Prevalence of Toxoplasmosis among HIV/AIDS patients and Correlation of Radiological Investigations with Laboratory findings

6 Abstract

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8 Introduction- Toxoplasmosis is a worldwide neglected tropical disease caused by the 9 intracellular protozoan named Toxoplasma gondii, which also causes severe disease in immunocompromised patients. Among patients with HIV/ AIDS, cerebral involvement is 10 11 more common and more serious than extra-cerebral toxoplasmosis. The definitive diagnosis is crucial for cerebral toxoplasmosis patients by directly demonstrating the presence of the 12 13 tachyzoite form of *Toxoplasma gondii* in the cerebral tissues. The presumptive diagnosis for 14 cerebral toxoplasmosis, including the clinical presentations, radio-imaging findings, 15 molecular and sero-diagnosis, and good response to anti-Toxoplasma therapy are widely 16 accepted in clinical practice.

17 Material and Methods- The present prospective hospital based study was conducted in the 18 Department of Microbiology, Government Medical College and Hospital, Nagpur, 19 Maharashtra, India. A total of 362 HIV positive patients were included in this study by 20 following criteria, either hospitalized or coming to ART clinic. The written informed consent 21 was obtained from each study participants and detailed clinical history, all relevant 22 investigations (including radiological for the diagnosis of toxoplasmosis) of each patient was 23 noted. Specimens of blood for ELISA test were taken by venipuncture. Serum samples were 24 then subjected to ELISA test for detecting anti-toxoplasma IgM and IgG antibodies as per the 25 manufacturer's instructions. Data was compiled in MS Excel and checked for its 26 completeness and correctness. Then it was analyzed.

Observation- Out of these 362 HIV positive patients, 226 (62.43%) were males and 136 (37.57%) were females. Most of the HIV positive patients, 359 (99.17%) were married and 313(86.46%) were from urban area whereas 49 (13.54%) were from rural area. Total 85 (23.48%) HIV positive patients were co-infected with toxoplasmosis. 65 (17.96%) were males and 20 (5.52%) were females. Majority of the co-infected patients were laborers 35 (9.67%) followed by drivers, skilled employee, house wives, farmers and others were 17 (4.70%), 13 (3.60%), 12 (3.31%), 3 (0.82%) and 5 (1.38%) respectively Both the ELISA and 1 | P age

34 the CT-scan were simultaneously positive in 75 (20.72%) and negative in 172 (47.51%) 35 cases, the overall correlation seen in 247 (68.23%). Radiological features suggestive of 36 toxoplasmosis among HIV-toxoplasmosis co-infected patients in the CT-scan head. Out of 37 these 85 HIV-toxoplasma co-infected patients, only hyper density was seen in 13 (15.29%) patients, only hypo density was present in 37 (43.52%) patients. Whereas, 25 (29.41%) cases 38 showed only ring enhancement as the radiological feature. 4(4.70%) patients had hyper 39 40 density and ring-enhancement features and 6 (7.05%) cases showed hypo density and ring-41 enhancement.

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43 Conclusion- We conclude from this study that the prevalence of toxoplasmosis in HIV
44 positive patients was high. Radiological investigations are good and provide better
45 localization of toxoplasmosis but less confirmatory than ELISA.

Key words: Toxoplasmosis, Sero-positivity, HIV/AIDS, ART Centre

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49 INTRODUCTION

Toxoplasma gondii causes severe disease in immunocompromised patients where reactivation 50 of latent infection causes symptomatic disease^{1, 2}. In immunocompromised individuals who 51 previously acquired latent infection can lead to reactivated toxoplasmosis with encephalitis. 52 53 Toxoplasmic encephalitis and disseminated toxoplasmosis have been observed in patients 54 with immunodeficiency due to various causes, such as Hodgkin's disease or 55 immunosuppressive therapy because of other malignancies. Disseminated toxoplasmosis may also complicate transplantation of organs or bone marrow. This may result either from 56 57 transplantation of an organ from a Toxoplasma gondii infected donor to a susceptible recipient or from reactivation of a latent Toxoplasma gondii infection in the recipient due to 58 immunosuppressive treatment.³⁻⁵ 59

