Clinical characteristics ofEcuadorian patients with Acquired Immunodeficiency Syndrome (AIDS) and Central Nervous System Infection.

Comment [IM1]: I would suggest "Clinical Characteristics of Central Nervous System Infections in Ecuadorian Patients with AIDS"

SUMMARY

~~Antecedents~~Background. Infection of the central nervous system (CNS) by ~~a variety of~~various opportunistic agents in individuals infected with the human immunodeficiency virus (HIV) remains a major cause of morbidity and mortality. The clinical and radiographic pattern of CNS infectionsin HIV immunocompromised patientsare sometimes sufficient to establish the diagnosis. The purpose of this study is to describe thedistribution of etiologies~~etiology distribution~~,clinical parameters, evaluation methods, management and complications in a group of patients treated in a hospital's AIDS unit~~from~~ in 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 infectionswere Toxoplasmosis 46%, Cryptococcosis 20%, Tuberculosis 19%, HIV Encephalopathy 5%, and Progressive Multifocal Leukoencephalopathy (PML) 5%. The main clinical manifestations were headache, fever, and focal neurological deficits~~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).

Comment [IM2]: Is this prevalence throughout the study or post 2005?

Comment [IM3]: I think this conclusion could be improved. What happened in 2005, and why is this new fact coming only in the conclusion. The results suggest nothing that relates to this last sentence. I think the conclusion could have some recommendation or a central message from the study.

Key worlds: *CNS, opportunistic, infection, HIV, AIDS, Clinical characteristics.*

1. 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~~ as it shifted from being a disease with a fatal outcome~~,~~ to a manageable chronic condition [1,2,3]. The level of accessibility to scientific and technological advancements, along with changes in socioeconomic conditions, has influenced the course of AIDS in developing countries. These factors have made AIDS a social burden with limited access to adequate and timely therapeutic options~~Thus, the level of accessibility to scientific-technological advancements, as well as thechangesin 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]. Theevolutionary changes of the virus and response of the hosthave also altered the way the diseasepresents 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~~.~~[9,10,11].

Therefore, it is essential to ~~know~~ understandthe magnitude of the clinical impact of AIDS-associated infectious diseases on the CNS; especially inhospital's AIDS unit in developing countries like Ecuador. Thus, the objective of this study was to retrospectively review ~~reviewretrospectively~~the ~~parameters of~~ evaluation, management, comorbidities, complications, and sequelae in a group of patients ~~with a diagnosis of~~diagnosed withhuman immunodeficiency virus (HIV) /AIDS.

2. Materials and Methods

Study Population and Statistical Analysis

An observational retrospective analytical study was conductedat 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~~)~~ /AIDSand 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 andMRI)~~(~~

[12,13,14]. Additionally, demographic variables, hospital care indicators, risk factors, clinical course, and therapeutic response were documented.We excluded medical records ~~with a lack of~~missing 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 wasperformedusing 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.

Comment [IM4]: Please include the ethics committee approval reference number and whether informed consent waiver was obtained.
Also include details on whether data was anonymised or pseudonymised to protect the patient confidentiality.

3. 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 statusbeing single (46%), followed bymarried (29%) and domestic partnership (17%) (see table 1).

Comment [IM5]: Are these risk factors found by the study or predefined risk factors and the study just evaluated their prevalence in this study sample? If they are pre-defined risk factors please include this in the text and cite the reference articles.

The prevalenceofopportunistic infectionsthat affect the CNSin AIDSpatientswereToxoplasmosis 46%, Cryptococcosis 20%, Tuberculosis 19%, HIV Encephalopathy 5%,Progressive Multifocal Leukoencephalopathy (PML) 5%, and unidentified infections 5%(see table2). The cumulative prevalence of CNS infections in AIDS patientsin the studied period (2002-2010)was5.9%.

