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Difference in *Toxoplasma gondii* Seroprevalence Rates Due to Low and High CD4 Counts in Patients with HIV/AIDS

HIV/AIDS Hastalarında Düşük ve Yüksek CD4 Sayısına Bağlı Toxoplasma gondii Seroprevalans Oranlarındaki Farklılık

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ABSTRACT

Objective: Since symptomatic toxoplasmosis in in human immunodeficiency virus (HIV)/Acquired immunodeficiency syndrome (AIDS) almost always occurs as a result of reactivation of chronic infection, screening Toxoplasma serology has an important role in the follow up of the main disease in these populations. In this meta-analysis, we aimed to reveal the difference in the seroprevalence rates of *Toxoplasma gondii* infection between groups in relation to CD4 counts (CD4-counts ≥200 and <200 cells/mm^3) HIV-infected population.

Methods: The meta-analysis was performed by searching for the studies in English that were published in the last 20-year period in databases including PubMed, Google Scholar, Embase, Science Direct and Web of Science. The process of searching was carried out using the keywords: "Acquired immunodeficiency syndrome", "AIDS", "Human immunodeficiency virus", "HIV", "Toxoplasma", "Toxoplasmosis", "*Toxoplasma gondii*", , "seroprevalence", "prevalence" and "immunoglobulin G".

Results: A total of 16 studies including 3982 seropositive samples of *T. gondii*, 2792 of which were in first group (HIV positive patients with CD4-counts ≥200 cells/mm^3) and 1190 were in second group (HIV positive patients with CD4-counts <200 cells/mm^3), were included in the meta-analysis. The seroprevalence of *T. gondii* was 40.03% in HIV-positive patients with CD4 counts ≥200 cells/mm^3, and 43.5% in the group with CD4 counts <200 cells/mm^3. Seroprevalence rates in the studies included in the meta-analysis showed variability (heterogeneity) in both groups and heterogeneity between studies was higher in group 1 [Group 1; Cochran Q=994.16, DF=15, I^2=98.49%, p<0.0001 and group 2; Cochran Q=368.50, DF=15, I^2=95.93%, p<0.0001].

Conclusion: We concluded that HIV/AIDS patients with low CD4 counts have higher epidemiological risk as well as immunological risk of toxoplasmosis. To the best of our knowledge, this is the first meta-analysis evaluating the seroprevalence of *T. gondii* in AIDS/HIV population by comparing the seroprevalance of *T. gondii* in subgroups formed according to CD4 counts.

Keywords: *Toxoplasma gondii*, seroprevalence, HIV, CD4, meta-analysis

ÖZ

Amaç: İnsan bağışıklık yetmezliği virüsü (HIV)/Edinilmiş bağışıklık yetmezliği sendromu (AIDS) hastalarında semptomatik toxoplazmoz, hemen hemen her zaman kronik enfeksiyonun yeniden aktivasyonu sonucu meydana gelmektedir. Bu hastalarda Toxoplazma serolojisinin taranmasının ana hastalığın takibindeki önemi büyüktür. Bu meta-analizde, HIV-pozitif popülasyondaki *Toxoplasma gondii* seroprevalans oranlarının düşük (CD4 <200 hücre/mm^3) ve yüksek (CD4 ≥200 hücre/mm^3) CD4 sayılarına sahip hastalarda farklılık gösterip göstermediğini araştırmayı amaçladık.

Yöntemler: Bu meta-analiz, PubMed, Google Akademik, Embase, Science Direct ve Web of Science veri tabanlarında son 20 yılda yayınlanmış olan İngilizce çalışmaları araştırmak suretiyle hazırlandı. Literatür taramasında "AIDS", "HIV", "Toxoplasma", "Toxoplasmosis", "*Toxoplasma gondii*", "seroprevalence", "prevalence" ve "immünoglobulin G" anahtar kelimeleri kullanıldı.

Bulgular: İki bin yedi yüz doksan ikisi birinci grupta (CD4 sayısı ≥200 hücre/mm^3) ve 1190'ı ikinci grupta (CD4 sayısı <200 hücre/mm^3) olmak üzere toplamda 3982 seropozitif *T. gondii* örneğini içeren toplam 16 çalışma meta-analize dahil edildi. *T. gondii* seroprevalansı, CD4 sayısı ≥200 hücre/mm^3 olan HIV pozitif hastalarda %40,03 iken CD4 sayısı <200 hücre/mm^3 olan grupta %43,5 idi. Meta-analize dahil edilen çalışmalardaki seroprevalans oranları her iki grupta da değişkenlik (heterojenite) göstermekteydi ve

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çalışmalar arasındaki heterojenite grup 1'de daha yüksekti [Grup 1; Cochran Q= 994,16, özgürlük derecesi (DF)=15, I^2=%98,49, p<0,0001 ve grup 2; Cochran Q=368,50, DF=15, I^2=%95,93, p<0,0001].

