ISSN: 2755-1067

Journal of Diseases Disorders & Treatments

SCIENTIFIC Research and Community

Research Article

Open Access

# Clinical Characteristics of Ecuadorian Patients with Acquired Immunodeficiency Syndrome (AIDS) and Central Nervous System Infection

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## SUMMARY

**Antecedents:** Infection of the central nervous system (CNS) by a variety of opportunistic agents in individuals infected with the human immunodeficiency virus (HIV) remain a major cause of morbidity and mortality. The clinical and radiographic pattern of CNS in HIV immunocompromised patients are sometimes sufficient to establish the diagnosis. The purpose of this study is to describe the etiology distribution, clinical parameters, evaluation, management and complications in a group of patients treated in a hospital's AIDS unit from a developing country.

**Methodology:** An observational retrospective analytical study was conducted at Eugenio Espejo Hospital, Quito-Ecuador, between April 2002 and June 2010.

**Results:** The prevalence of CNS infections in HIV patients was 5.9%. The most common opportunistic infections were Toxoplasmosis 46%, Cryptococcosis 20%, Tuberculosis 19%, HIV Encephalopathy 5%, and Progressive Multifocal Leukoencephalopathy (PML) 5%. The main clinical manifestations were headache, fever, and neurological focality. In the first decade of the 2000s, antiretroviral therapeutic (ART) regimens were established in 84% cases of which 66% followed the guidelines for treatment-naïve patients (AZT / 3TC / EFV). The prevalence of mortality was 21.31%, being the most common fatal complications lactic acidosis (38%), Systemic Inflammatory Response Syndrome (SIRS) (38%) and Immune Reconstitution Inflammatory Syndrome (IRIS) 23%.

**Conclusion:** The prevalence presented in our study, is comparable to other studies conducted in developing countries in the same period. The high percentages of HIV-associated opportunistic CNS infection reported by 2005 was followed by a dramatic reduction since the advent and consolidation of highly active antiretroviral therapy (HAART).

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**Received:** June 15, 2022; **Accepted:** June 22, 2022; **Published:** June 30, 2022

**Keywords:** CNS, Opportunistic, Infection, HIV, AIDS, Clinical Characteristics

## Introduction

Since 1981, when the first cases of Acquired Immunodeficiency Syndrome (AIDS) were described, research in this field has developed rapidly, which in turn affected clinical-therapeutic demand. The socio-economic repercussions of the disease changed as well, since it shifted from being a disease with a fatal outcome, to a manageable chronic condition [1-3]. Thus, the level of accessibility to scientific-technological advancements, as well as the changes in socioeconomic conditions, have influenced the evolutionary course of AIDS in developing countries, making it a social burden that has limited access to adequate and timely therapeutic options [4,5]. The evolutionary changes of the virus and response of the host have also altered the way the disease presents itself, causing ambiguity and even uncertainty in regards to the clinical behavior of AIDS [1,6]. For example, central nervous system (CNS) involvement is reportedly more common in AIDS-related infections. The clinical and evolutionary discordance, together with the limited resources and the lack of sufficiently precise diagnostic tests that differentiate between opportunistic agents, have led to the implementation of certain strategies that combine empirical treatment and clinical probability as instruments for decision-making [7,8]. Therapeutic response is also ambiguous due to the complex structural characteristics of the CNS, the magnitude of the inflammatory response, and the vascular, cellular, and molecular changes caused by different opportunistic infections [9-11].

Therefore, it is essential to know the magnitude of the clinical impact of AIDS-associated infectious diseases on the CNS;

especially in hospital's AIDS unit in developing countries like Ecuador. Thus, the objective of this study was to review retrospectively the parameters of evaluation, management, comorbidities, complications, and sequelae in a group of patients with a diagnosis of human immunodeficiency virus (HIV) /AIDS.

