Histoplasmosis, An Underdiagnosed Disease Affecting People
104 Living With HIV/AIDS in Brazil: Results of a Multicenter Prospective Cohort Study Using
105 Both Classical Mycology Tests and Histoplasma Urine Antigen Detection. Open Forum
106 Infectious Diseases, [s. l.], 2019.
- 107 [3] FERREIRA , Bianca da Silva et al. Disseminated histoplasmosis in AIDS patients:
108 an urban disease. Experience in a metropolis in the middle east of Brasil. Le infezione
109 in medicina, [s. l.], 22 out. 2021.
- 110 [4] Chastain DB, Henao-Martínez AF, Franco-Paredes C. Opportunistic Invasive
111 Mycoses in AIDS: Cryptococcosis, Histoplasmosis, Coccidioidomycosis, and
112 Talaromycosis. Current Infectious Disease Reports. 2017;19(10):1–9.
- 113 [5] Almeida M de, Almeida-Silva F, Guimarães AJ, Almeida-Paes R, Zancopé-Oliveira
114 RM. The occurrence of histoplasmosis in Brazil: A systematic review. International
115 Journal of Infectious Diseases. 2019;86:147–56.
- 116 [6] Wheat J, Myint T, Guo Y, Kemmer P, Hage C, Terry C, et al. Central nervous system
117 histoplasmosis: multicenter retrospective study on clinical features, diagnostic approach
118 and outcome of treatment. Medicine. 2018;97(13):e245–5
- 119 [7] Stokhamer D, Bejarano G, Gañete M, Sanillán P, Sampere C. Infección cerebral por
120 *Histoplasma capsulatum* en paciente con sida. Actualizaciones en SIDA e Infectología.
121 2015;23(88):42–5.
- 122 [8] Wheat J, Myint T, Guo Y, et al. Central nervous system histoplasmosis: multicenter
123 retrospective study on clinical features, diagnostic approach and outcome of treatment.
124 Medicine (Baltimore) 2018;97(13):e0245
- 125 [9] Azar MM, Loyd JL, Relich RF, Wheat LJ, Hage CA. Current concepts in the
126 epidemiology, diagnosis, and management of histoplasmosis syndromes. Seminars in
127 Respiratory and Critical Care Medicine. 2020;41(01):13–3
- 128 [10] Nyalakonda H, Albuerne M, Suazo Hernandez LP, et al. Central Nervous System
129 Histoplasmosis in Acquired Immunodeficiency Syndrome. Am J Med Sci 2016;351:177–
130 86.

- 131 [11] Richer SM, Smedema ML, Durkin MM, et al. Improved diagnosis of acute
132 pulmonary histoplasmosis by combining antigen and antibody detection. *Clin Infect Dis*
133 2016;62(07):896–902.
- 134 [12] Wheat LJ, Freifeld AG, Kleiman MB et al. Clinical practice guidelines for the
135 management of patients with histoplasmosis: 2007 update by the Infectious Diseases
136 Society of America. *Clin Infect Dis*. 2007;45(7):807–25.
- 137 [13] Unis G, De Mattos Oliveira F, Severo LC. Histoplasmoze disseminada no Rio
138 Grande do Sul. *Rev Soc Bras Med Trop*. 2004;37(6):463–8.
- 139 [14] Vipul V. Jain, Timothy Evans, Michael W. Peterson, Reactivation histoplasmosis
140 after treatment with anti-tumor necrosis factor α in a patient from a nonendemic area,
141 *Respiratory Medicine*, Volume 100, Issue 7, 2006, Pages 1291-1293, ISSN 0954-6111,
142 <https://doi.org/10.1016/j.rmed.2005.09.020>.
- 143 [15] Wheat J, Myint T, Guo Y, Kemmer P, Hage C, Terry C, et al. Central nervous system
144 histoplasmosis: multicenter retrospective study on clinical features, diagnostic approach
145 and outcome of treatment. *Medicine*. 2018;97(13):e245–5
- 146 [16] Vigil DESDE, Sa NEM, Epidemiol N, Cordena G, Doen GDE, Transmiss AS, et al.
147 Proposta de vigilância e controle da Histoplasmoze capsulata [Internet]. Brasília:
148 Brasil/Ministério da Saúde; 2010 p. 1–15. Available from:
149 http://www.sgc.goias.gov.br/upload/arquivos/2012-05/proposta_ve-histoplasmoze.pdf
- 150 [17] Woods JP. Revisiting old friends: Developments in understanding *Histoplasma*
151 *capsulatum* pathogenesis. *J Microbiol* 2016; 54:265.
- 152 [18]. Adenis A a, Aznar C, Couppié P. Histoplasmosis in HIV-Infected Patients: A
153 Review of New Developments and Remaining Gaps. *Curr Trop Med reports* [Internet].
154 2014;1:119–28. Available from:
155 [http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4030124&tool=pmce](http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4030124&tool=pmcentrez&rendertype=abstract)
156 [ntrez&rendertype=abstract](http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4030124&tool=pmcentrez&rendertype=abstract).