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The initial presentation of toxoplasmic encephalitis in patients with AIDS may be subacute. Patients present with altered mental status (62%), headaches (59%), and fever (41%) associated with focal neurologic deficits. Progression of the infection can lead to confusion, drowsiness, seizures, hemiparesis, hemianopsia, aphasia, ataxia, and cranial nerve palsies. Motor weakness and speech disturbance are seen as the disease progresses. If not treated promptly, patients may progress to coma within days to weeks. Toxoplasmosis may rarely present as a rapidly fatal form of diffuse or global encephalitis with profound mental status
changes, nausea, and vomiting, usually indicating elevated intracranial pressure.⁶⁻¹⁰

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70 Among patients with AIDS, cerebral involvement is more common and more serious than 71 extra-cerebral toxoplasmosis. The definitive diagnosis is crucial for cerebral toxoplasmosis patients by directly demonstrating the presence of the tachyzoite form of Toxoplasma gondii 72 73 in the cerebral tissues. The presumptive diagnosis for cerebral toxoplasmosis, including the 74 clinical presentations, radio-imaging findings, molecular and sero-diagnosis for Toxoplasma 75 infection and good response to anti-toxoplasma therapy are widely accepted in clinical 76 practice. The favorable outcome of cerebral toxoplasmosis is the improvement of clinical and 77 radiological features after 2 to 3 weeks of initiated empirical therapy. The clinical diagnosis 78 is a dilemma because cerebral toxoplasmosis mimics with other brain diseases making it 79 difficult to diagnose. Differential diagnosis of AIDS-associated cerebral toxoplasmosis is 80 extremely important and the local neuro-epidemiology and the degree of immunosuppression 81 in the host are two key factors involved. Primary CNS lymphoma is the main differential 82 diagnosis of cerebral toxoplasmosis reported from developed countries. While, focal forms of 83 cerebral tuberculosis (tuberculoma and, less likely tuberculous brain abscess) allow for differential diagnosis of cerebral toxoplasmosis mainly in developing countries.¹¹⁻¹³ 84

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Radio-imaging findings, either by computed tomography (CAT scan) or magnetic resonance imaging (MRI), are useful tools for the presumptive or empirical diagnosis of cerebral toxoplasmosis. Cerebral toxoplasmosis usually causes unifocal, and more frequently multifocal lesions, and less likely diffuse encephalitis. These findings are however not pathognomonic of cerebral toxoplasmosis. Radiological diagnosis can be classified as typical findings of hypodense lesions with ring enhancing and perilesional edema are observed in nearly 80% of cerebral toxoplasmosis cases.¹⁴

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94 Cerebral toxoplasmosis poses a diagnostic problem that relies on classical serological 95 methods to detect anti-toxoplasma immunoglobulins because clinical blood samples from 96 patients with immunodeficiency can fail to produce sufficient titers of specific antibodies. 97 Sero-evidence of toxoplasma infection, independent of antibody levels is generally seen in all 98 patients before developing cerebral toxoplasmosis. Most cerebral toxoplasmosis patients have 99 high titers of anti-toxoplasma IgG antibodies with high IgG avidity that provides serological 100 evidence of infection and this also supports a conclusion that this is the result of a secondary 101 reactivation of latent or chronic toxoplasma infection. Therefore, it is important to determine 102 the toxoplasma sero-status in all HIV-infected patients in order to define the population at 103 risk for cerebral toxoplasmosis. At the onset of cerebral toxoplasmosis, significant rises in 104 anti-toxoplasma antibody titers are found in only a marginal number of these patients. The 105 level of rising titers may occur before the onset of cerebral toxoplasmosis and it does not 106 seem to predict the occurrence of cerebral toxoplasmosis. Anti-Toxoplasma IgM antibody, as 107 measured by the indirect fluorescent or ELISA tests, is rarely found in cerebral toxoplasmosis 108 patients. In cases of cerebral toxoplasmosis, a negative or low titer of serological results or 109 even the absence of anti-toxoplasma antibodies does not exclude positive diagnosis and the 110 anti-toxoplasma therapy should be started without delay if clinical and radiological 111 presentations are consistent with cerebral toxoplasmosis. A positive serology result seems to 112 be even less useful in areas where there is a high prevalence of toxoplasmosis in the general population, while a negative result does have a high negative predictive value.¹⁵⁻¹⁶ Therefore. 113 114 the present study was undertaken to assess the prevalence of toxoplasmosis among HIV 115 patients and role of radiological investigation in the diagnosis.