## Materials and Methods

### Study Population and Statistical Analysis

An observational retrospective analytical study was conducted at Eugenio Espejo Hospital, Quito-Ecuador, between April 2002 and June 2010. The sample was non-probabilistic and consecutive; the inclusion criteria were patients with a diagnosis of human immunodeficiency virus (HIV) /AIDS and CNS infection with a complete medical record. Further, the study followed the management guidelines of the Center for Disease Prevention and Control (CDC), and it was supported by clinical, analytical parameters (CSF study) and neuroimaging techniques (CT and MRI) [12-14]. Additionally, demographic variables, hospital care indicators, risk factors, clinical course, and therapeutic response were documented. We excluded medical records with a lack of important medical information. Thus, 61 medical records from patients living with HIV and Central Nervous System Infection of both genders were reported.The Academic Ethic Committee of Eugenio Espejo Hospital approved the study. The data was coded and entered into a database, to which only the researcher had access. The statistical analysis was performed using SPSS version 20. The qualitative variables were described as absolute and relative values, whereas the quantitative variables were described through central tendency and variability measures. Statistical significance to compare proportions was established at a p-value $<0.05$.

## Results

The average age of AIDS patients with neurological infections was 34.6 years (SD +/- 8.5). The risk factors associated with HIV transmission were alcohol consumption (36%), sustaining male homosexual relations (MSM) (36%), drug abuse/dependence (17%), and others (11%). Blood transfusions and having tattoos were not relevant risk factors in this study. Most patients came from the Ecuadorian highlands (85%), specifically from Pichincha province (66%), where the national reference center for AIDS is located. Hospitalized patients accounted for 85% and the remaining 15% were outpatients. Most of the patients were male (90%), with the predominant civil status being single (46%), followed by married (29%) and domestic partnership (17%) (See Table 1).

**Table 1: Demographic and Clinical Characteristics**

| | N | Sample % |
|---|---|---|
| Age (average; SD) 34,6±8,5 | | |
| **Gender** | | |
| Female | 6 | 10 |
| Male | 55 | 90 |
| **Marital Status** | | |
| Single | 28 | 46 |
| Married | 18 | 29 |
| Domestic Partnership | 10 | 17 |
| Other | 5 | 8 |
| **Risk factors** | | |
| Alcohol consumption | 22 | 36 |
| Male homosexual relations (MSM) | 22 | 36 |
| Drug abuse/dependence | 10 | 17 |
| Other | 7 | 11 |
| **Medical Attention** | | |
| Outpatient | 9 | 15 |
| Inpatient | 52 | 85 |

**Table 1:** Shows sample size, average of age, frequency and percentage of gender, marital status, risk factors and medical attention of patients with AIDS and Central Nervous System Infection.

The prevalence of opportunistic infections that affect the CNS in AIDS patients were Toxoplasmosis 46%, Cryptococcosis 20%, Tuberculosis 19%, HIV Encephalopathy 5%, Progressive Multifocal Leukoencephalopathy (PML) 5%, and unidentified infections 5% (See Table 2). The cumulative prevalence of CNS infections in AIDS patients in the studied period (2002-2010) was 5.9%.

**Table 2: Opportunistic Infections of CNS in HIV patients**

| | N | Sample % |
|---|---|---|
| Toxoplasmosis | 28 | 46 |
| Cryptococcosis | 12 | 20 |
| Tuberculosis | 12 | 19 |
| HIV Encephalopathy | 3 | 5 |
| Progressive Multifoca leukoencephalopathy | 3 | 5 |
| Unidentified infections | 3 | 5 |

**Table 2:** Shows frequency and percentage of the main opportunistic infections of Central Nervous System in patients with AIDS.

The confirmation of cerebral Toxoplasmosis was done through imaging studies and indirectly by treatment response in 78% of cases; through imaging, serology, and treatment response in 15% of cases; and was not specified in 7% of cases. Cerebral Cryptococcosis was diagnosed through cerebral spinal fluid (CSF) analysis, India ink staining, positive culture, and imaging (CT/ MRI) in 8% of cases. Through CSF analysis, India ink staining and positive culture in 23% of cases. India ink staining and positive culture in 46% of cases; imaging and treatment in 15% of cases; and by positive serology for Cryptococci antigens in blood and treatment in 8%. Brain Tuberculosis was diagnosed through clinical manifestations, CSF analysis and imaging in 54% of cases. Through clinical manifestations, imaging, and treatment response in 46%. The clinical presentations were tuberculous myelitis in 20%, isolated cerebral tuberculosis in 20% and meningitis associated with tuberculomas in 60% of cases. Progressive Multifocal Leukoencephalopathy (PML) was diagnosed by imaging and treatment response in 100% of cases (See Table 3). HIV encephalopathy was diagnosed through clinical manifestations, serology, treatment response, and normality of imaging studies in 100% of cases. For the diagnosis of other infectious processes, the absence of treatment response to other opportunistic infections, CSF analysis, imaging, and clinical manifestations was taken into account.