Cerebral toxoplasmosis was confirmed through imaging studies and treatment response in 78% of cases, through imaging, serology, and treatment response in 15% of cases, and was unspecified in 7% of casesThe confirmation of cerebral *Toxoplasmosis* was done through imaging studies andindirectlyby 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 in various ways: through cerebrospinal 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; through India ink staining and positive culture in 46% of cases; through imaging and treatment in 15% of cases; and through positive serology for cryptococcal antigens in blood and treatment in 8% of cases.Cerebral *Cryptococcosis* was diagnosed throughcerebral spinal fluid (CSF) analysis, India ink staining, positive culture, and imaging (CT/ MRI) in 8% of cases.Through CSF analysis, India ink stainingand 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*Tuberculous meningitis was diagnosed through clinical manifestations, CSF analysis and imaging in 54% of cases.; andThroughthroughclinical manifestations, imaging, and treatment response in 46%. The clinicalpresentationswere tuberculous myelitis in 20%, of cases,isolated cerebral tuberculosis in 20% and meningitis associated with tuberculomas in 60% of cases. Progressive Multifocal Leukoencephalopathy (PML) was diagnosedby based on imaging and treatment response in 100% of cases (see table 3.)HIV encephalopathy was diagnosed in 100% of cases based on clinical manifestations, serology, treatment response, and normal imaging studies.HIV encephalopathy was diagnosed through clinical manifestations, serology, treatment response, and normality of imaging studies in 100% of cases. The diagnosis of other infectious processes considered the lack of response to treatment for other opportunistic infections, along with CSF analysis, imaging, and clinical manifestations.For the diagnosis of other infectious processes, the absence of

~~treatmentresponse to other opportunistic infections, CSF analysis, imaging, and clinical manifestations was taken into account.~~

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~~ foundbetween clinical manifestations and the ~~different~~ various describednosological entities ~~described~~.

Imaging studies (CT and/or MRI) were performed in 78% of cerebral toxoplasmosis cases. CNS involvement was observed as single focal lesions in 41.6% of cases, multiple focal lesions in 40.7%, and hyperintense lesions in 18%. Predominant involvement was noted in the midbrain, thalamic, peduncular, and cerebellar areas, with perilesional edema present in 45% of cases~~TheCNS 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 edemasin 45% of cases~~. Radiological findings in patients affected by Cryptococcus who underwent CT scans (58%) and MRI (50%) showed varied results. CT scans were normal in 71% of cases, while MRIs were normal in 33%. Abnormal findings included multiple focal lesions, hyperintense lesions with associated edema in the basal ganglia, semi-oval centers, pons, periaqueductal region, and cerebellum, sometimes with annular enhancement~~Radiological findings in patients who underwent CT scans(58%) and MRI (50%), in the group affected by Cryptococcus, range from normality in 71% of CTs and in 33% of MRIs, to the presence of multiple focal lesions and hyperintense lesionsassociated 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 edemain 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, reports vary from normal findings and cerebral edemas on CT scans to the presence of hypo- and hyperintense lesions in the semi-oval centers, globus pallidus, and corticospinal tracts in the brainstem, without contrast medium enhancement~~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).

During the first decade of the 2000s, antiretroviral therapy (ART) regimens were established in 84% of cases. Among these, 66% followed guidelines for treatment-naïve patients (AZT/3TC/EFV), while 34% involved adjustments in nucleoside and non-nucleoside components based on physiological conditions such as pregnancy (2%), toxicity (17%), and therapeutic failure (15%)~~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 caseswith 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 ARTand antimicrobial drugswas observed in 36.21% of patients. Only clinical response was evidenced in 5.17% of the patients, virological failuresin 6.89%,immune-virological dissociation in 1.72%, and the rest wereunknown situations.Mean CD4 lymphocyte count was 85 cells / mm^3 (SD +/- 89), and HIV viral load was 716 536 RNA copies / ml of serum (SD +/- 1 213 396).

Comment [IM6]: Could you please clarify what is meant by this statement? Is it that 54% of the patients were still on the HAART they were initiated on and had not had any changes?

Comment [IM7]: Could you please clarify what you mean here, was this adverse clinical, immunological and virological response? Was it failure to treatment?

Readmissions for various pathologies after hospital discharge was 29%.The mean time intervals from HIV and/or AIDS diagnosis to the presentation of the first clinical manifestations were 20.5 weeks (SD +/- 56.2) and 5.9 weeks (SD +/- 14.7), respectively~~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~~. The time interval between diagnosis according to the inclusion criteria and therapeutic intervention with ART was 5.0 weeks (SD +/- 5.17), excluding cases where therapeutic initiation occurred years

prior to central nervous system (CNS) involvement (3.4%)~~Therapeutic intervention, evaluated through the time interval between diagnosis according to the inclusion criteria and therapeutic intervention with ARTwas 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 ARTrepresented 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 being 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).

Comment [IM8]: Could you please include a figure showing these trends you are speaking of?