Sonuç: CD4 sayısı düşük HIV/AIDS hastalarında halihazırda bilinen immünolojik olarak artmış riskin yanı sıra epidemiyolojik olarak da toxoplazmozis riskinin daha yüksek olduğu sonucuna vardık. Bildiğimiz kadarıyla çalışmamız, AIDS/HIV hastalarında *T. gondii*'nin seroprevalansını, CD4 sayısına göre oluşturulan alt gruplardaki seroprevalans oranlarını karşılaştırmak suretiyle değerlendiren ilk meta-analizdir.

Anahtar Kelimeler: *Toxoplasma gondii*, seroprevalans HIV, CD4, meta-analiz

INTRODUCTION

About 30% of the population in the world is estimated to have infected by *Toxoplasma gondii* which is a cause of zoonotic multisystemic parasitosis (1). Toxoplasmosis has mainly an asymptomatic course in immunocompetent people, while it may have severe consequences in immunocompremised patients like people living with human ımmunodeficiency virus (HIV). Almost 37 million people in the world have HIV infection, and pooled worldwide prevalence of *T. gondii* in HIV-infected patients is estimated to be 35.8% (2,3). In another meta-analysis, patients with HIV/AIDS compared to HIV-negative population had higher seroprevalence of *T. gondii*; the rates were 46.12% vs 36.56%, respectively (4). Although the rate declined after highly active antiretroviral treatment era, cerebral toxoplasmosis is still considered to be one of the most common of the opportunistic central nervous system infections of patients with HIV infection (5). Cerebral toxoplasmosis occurs most commonly in HIV-infected patients having CD4 counts below 100 cells/mm^3; however, rare cases are reported among patients having CD4 counts up to 200 cells/mm^3 (6). Since toxoplasmosis is known to occur mainly as reactivation of latent infection, hence screening patients for anti-Toxoplasma antibodies is one of the main requirements in HIV management. In literature, there are many studies and some meta-analysis assessing the seroprevalence of *T. gondii* infection in people with HIV infection compared to normal population, and there are also studies assessing the differences in the seroprevalence rates between subgroups in relation to CD4 counts. In this meta-analysis, we aimed to reveal the difference in the seroprevalence rates of *T. gondii* infection between groups in relation to CD4 counts in HIV-infected population.

METHODS

The literature search was commenced on April 20, 2019 and the analysis procedure was carried on between April 20, 2019 and May 25, 2019 in accordance with the Preferred Reporting Items for Systematic Reviews and meta-analysis statement (Figure 1) (7).

Search Strategy

We searched the studies in English that were published in the last 20 years-period (between January 1999 and May 2019) in databases, including PubMed, Google Scholar, Embase, ScienceDirect and Web of Science. The process of searching was carried out using the keywords: "Acquired immunodeficiency syndrome (AIDS)", "HIV", "Toxoplasma", "Toxoplasmosis", "*Toxoplasma gondii*", "seroprevalence", "prevalence" and "immunoglobulin G".

Inclusion and Exclusion Criteria

Cross sectional, case-control and cohort studies published in last 20-years-period that investigated the seroprevalence of *T. gondii* in HIV infected patients were included in the meta-analysis. Review and meta-analysis studies, studies that only presented the percentages instead of the numbers of the patients, studies not providing the raw data, articles that were not available in English full-text, the studies not conducted on humans, studies providing seroprevalence rates in non-HIV groups, studies not including CD4 groups according to cut-off level of 200 cells/mm^3 were excluded from the study. The exclusion criteria are presented at Figure 1.

Data Extraction

The data extracted from each eligible study included the surname of the first author, study location (country), publication year, total sample size of in first group (HIV positive patients with CD4 counts over 200 cells/mm^3) and second group (HIV positive patients with CD4 counts below 200 cells/mm^3), number of seroposive patients for *T. gondii* in each groups. The eligibility of the articles with full-text included in the study was assessed by two different reviewers (EY, RAC). Disputes between the two reviewers who gather work data were resolved through discussion. Whenever it was necessary, a third reviewer (LG) was consulted.