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117 MATERIAL AND METHODS

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119 Study design

120 The present prospective hospital based study was conducted in the Department of 121 Microbiology, Government Medical College and Hospital, Nagpur, Maharashtra, India. A 122 total of 362 HIV positive patients included through following criteria, either hospitalized or 123 coming to ART clinic during this study period.

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125 Inclusion criteria

- All volunteered confirmed HIV/AIDS positive patients with CNS signs and symptomssuggestive of toxoplasmosis were included in this study.
- 128

129 Exclusion criteria

Patients with immunocompromised status due to other than HIV infection were excludedfrom this study.

To maintain the strict confidentiality and to conceal the identity of the patient, coding system for sample was followed which was known only to investigator. After taking written informed consent, detailed clinical history and all relevant investigations (including radiological for the diagnosis of toxoplasmosis) of each patient was done and findings were noted as per standard predesigned and pretested clinical proforma.

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Specimens of blood to provide the sera for ELISA test were taken by venipuncture. At least 5ml of blood was obtained to ensure that there will be enough serum for the test. Immediately blood was transferred from the syringe into dry stoppered sterile tube and allowed to clot. When the serum has separated, it was pipetted off into a sterile tube.¹⁷ Serum samples were then subjected to ELISA test for detecting anti-toxoplasma IgM and IgG antibodies as per the manufacturer's instructions. Process was performed as per standard protocol.¹⁸

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Data was compiled in MS Excel and checked for its completeness and correctness. Then it was analyzed. Final diagnosis (based on ELISA) was compared with the Radiological findings to assess the accuracy of radiological investigations. Online statistical calculator was also used and qualitative test were applied with p value of < 0.05 was considered statistically significant for interpretation of the findings. The prior ethical approval was sought for this study by the institutional ethics committee.

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153 **RESULTS**

154 Out of these 362 HIV positive patients, 226 (62.43%) were males and 136 (37.57%) were 155 females. Most of the HIV positive patients, 359 (99.17%) were married and only 3 (0.83%) 156 were unmarried and 313(86.46%) were from urban area whereas 49 (13.54%) were from 157 rural area. Majority of the patients were laborers 144 (39.78%) followed by house wives, 158 skilled employee, drivers, farmers and others were 75 (20.72%), 64 (17.68%), 52 (14.91%), 12 (3.31%) and 15 (4.14%) respectively. Total 85 (23.48%) HIV positive patients were co-159 160 infected with toxoplasmosis. 65 (17.96%) were males and 20 (5.52%) were females. All of 161 the co-infected patients were married and 78 (21.55%) were from urban area whereas 7 162 (1.93%) were from rural area. Majority of the co-infected patients were laborers 35 (9.67%) 163 followed by drivers, skilled employee, house wives, farmers and others were 17 (4.70%), 13 164 (3.60%), 12 (3.31%), 3 (0.82%) and 5 (1.38%) respectively (**Table 1**).

- 166 Table 1: Prevalence of Toxoplasmosis co-infection among HIV positive patients
- 167 according to socio-demography.
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Variables	HIV Positive (%) N=362	IgG positive (%), N=71	P value	IgM positive (%), N=14	P value	IgG + IgM (%)
Age in Years	11-502					
15-24	23 (6.32)	3 (0.82)	0.488	0 (0)	0.734	3 (0.82)
25-34	171(47.23)	32 (8.84)	-	6 (1.66)		38 (10.50)
35-44	133(36.74)	31 (8.56)	_	5 (1.38)		36 (9.94)
45-54	29(8.01)	5 (1.38)	_	2 (0.55)		7 (1.93)
55 and above	6 (1.66)	0 (0)	_	1 (0.28)		1 (0.28)
Total	362 (100)	71(19.61)		14 (3.86)		85 (23.48)
Sex						
Male	226 (62.43)	53 (14.72)	0.018*	12 (3.31)	0.093	65 (17.96)
Female	136(37.57)	18 (4.97)	1	2 (0.55)		20 (5.52)
Marital						
Status						
Married	359 (99.17)	71 (19.61)	0.390	14 (3.86)	0.737	85 (23.48)
Unmarried	3 (0.83)	0 (0)	7	0 (0)	-	0 (0)
Residence						
Rural	49(13.54)	6 (1.66)	0.162	1 (0.28)	0.531	7 (1.93)
Urban	313 (86.46)	65 (17.96)	1	13 (3.60)		78 (21.55)
Occupation						
Driver	52 (14.91)	15 (4.14)	0.488	2 (0.55)	0.749	17 (4.70)
Farmer	12 (3.31)	3 (0.82)		0 (0)	-	3 (0.82)
Laborer	144 (39.78)	28 (7.73)		7 (1.93)		35 (9.67)
Housewife	75 (20.72)	11 (3.03)		1 (0.28)		12 (3.31)
Skilled	64 (17.68)	11 (3.03)		2 (0.55)		13 (3.60)
Employee						
Others	15 (4.14)	3 (0.82)	7	2 (0.55)]	5 (1.38)