**Table 3: Diagnosis Methods**

| | Sample % |
|---|---|
| **Toxoplasmosis** | |
| Imaging and Treatment | 78 |
| Imaging, Serology, and Treatment | 15 |
| Not specified | 7 |
| **Cryptococcosis** | |
| CSF analysis, India ink, Culture, and Imaging | 8 |
| CSF analysis, India ink, Culture | 23 |
| India ink and Culture | 46 |
| Imaging and Treatment | 15 |
| Serology and Treatment | 8 |
| **Tuberculosis** | |
| CSF analysis, Imaging, and Clinical manifestations | 54 |
| Imaging, Clinical manifestations and Treatment | 46 |
| **HIV Encephalopathy** | |
| Clinical manifestations, Serology, Treatment, and Imaging | |
| **Progressive Multifocal Leukoencephalopathy** | |
| Imaging and Treatment | |

**Table 3:** shows percentage of methods used for the diagnosis of the opportunistic infections of Central Nervous System in patients with AIDS.

The most common clinical manifestations were headache, fever, cough and dyspnea. Motor disorders occurred in 69% of cases, with cranial nerve involvement (II, III, VI, VII, VIII, and IX) in 18% of cases and seizures in 13% of them. No significant risk association was demonstrated between clinical manifestations and the different nosological entities described.

Imaging studies (CT and/or MRI) were performed in 78% of cerebral toxoplasmosis cases. The CNS involvement was presented as single focal lesions in 41.6%, multiple focal lesions 40.7%, and hyperintense lesions in 18% of cases; with predominant midbrain, thalamic, peduncular, and cerebellar involvement, observing perilesional edemas in 45% of cases. Radiological findings in patients who underwent CT scans (58%) and MRI (50%), in the group affected by Cryptococcus, range from normality in 71% of CTsand in 33% of MRIs, to the presence of multiple focal lesions andhyperintense lesions associated with edema in the basal ganglia, semi-oval centers, pons, periaqueductal region and cerebellum, with and without annular enhancement.Patients who were diagnosed of CNS Tuberculosis underwent CT scans in 59% of cases and MRI scans in 78%. Cerebral presentation was in the form of meningitis, tuberculomas, or mixed forms. Abnormal findings were characterized by hypo and hyperintensities, with the involvement of the temporal, occipital and parietal regions, the caudate nucleus, basal ganglia, and the midbrain. We found significant cerebral edema in 36% and perilesional edema in 9% of cases. In PML, the findings demonstrated subcortical involvement with hyperintensities, especially T2 and Flair, in cerebral peduncles, cerebellar hemispheres, and reticular tissue, with and without contrast enhancement. No cerebral edemas were found in the cases described. In HIV encephalopathy, the reports collected range from normality and cerebral edemas on CT scans, to the presence of hypo and hyperintense lesions in semi-oval centers, globus pallidus, and corticospinal tracts in the brainstem, without modification of the contrast medium (See Table 4).