Statistical Analysis

Study design was created through the Medical Research Support (MedicReS) e-picos assistant program. The data included in the study was recorded in the Microsoft Office 2016 Professional Plus excel program. Medcalc© software version 19.0.3 program was used for meta-analysis. Author, country, publication year, total sample size of in each groups and number of seroposive patients for *T. gondii* in each groups were transferred from excel to Medcalc© for analysis. Statistical test for heterogeneity was performed to measure the heterogeneity of data. According to this; $I^2 \leq 25\%$ heterogeneity was assumed to be insignificant, and fixed effect was used in case $I^2 \leq 25\%$. On the other hand, $I^2 > 25\%$ heterogeneity was assumed to be significant; the study data were considered as nonhomogeneous and the random effect value was used. A funnel plot was designed to evaluate possible bias.

RESULTS

We reached a total of 7072 studies in the initial electronic search process. Among these, 1523 articles were removed due to duplication. Of the remaining 5549 studies, 4618 were removed after reviewing titles whereas 757 were excluded after reviewing the abstracts. The remaining 174 full-text-articles were evaluated according to the pre-determined inclusion criteria, and 158 of them were excluded from meta-analysis because they did not meet the eligibility criteria. As a result, a total of 16 studies were included in the meta-analysis (Figure 1). Except one (Brazil), all of the studies were conducted in Africa [Ghana, Ethiopia, Nigeria (n=3), South Africa] and Asia/Middle East [Turkey, Iran (n=3), India, China, Thailand, Taiwan, Malaysia]. The publication dates of the studies were the year 2003 and after (Table 1).

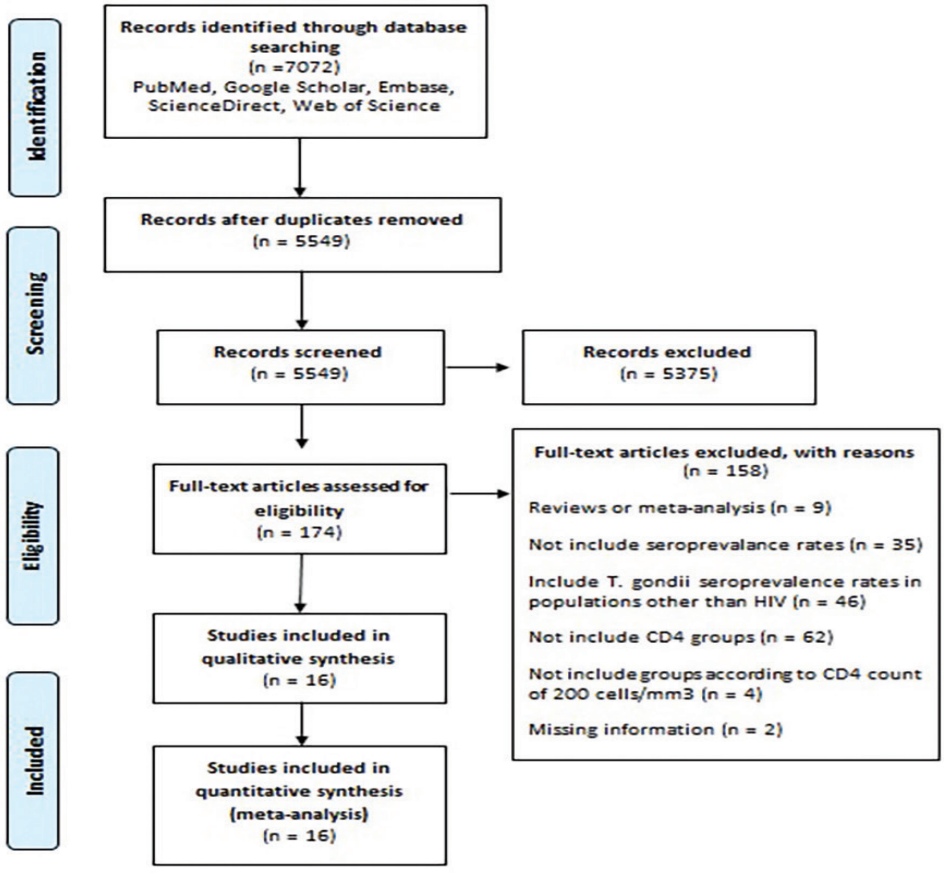

Figure 1. Flow chart for literature search and study selection in accordance with PRISMA statement
HIV: Human ımmunodeficiency virus, PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis

Table 1. Characteristics of *T. gondii* seroprevalence studies which were included in meta-analysis