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- 171 Table 2: Prevalence of Toxoplasmosis co-infection among HIV positive patients
- 172 according to signs, symptoms and other risk factors.

Variables	IgG positive (%)	P value	IgM positive (%)	P value	IgG + IgM
Signs and symptoms					
Headache	68 (18.78)	0.000*	12 (3.31)	0.019*	80 (22.10)
Fever	57 (15.75)	0.000*	12 (3.31)	0.013*	69 (19.06)
Increased	21 (5.80)	0.555	8 (2.20)	0.004*	29 (8.01)

	1	1	1	1
				11(3.04)
4 (1.10)	0.573	3 (0.82)	0.024*	7 (1.93)
			0.001*	9 (2.49)
2 (0.55)	0.547	0 (0)	-	2 (0.56)
37 (10.22)	0.000*	6 (1.66)	0.002*	43 (11.88)
34 (9.40)		8 (2.20)		42 (11.60)
54 (14.91)	0.000*	13 (3.600	0.000*	67 (18.50)
17 (4.70)		1 (0.28)	-	18 (4.98)
5 (1.38)	0.000*	0 (0)	-	5 (1.38)
66 (18.23)		14 (3.87)		80 (22.10)
64 (17.68)	0.487	12 (3.31)	0.516	76 (20.10)
0 (0)	-	0 (0)	-	0 (0)
7 (1.93)	-	2 (0.55)	-	9 (2.49)
20 (5.52)	0.227	2 (0.55)	0.292	22 (6.08)
10 (2.76)	1	3 (0.82)	1	13 (3.60)
28 (7.73)	1	9 (2.49)	1	37 (10.22)
13 (3.59)	1	0 (0)	1	13 (3.60)
51 (14.10)	0.000*	12 (3.31)	0.000*	63 (17.40)
	-	2 (0.55)	-1	22 (6.08)
	34 (9.40) 54 (14.91) 17 (4.70) 5 (1.38) 66 (18.23) 64 (17.68) 0 (0) 7 (1.93) 20 (5.52) 10 (2.76) 28 (7.73) 13 (3.59)	$\begin{array}{c ccccc} 4 & (1.10) & 0.573 \\ \hline & 0.095 \\ \hline & 0.095 \\ \hline & 0.55) & 0.547 \\ \hline & & \\ \hline \hline & & \\ \hline & & \\ \hline \hline & & \\ \hline & & \\ \hline \hline \hline & & \\ \hline \hline & & \\ \hline \hline & & \\ \hline \hline \hline & & \\ \hline \hline \hline & & \\ \hline \hline \hline \hline$	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$

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174 As shown in table 2, the toxoplasmosis co-infection among HIV positive patients according 175 to signs, symptoms and other risk factors was assessed. The signs and symptoms associated with co-infection showed that majority of the patients had headache (80 (22.10%) and fever 176 (69 (19.06%). Whereas, 29 (8.01%), 11(3.04%), 7 (1.93%), 9 (2.49%) and 2 (0.56%) co-177 infected patients had symptoms of increased intracranial tension, seizure, altered sensorium, 178 179 papillo-edema and cerebellar signs respectively. Almost half of the patients (43 (11.88%) had 180 history of pet contact, 67 (18.50%) history of meat ingestion and 5 (1.38%) had past history 181 of toxoplasmosis, which were statistically significant. Mode of transmission was through