**Table 4: Imagin Study**

| | Sample % | Localization |
|---|---|---|
| **Toxoplasmosis** | | |
| CT / MRI | 78 | |
| Single focal lesions | | Midbrain Thalamic Peduncular Cerebellar |
| Multiple focal lesions | | |
| Hyperintense lesions | | |
| Edema | 45 | Perilesional |
| **Cryptococcosis** | | |
| CT | 29 | |
| MRI | 67 | |
| Multiple focal lesions | | Basal ganglia Semi-oval centers Pons Periaqueductal Cerbellum |
| Hyperintense lesions | | |
| Edema | | Cerebral |
| **Tuberculosis** | | |
| CT | 59 | |
| MRI | 78 | |

| | | |
|---|---|---|
| Hypointense lesions | | Caudate nucleus<br>Basal ganglia<br>Midbrain |
| Hyperintense lesions | | |
| Edema | 36 | Cerebral |
| | 9 | Perilesional |
| **Progressive Multifocal Leukoencephalopathy** | | |
| Hyperintense lesions | | Cerebellar hemispheres<br>Cerebral peduncles<br>Reticular tissue |
| Edema | 0 | |
| **HIV Encephalopathy** | | |
| Hypointense lesions | | Semi-oval centers<br>Globus pallidus<br>Corticospinal tracts |
| Hyperintense lesions | | |

**Table 4:** shows percentage and localization of imaging study findings of different opportunistic infections of Central Nervous System in patients with AIDS.

In the first decade of the 2000s, antiretroviral therapeutic (ART) regimens were established in 84% cases of which 66% followed the guidelines for treatment-naïve patients (AZT / 3TC / EFV), and 34% of cases with adjustments in nucleosides and non-nucleosides depending on physiological conditions such as pregnancy (2%), toxicity (17%) and therapeutic failure (15%). The original antiretroviral therapy showed continuity in 54% of the patients who started highly active antiretroviral therapy (HAART). Clinical, immunological and virological response to ART and antimicrobial drugs was observed in 36.21% of patients. Only clinical response was evidenced in 5.17% of the patients, virological failures in 6.89%, immune-virological dissociation in 1.72%, and the rest were unknown situations. Mean CD4 lymphocyte count was 85 cells / mm3 (SD +/- 89), and HIV viral load was 716 536 RNA copies / ml of serum (SD +/- 1 213 396). Readmissions for various pathologies after hospital discharge was 29%. The mean time intervals from the diagnosis of HIV and/or AIDS and the presentation of the first clinical manifestations were 20.5 (SD +/- 56.2) and 5.9 (SD +/- 14.7) weeks, respectively. Therapeutic intervention, evaluated through the time interval between diagnosis according to the inclusion criteria and therapeutic intervention with ART was 5.0 weeks (SD +/- 5.17), excluding the cases in which therapeutic initiation went back to years prior to SNC involvement (3.4%) (See Table 5). The group of patients without timely access to ART represented 3.4%; patients transferred to other provinces represented 3.4%; and the group of deceased patients on whom antiretroviral therapy was not established represented 8.47%.

The cumulative prevalence of mortality of AIDS patients with CNS infections in the studied period was 21.31%, being the most common fatal complications lactic acidosis (38%), Systemic Inflammatory Response Syndrome (SIRS) (38%) and Immune Reconstitution Inflammatory Syndrome (IRIS) 23%. Maintained stability on survival rate was observed by 2009, which was influenced by the antiretroviral treatment, in favor of those included in the therapeutic regimens.

Regarding the operational parameters in evaluation and care, an average hospitalization stay of 31.5 days was observed (SD +/- 21.7). Outpatient follow-up was done for 76% of the studied cohort, with a mean of 98.3 weeks (SD +/- 105.8) after hospital discharge (See Table 5).

**Table 5: Medical Attention Parameters**

| | Average | SD |
|---|---|---|
| Hospitalization stay | 31,5 dy | ±21,7 |
| Outpatient follow-up | 98,3 wk | ±105,8 |
| Intervals diagnosis of HIV/AIDS | 20,5 wk | ±56,2 |
| First clinical manifestation | 5,9 wk | ±14,7 |
| Therapeutic intervetion | 5,0 wk | ±5,17 |

**Table 5:** Shows the time average and SD medical attention parameters of patients with AIDS.

**Discussion**

Data from reference centers in developed countries of the region report HIV prevalence of 26 to 42.7% [15,16]. United Nations Programme on HIV/AIDS (UNAIDS) estimates that since the beginning of the epidemic, 76 million people have been infected with the HIV virus around the world, with a predominance of males in the productive age group. The most common forms of transmission, MSM, alcohol/drug use, single marital status, male gender, age 15 - 49 years. The high mortality rate (1 to 2%) reported worldwide reflect the demographic indicators of our retrospective cohort [1]. Data form Pan American Health Organization (PAHO), during the study period, reports a prevalence of people infected with HIV ranged from 0.3 to 0.7%. [17].Accordingly, the HIV/AIDS Unit of Eugenio Espejo Hospital (HEE)-Quito recorded an annual prevalence of 0.7%.