4. Discussion

Data from reference centers in developed countries of the regionreport 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 virusaround the world, with a predominance of males in the productive age group. The most common forms of transmission include~~,~~MSM, alcohol/drug use, ~~single marital status~~being single, male gender, and age 15 - 49 years. The high mortality rate (1 to 2%) reported worldwidereflect the demographic indicators of our retrospective cohort[1].Data form Pan American Health Organization (PAHO), during the study period, report~~s~~eda prevalence of ~~people infected with~~ HIV ~~ranged~~ ranging from 0.3 to 0.7%~~.~~[17]. Accordingly, the HIV/AIDS Unit of Eugenio Espejo Hospital (HEE)-Quitorecorded an annual prevalence of 0.7%.

Comment [IM9]: Developed or developing countries? Please clarify
Brazil is a high middle income country still categorized as a developing country.

Since HIV emerged as a determinant of AIDS in the 1980s, its incidence has varied over time. There was an initial rebound in transmission and mortality rates during the 1990s, followed by

Comment [IM10]: We need a graph/figure of these trends please.

periods of stability. Underreporting has been a persistent issue since then~~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 trend extends to HIV-associated opportunistic CNS infections since the introduction and widespread use of HAART. This is evidenced by a significant reduction in HIV dementia, decreased incidence of diseases like toxoplasmosis and brain cryptococcosis, and prevention of the development of PML and primary CNS lymphoma in developed countries~~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 lymphomain 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.

Comment [IM11]: We need a graph/ figureof these trends please

Comment [IM12]: Developed or developing countries? Please clarify

Comment [IM13]: Include this comparison in the suggested figures

The diagnostic confirmation methods used in this study align with the inclusion criteria employed in various studies and correlate with the imaging patterns observed in cerebral toxoplasmosis, which is often differentially diagnosed from primary CNS lymphomaThe diagnostic confirmation methods used hereinare in accordancewith 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 imaging findings reported in the literature, which describe no abnormalities in 69% of tomographic studies for cryptococcosisSimilar 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 preferred radiological method for the non-invasive diagnosis of these bilateral and asymmetric lesions in the subcortical white matter. These lesions typically show hypointense signals on T1 and hyperintense signals on T2, primarily affecting the parieto-occipital regions, without contrast enhancement or mass effectMagnetic 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 imaging findings includeimage described is cerebral atrophy of the basal ganglia and diffuse hyperintensities of inthe periventricular white matter [34]. In our study, we observed hypo- and hyperintense lesions that did not align with the radiological characteristics described in the literature. This highlights the importance of centralized interpretation of studies by specialized personnel to reduce discrepancies between observed findings and those used as reference for diagnosing HIV encephalopathyIn 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~~.

Cerebrospinal fluid (CSF) analysis reveals distinct characteristics for each of the described conditions~~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/mm^3, with a lymphocyte predominance of 30 to 90%.~~,~~Protein presence is common, and hypoglycorrhachia is typical, although normal protein levels have been reported in 43% of cases, and glucose levels are occasionally normal as well. Positive cultures are found in 22% to 27% of cases~~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/mm^3 and a mean proteinconcentration 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].

CSF study in toxoplasmosis is often challenging due to the variability of lesion manifestations, particularly brain edemas. Sporadic abnormalities like elevated spinal protein levels and pleocytosis cannot reliably serve as diagnostic references~~The study of CSF in toxoplasmosis is not frequently accessible due to the uncertainty of the produced lesions, especially brain edemas;meaning thatsporadicabnormalities, such as increased spinal protein levels and pleocytosis, cannot be used as references~~[38]. In PML, CSF findings are typically mild, with hypoglycorrhachia occurring in 1% of cases, abnormal protein levels in 55% (usually not exceeding 208 mg/dL)~~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/mm^3[39]. In HIV encephalopathy,none of the CSF biomarkers are clinically applicable for diagnosing~~to diagnostic~~ HIV-associated neurocognitive disorders. In advanced stages, neurological alterations are correlated with viral load in the CSF, rather than with viral load in the blood~~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 of less than 12% for IgG, 6% for IgM, and 7% for IgA in serum, do not provide sufficient post-test probability projections given the