- sexual contact among 76 (20.10%), whereas, among 9 (2.49%) patients the transmission was
- unknown. Decreased CD4 cell count was observed <100 among 22 (6.08%), 101-200, 201-
- 184 500 and >501 CD4 cells among 13 (3.60%), 37 (10.22%) and 13 (3.60%) respectively.
- 185 However, majority of the patients, 63 (17.40%) responded to treatment.
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187 Table 3: Correlation between radiological features in CT-scan head and ELISA for

188 anti-toxoplasma antibodies

	ELISA	ELISA		
Radiology	Positive (%)	Negative (%)	Total (%)	
Positive	75(20.72)	105(29.00)	180(49.72)	
Negative	10(2.76)	172(47.51)	182(50.28)	
Total (%)	85(23.48)	277(76.52)	362(100)	

189 McNemars x^2 test=78.48 (Software used: Stata ver.10.0), Odd's Ratio =12.29, 95%

190 Confidence Intervel = (5.84-26.53); p value <0.0001 considered significant.

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The correlation between the ELISA sero-positivity and radiological feature is shown in **Table 3 and 4**, both the ELISA and the CT–scan were simultaneously positive in 75 (20.72%) and negative in 172(47.51%) cases, the overall correlation seen in 247(68.23%). Strong association between ELISA and CT-scan by McNemars x^2 test was found. 10 (2.76%) cases were positive by ELISA and negative by radiological examination for toxoplasma. The Odds ratio was found to be 12.29 with 95% CI = (5.84-26.53) which was found to be statistically significant.

Table 4: Comparative evaluation of Radiological test with ELISA

Statistic	Formula	Value	95% CI
Sensitivity	$rac{a}{a+b}$	88.24%	79.43% to 94.21%
Specificity	$rac{d}{c+d}$	62.09 %	56.10% to 67.83%
Positive Likelihood Ratio	${Sensitivity\over 100-Specificity}$	2.33	1.96 to 2.76
Negative Likelihood Ratio	$rac{100-Sensitivity}{Specificity}$	0.19	0.11 to 0.34

Positive Predictive Value	$\frac{a}{a+c}$	41.67% (*)	34.38% to 49.23%
Negative Predictive Value	$rac{d}{b+d}$	94.51 % (*)	90.13% to 97.33%

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201 Table 5: Radiological features in HIV-toxoplasmosis co-infected patients (N=85).

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Radiological features	No. of cases (%)	p-value
Only Hyperdensity	13(15.29)	0.408
Only Hypodensity	37(43.52)	0.026*
Only Ring-enhancement	25(29.41)	0.00*
Hyperdensity + Ring-enhancement	04(4.70)	0.384
Hypodensity + Ring-enhancement	06(7.05)	0.280
Total (%)	85(100)	-

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204 **Table 5** shows the radiological features suggestive of toxoplasmosis in HIV-toxoplasmosis 205 co-infected patients in the CT-scan head. Out of these 85 HIV-toxoplasma co-infected 206 patients, only hyper density was seen in 13(15.29%) patients, only hypo-density was present 207 in 37 (43.52%) patients. Whereas, 25 (29.41%) cases showed only ring enhancement as the radiological feature. Only 4 (4.70%) patients had hyper density and ring-enhancement 208 209 features. Whereas, 6(7.05%) cases showed hypo density and ring-enhancement. Only hypo 210 density and only ring-enhancement were the radiological features which were found to be 211 statistically significant (p<0.05).