Ref	Author	Country	Publication year	Study period	Group 1 (n) total	Group 1 (n) IgG+	Group 2 (n) total	Group 2 (n) IgG+
12	Senoglu	Turkey	2018	2006-2017	459	192	155	75
13	Shen	China	2016	No data	179	21	80	4
14	Pappoe	Ghana	2017	2015	349	257	45	36
15	Chemoh	Thailand	2015	2009-2010	248	87	52	22
16	Yohanes	Ethiopia	2014	2013	123	110	13	11
17	Anuradha	India	2014	2013	60	19	32	14
18	Ogoina	Nigeria	2013	2008	81	33	30	10
19	Xavier	Brazil	2013	2009-2010	204	168	46	32
20	Daryani	Iran	2011	2007-2008	55	40	7	5
21	Mohraz	Iran	2011	2004-2005	144	70	57	30
22	Hari	South Africa	2007	No data	257	20	50	5
23	Hung	Taiwan	2005	1994-2003	155	12	365	39
24	Nissapatorn	Malaysia	2003	2002	173	70	118	51
25	Amuta	Nigeria	2012	No data	40	20	38	19
26	Yusuf	Nigeria	2015	2014	175	13	98	71
27	Rostami	Iran	2014	2011	90	18	4	0
Number of total samples					2792	1150	1190	424

Ref: Reference, Group 1: HIV positive patients with CD4 counts ≥200 cells/mm^3, Group 2: HIV positive patients with CD4 counts <200 cells/mm^3, IgG: Immunoglobulin G

The meta-analysis included 3982 seropositive samples for *T. gondii*, 2792 of which were in first group (HIV positive patients with CD4-counts ≥200 cells/mm^3) and 1190 were in second group (HIV positive patients with CD4-counts <200 cells/mm^3) (Table 1).

In subgroup analysis regarding the CD4 levels in patients, results revealed a very strong heterogeneity in the included studies in both CD4-groups (Group 1; Cochran Q=994.16, DF=15, I^2=98.49%, p<0.0001 and group 2; Cochran Q=368.50, DF=15, I^2=95.93%, p<0.0001). Because there was a wide variation in the included studies, the random effect value was used for the evaluation.

Publication bias was visually estimated by a funnel plot and the funnel plot showed asymmetry, hence, the publication bias among included studies could not be ignored (Figure 2, 3).

Overall, the seroprevalence of *T. gondii* was higher in HIV-positive patients with CD4-counts <200 cells/mm^3 compared with HIV-positive patients with CD4-counts ≥200 cells/mm^3 (43.5% vs. 40.03%). Subgroup analysis results and its details are summarized in Tables 2, 3 and Figures 4, 5.

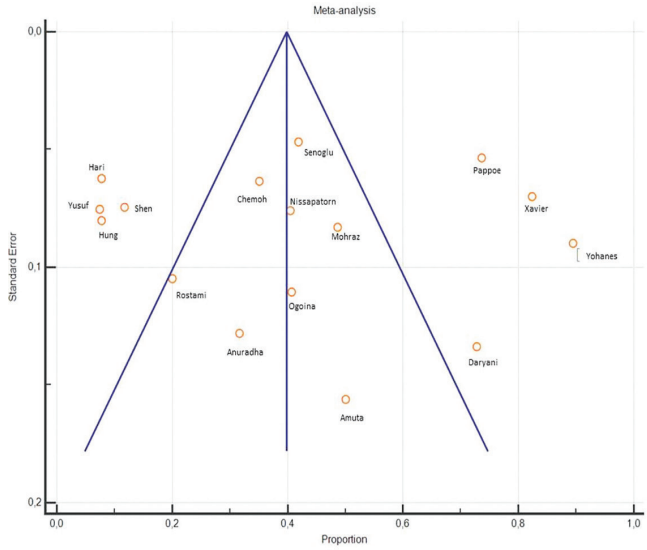

Figure 2. Funnel plot of studies with CD4-counts ≥200 cells/mm^3 (Group 1)

Table 2. Meta-analysis table of *T. gondii* seroprevalence in HIV-positive patients with CD4-counts ≥200 cells/mm^3 (Group 1)