Since the emergence of HIV as a determinant of AIDS in the 1980s, incidence has multiplied with a variable behavior over time, as reflected in a rebound in the rates of transmission and mortality of the disease, followed by stability, at the beginning and end of the '90s, respectively, without exceeding the underreporting since then [18]. The same trend is replicated in HIV-associated opportunistic CNS infection since the advent and consolidation of HAART, as demonstrated in the dramatic reduction of HIV dementia and the decrease in the incidence of diseases such as Toxoplasmosis and brain Cryptococcosis, in addition to the prevention of the development of PML and primary CNS lymphoma in developed countries. [19-23].In our study, like in others carried out in developing countries, we identified an ascending curve of CNS diseases in the first 6 years of accessibility to the National AIDS Program, followed by a decrease from 2008 onwards [24, 25].

The epidemiological profile of HIV-associated opportunistic CNS infection, reported by Oliveira et al, from Brazil, shows a prevalence of 42.3% for Toxoplasmosis; 12.9% Cryptococcosis; 10.8% Tuberculosis; 4.6% HIV Dementia; 3.6% Progressive Multifocal Leukoencephalopathy; and 11% attributed to other unidentified CNS infections. [15]. These results are comparable with our study population, despite the socioeconomic differences between the two countries.

The most prevalent signs and symptoms in cerebral tuberculosis reported are headache (50-80%), fever (60-95%), weight loss (60-80%), neck stiffness (40-80%), and coma (30-60%) [26]. In Cryptococcosis are fever (81%), cough (63%), dyspnea (50%), weight loss (47%), and headache (41%) [27]. The symptomatic triad in PML shows weakness (42%), speech abnormalities (40%), cognitive deficit (36%), and visual deficit (19%) [28]. The clinical characteristics of HIV encephalopathy occur in the neurocognitive, motor, and behavioral fields, and are related by up to 30% in histopathological studies [26,29]. The results obtained in our

study in the clinical presentation maintain similar frequencies to the studies reported, without significant associations between the signs and symptoms in the cohort.

The diagnostic confirmation methods used herein are in accordance with the inclusion criteria used in different studies, correlated with the image patterns in cerebral toxoplasmosis, whose differential diagnosis focuses on primary CNS Lymphoma [14, 30]. Similar to the imaging findings reported in bibliography, which describe an absence of alterations in 69% of tomographic studies for Cryptococcosis [31], in our study we defined alterations without a specific radiological pattern. In cerebral tuberculosis, its different forms of a clinical presentation show radiological patterns in any part of the brain, ranging from leptomeningeal thickening and communicating hydrocephalus, to parenchymal involvement in supratentorial locations, with non-specific central calcifications, and isointense signals in T1 and T2, which depended on the stage of disease progression [32].Magnetic resonance imaging (MRI) is the radiological method of choice, which contributes to the non-invasive diagnosis of these bilateral and asymmetric lesions of the subcortical white matter, with hypointense signals on T1 and hyperintense signals on T2, with parieto-occipital involvement, without contrast enhancement or mass effect [33]. In the cases presented in the study, we describe similar radiological patterns.

In HIV encephalopathy, the typical image described is cerebral atrophy of the basal ganglia and diffuse hyperintensities of the periventricular white matter [34]. In our study, we only reported hypo and hyperintense lesions, and they do not coincide with the radiological characteristics described in the literature, demonstrating the need to centralize the interpretation of studies with specialized personnel in order to reduce the discrepancy between the observed and reported findings used as reference for the diagnosis of HIV encephalopathy.