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prevalence observed in this and other studies~~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 demonstrate high sensitivity and specificity, both exceeding 93%. This allows for a positive post-test probability of 25% and a negative post-test probability of 0.2% given the prevalence found in our study (0.02%), effectively ruling out the condition in cases of a negative test~~In cerebral cryptococcosis, highCryptococcal 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%.~~,~~This yields a positive post-test probability of 50.6% and a negative probability of 0.5%, which effectively allows for exclusion of the diagnosis when the antigen is absent~~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%.~~,~~Given our prevalence rate of 5%, this results in a negative post-test probability of 1.1%, allowing us to effectively rule out the diagnosis when the test is negative~~which, when used according to ourprevalence 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 toxoplasmaPCR[45]. However,studies similar to ours have identified predictive factors ~~of~~ for partial clinical response to treatment.~~,~~These include an odds ratio (OR)~~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 score~~when it is~~ less than 12;all of which arestatistically significant[46]. Quantitative PCR techniques for the detection of JC virus in biological fluids are currently under study~~continue to be studied~~[39, 47].

Availability, access, and adherence to ARTin 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 oftwo nucleosides and one non-nucleoside with treatment-naïve patients, with adjustments allowed according to basic clinical situation, toxicity, resistance, adherence, and availability[49]. During the 8-year cohort study, resistance rates and toxicity findings were sporadic and did not yield significant data. In contrast, larger series have reported adverse effects and dropout rates reaching up to 15% and 25%, respectively~~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 fortreatment adherence and reducing the risk of infections, combined with~~reduction of risk infections, added to~~ individual commitment, significantly~~notably~~ improve both the virological response and ART resistance rates~~the rates of resistance to ART~~.

5. CONCLUSION

This hospital-based study provides historical information regarding diagnosis methods, clinical presentationand etiologthey distribution of pathogens causing CNS infections among people living with HIVat Eugenio Espejo Hospital, Quito, Ecuador, ~~in~~ during the period 2002-2010~~at Eugenio EspejoHospital, Quito, Ecuador~~. It reported high prevalence of HIV-associated opportunistic CNS infectionsince 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 certain conditions.~~under conditioned circumstances.~~Consequently, many of the diagnostic methods described here are still in use today~~thus many of the diagnostic methods described here have been maintained to nowadays~~.

Comment [IM14]: I am of the opinion that this conclusion section could be improved a bit more with a final central message. You did this excellent study, but then what is the key message? What is the answer to "you did the study, then what?"

Align this conclusion to the conclusion in the abstract

6. References

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TABLES

Table 1. *Demographic and Clinical Characteristics*

	SampleFrecuency	Sample %
Age (average; SD) 34,6±8,5		
Gender		
Female	6	10
Male	55	90
Marital Status		
Single	28	46
Married	18	29
DomesticPartnership	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.

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

	SampleFrecuency	Sample %
Toxoplasmosis	28	46
Cryptococcosis	12	20
Tuberculosis	12	19
HIV Encephalopathy	3	5
Progressive Multifocal Leukoencephalopathy	3	5
Unidentifiedinfections	3	5

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

Table 3. Diagnosis Methods

	Sample %
Toxoplasmosis	
Imaging and Treatment	78
Imaging, Serology, and Treatment	15

Notspecified	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	100
Progressive Multifocal Leukoencephalopathy	
Imaging and Treatment	100

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

Table 4. ImaginStudy

	Sample %	**Localization**
Toxoplasmosis		
CT / MRI	78	
Single focal lesions Multiple focal lesions Hyperintenselesions		MidbrainThalamic Peduncular Cerebellar
Edema	45	Perilesional
Cryptococcosis		
CT	29	
MRI	67	
Multiple focal lesions		Basal gangliaSemi-oval centers Pons PeriaqueductalCerbellum
Hyperintenselesions		
Edema		Cerebral
Tuberculosis		
CT	59	
MRI	78	
Hypointenselesions		Caudate nucleus Basal ganglia Midbrain
Hyperintenselesions		
Edema	36 9	Cerebral Perilesional
Progressive Multifocal Leukoencephalopathy		

Hyperintenselesions		Cerebellarhemispheres Cerebral peduncles Reticular tissue
Edema	0	
HIV Encephalopathy		
Hypointenselesions		Semi-oval centers GlobuspallidusCorticospinaltracts
Hyperintenselesions		

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

Table 5. *Medical attentionparameters*

	Average	**SD**
Hospitalizationstay	31,5 dy	±21,7
Outpatientfollow-up	98,3 wk	±105,8
Intervals diagnosis of HIV/AIDS	20,5 wk	±56,2
Firstclinicalmanifestation	5,9 wk	±14,7
Therapeuticintervetion	5,0 wk	±5,17

Table 5 shows the time average and SD medical attention parameters of patients with AIDS.