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213 DISCUSSION

Toxoplasmosis is the most common opportunistic infection in HIV-infected patients. A high seroprevalence of anti-*Toxoplasma gondii* IgG antibody has been reported in HIV-infected subjects¹⁹⁻²¹. To our understanding, there is no adequate information on the prevalence of *Toxoplasma gondii* infection in HIV/AIDS patients in India. In our study, the seroprevalence of *Toxoplasma gondii* showed 23.48%. The co-infection occurred most among married male from urban population with the history of pet contact, meat ingestion and unsafe sexual activity. This rate is almost comparable with the other studies reported elsewhere such as 221 study by Holliman 1990, in which the seropositivity of toxoplasmosis found to be 26.06%, 222 Sykora et al 1992 found seropositivity of toxoplasmosis 29.8% in HIV positive patients. 223 Brindle et al 1991 found seropositivity of toxoplasmosis to be 22%. Oksenhendler et al 1994 224 found that 25.4% was seropositivity rate. Similarly, Minkoff et al 1997 found that 20.2% was 225 the seroprevalence of toxoplasmosis. Millogo et al 2000 found seropositivity in 25.4%. The seropositivity was found as 67.8%, 23.2%, 22.4%, & 21% by studies conducted by different 226 227 authors like Sukthana et al 2000, Nissapatorn et al 2001 and Nissapatorn et al 2002, respectively. Also, Hari et al 2007, Akanmu et al 2010 and Oshinaike et al 2010, carried out 228 229 study to find out seroprevalence of toxoplasmosis and found out to be 8%, 54% and 85.5% respectively²²⁻³³. Our study demonstrates that the high prevalence of *Toxoplasma gondii* co-230 231 infection in HIV/ AIDS patients suggesting that HIV-infected populations should be 232 protected from Toxoplasma gondii infection to reduce the prevalence and morbidity and 233 burden of the disease.

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235 In the present study, both the ELISA and the CT-scan were simultaneously positive in 75 236 (20.72%) and negative in 172 (47.51%) cases, the overall correlation seen in 247 (68.23%). In fact we found strong association between ELISA and CT-scan by McNemars x^2 test. 237 238 Software used for the analysis of the data was Stata ver.10.0. Also, p=0.000 was found to be highly significant. A study was done by Venugopal A et al 2012, among AIDS patients in a 239 tertiary care hospital in Mangalore, India ³⁴. It was a retrospective study done by reviewing 240 241 medical records of HIV-positive diagnosed with toxoplasmosis from Jan 2000 to Dec 2010. 242 Diagnosis was based on clinical features, demonstration of elevated IgG by ELISA and 243 associated CT-scan findings. 2826 HIV positives attended Infections Disease Cell from 2000 244 -2010, of which 33 (1.12%) had CNS toxoplasmosis. Mean level of IgG was 255.69. CT / 245 MRI finding of ring enhancing lesion or cerebritis was seen in 79 % of the cases with 18% of 246 lesions in both basal ganglia and parietal lobes. Cerebritis was most common lesion in 247 CT/MRI, seen in 16 cases while ring enhancing lesions were seen in 10 cases. 82% improved 248 with treatment and 18% died of complications. The possibility of cerebral toxoplasmosis 249 should be considered in every HIV-positive patient with neurological symptoms parietal lobe 250 lesions were common in their study, contrary to other existing data which say toxoplasma 251 lesions are usually midline lesions.

253 In the present study, out of these 85 HIV-toxoplasma co-infected patients, only hyperdensity 254 was seen in 13(15.29%) patients, only hypodensity was present in 37 (43.52%) patients 255 whereas 25 (29.41%) cases showed only ring enhancement as the radiological feature. 4 256 (4.70%) patients had both hyperdensity & ring-enhancement features whereas 6(7.05%) cases 257 showed hypodensity and ring-enhancement simultaneously. Similar radiological features 258 were reported by other studies. In a study done by Vidal et al 2005a, they found that typical 259 findings of hypodense lesions with ring enhancing and perilesional edema were present in nearly 80% of cerebral toxoplasma patients¹⁰. And in nearly 20% cases a typical pattern of 260 261 hypodense lesions without contrast enhancing and with an expansive effect, cerebral 262 toxoplasma patients without focal lesions and MRI demonstrating focal lesions and diffuse 263 cerebral encephalitis without visible focal lesions was found. In another study carried out by 264 Pereira-Chioccola VL and Vidal JE, Sao Paulo in patients with toxoplasma encephalitis 265 various lesions found were hypodense lesion with ring-enhancing and perilesional edema, 266 nodular enhancing and perilesional edema and ring-enhancing lesion with small, enhancing asymmetric nodule along wall of the lesions ¹⁵. 267

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269 CONCLUSION

We conclude that from findings of this study the prevalence of toxoplasmosis in HIV positive patients was high, especially among married male patients from urban area having contact with pet animals, history of meat ingestion and major transmission by unsafe sexual activities with most common symptoms of headache, fever, increased intracranial tension and seizure. Although Radiological investigations are good and provide better localization of toxoplasmosis but less confirmatory than ELISA. So combination of modalities should be used in diagnosis of toxoplasmosis for appropriate management.

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