The cerebrospinal fluid (CSF) analysis shows special behavior in each of the entities described. In tuberculous meningitis, cellularity has a range of 5 to 1000 cells/mm3, with a lymphocyte predominance of 30 to 90%, presence of proteins, and hypoglycorrhachia in most cases. However, protein normality has been reported in 43% of cases, and glucose levels are occasionally normal as well, with positive cultures found in 22% to 27% cases [29,35]. In Cryptococcal meningoencephalitis, CSF differs according to the patient's immune status, with a mean cell concentration of 12.5 cells/mm3 and a mean protein concentration of 70 mg/dl; only 30% have hypoglycorrhachia, with positive India ink staining in 87,8% of cases and cultures with Cryptococcus growth in 88.6% of cases [36,37]. The study of CSF in toxoplasmosis is not frequently accessible due to the uncertainty of the produced lesions, especially brain edemas; meaning that sporadic abnormalities, such as increased spinal protein levels and pleocytosis, cannot be used as references [38]. In PML, the behavior of the CSF is discreet, with hypoglycorrhachia in 1% of cases, abnormal protein levels in 55%, not exceeding 208 mg/dl , and an average count of 7.7 cells/mm3 [39]. In HIV encephalopathy, none of the CSF biomarkers are clinically applicable to diagnostic HIV-associated neurocognitive disorders. In advanced stages, the viral load in CSF is correlated with neurological alterations, but not with the viral load in the blood [40,41].

Serological studies of toxoplasmosis with sensitivities lower than 12% IgG, 6% IgM, and 7% IgA in serum, do not allow projecting relevant post-test probabilities with the prevalence of this and other studies[21,42,43]. In cerebral cryptococcosis, high Cryptococcal antigen titers in the CSF have high sensitivity and specificity, greater than 93% which allow determine a positive post-test probability of 25% and a negative one of 0.2 with the prevalence found in our study (0.02%), allowing us to exclude in case of negativity. Additionally, serum determination of Cryptococcal antigen,provides a sensitivity of 97.3% and a specificity of 86.2%, with a positive post-test probability of 50.6% and a negative probability of 0.5%, which once again makes it possible to exclude the diagnosis in its absence [37,44].

Polymerase chain reaction (PCR) tests using peripheral blood samples for toxoplasmosis have a sensitivity of 80% and a specificity of 98%, which, when used according to our prevalence of 5%, allows us to exclude, with a negative post-test probability of 1.1% [21,38]. Clinical manifestations showed no statistically significant association with toxoplasma PCR [45]. However, studies similar to ours identified predictive factors of partial clinical response to treatment, showing an OR of 22.3 for altered consciousness; 14.9 for psychomotor retardation; 5.9 for seizures; and 12.4 for the Glasgow coma scale when it is less than 12; all statistically significant [46]. Quantitative PCR techniques for the detection of JC virus in biological fluids continue to be studied [39,47].

Availability, access, and adherence to ART in a majority group of patients, after their hospital discharge, as well as adequate management of the disease and its comorbidities,have shown a significant reduction of the probability of death 1 year after the start of antiretroviral treatment [48,49]. The recommendations established in the management guidelines are based on schemes consisting of two nucleosides and one non-nucleoside with treatment-naïve patients, with adjustments allowed according to basic clinical situation, toxicity, resistance, adherence, and availability [49]. The resistance rates, as well as the toxicity found in our study, do not provide significant data, other than sporadically, during the 8 years of the cohort, unlike the large series in which adverse effects and dropout reach rates of up to 15% and 25%, respectively [50-52]. The strategies for treatment adherence and reduction of risk infections, added to individual commitment, notably improve both the virological response and the rates of resistance to ART.

## Conclusion

This hospital-based study provides historical information regarding diagnosis methods, clinical presentation and etiology distribution of pathogens causing CNS infections among people living with HIV in the period 2002-2010 at Eugenio Espejo Hospital, Quito, Ecuador. It reported high prevalence of HIV-associated opportunistic CNS infection since 2005, followed by a dramatic reduction due to the advent and consolidation of antiretroviral therapy. In resource-limited developing countries like Ecuador, molecular testing can only be recommended under conditioned circumstances, thus many of the diagnostic methods described here have been maintained to nowadays.

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