Author (Ref)	Sample size	Proportion (%)	95% CI	Weight (%)	
				Fixed	Random
Senoglu (12)	459	41.83	37.274 to 46.492	16.38	6.35
Shen (13)	179	11.73	7.411 to 17.373	6.41	6.30
Pappoe (14)	349	73.64	68.685 to 78.187	12.46	6.34
Chemoh (15)	248	35.08	29.150 to 41.373	8.87	6.32
Yohanes (16)	123	89.43	82.605 to 94.251	4.42	6.26
Anuradha (17)	60	31.67	20.258 to 44.956	2.17	6.13
Ogoina (18)	81	40.74	29.949 to 52.230	2.92	6.19
Xavier (19)	204	82.35	76.416 to 87.324	7.30	6.31
Daryani (20)	55	72.73	59.038 to 83.862	1.99	6.10
Mohraz (21)	144	48.61	40.205 to 57.076	5.16	6.28
Hari (22)	257	7.78	4.818 to 11.763	9.19	6.33
Hung (23)	155	7.74	4.064 to 13.133	5.56	6.28
Nissapatorn (24)	173	40.46	33.081 to 48.177	6.20	6.29
Amuta (25)	40	50.00	33.802 to 66.198	1.46	6.01
Yusuf (26)	175	7.43	4.015 to 12.368	6.27	6.30
Rostami (27)	90	20.00	12.306 to 29.754	3.24	6.21
Total (fixed effects)	2792	39.79	37.976 to 41.631	100.00	100.00
Total (random effects)	2792	40.03	25.723 to 55.253	100.00	100.00
Test for heterogeneity					
Q	994.1587				
DF	15				
Significance level	p<0.0001				
I^2 (inconsistency)	98.49%				
95% CI for I^2	98.14 to 98.78				

CI: Confidence interval, DF: Degree of freedom, HIV: Human ımmunodeficiency virus

Table 3. Meta-analysis table of *T. gondii* seroprevalence in HIV-positive patients with CD4-counts <200 cells/mm^3 (Group 2)

Author (Ref)	Sample size	Proportion (%)	95% CI	Weight (%)	
				Fixed	Random
Senoglu (12)	155	48.39	40.296 to 56.541	12.94	6.74
Shen (13)	80	5.00	1.379 to 12.310	6.72	6.63
Pappoe (14)	45	80.00	65.404 to 90.424	3.81	6.45
Chemoh (15)	52	42.31	28.728 to 56.795	4.39	6.51
Yohanes (16)	13	84.61	54.553 to 98.079	1.16	5.68
Anuradha (17)	32	43.75	26.364 to 62.337	2.74	6.31
Ogoina (18)	30	33.33	17.287 to 52.812	2.57	6.27
Xavier (19)	46	69.56	54.245 to 82.257	3.90	6.46
Daryani (20)	7	71.43	29.042 to 96.331	0.66	5.03
Mohraz (21)	57	52.63	38.965 to 66.015	4.81	6.54
Hari (22)	50	10.00	3.328 to 21.814	4.23	6.49
Hung (23)	365	10.68	7.709 to 14.316	30.35	6.81
Nissapatorn (24)	118	43.22	34.133 to 52.656	9.87	6.70
Amuta (25)	38	50.00	33.379 to 66.621	3.23	6.39
Yusuf (26)	98	72.45	62.501 to 80.995	8.21	6.67
Rostami (27)	4	0.00	0.000 to 60.236	0.41	4.33
Total (fixed effects)	1190	33.54	30.876 to 36.283	100.00	100.00
Total (random effects)	1190	43.50	29.131 to 58.440	100.00	100.00
Test for heterogeneity					
Q	368.5043				
DF	15				
Significance level	p<0.0001				
I^2 (inconsistency)	95.93%				
95% CI for I^2	94.57 to 96.95				

CI: Confidence interval, DF: Degree of freedom, HIV: Human ımmunodeficiency virus

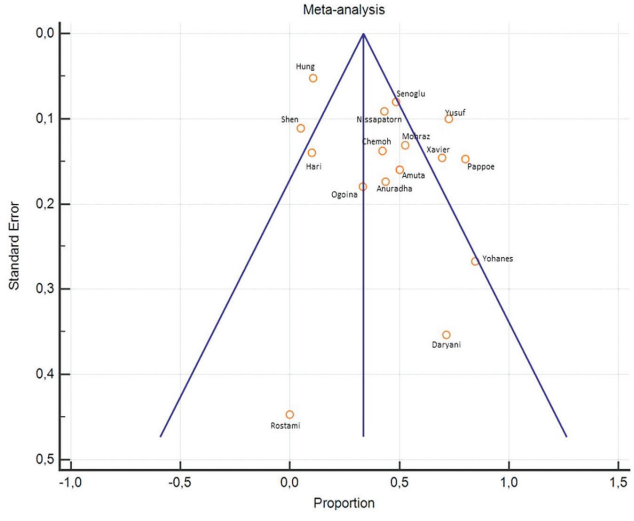

Figure 3. Funnel plot of studies with CD4-counts <200 cells/mm^3 (Group 2)

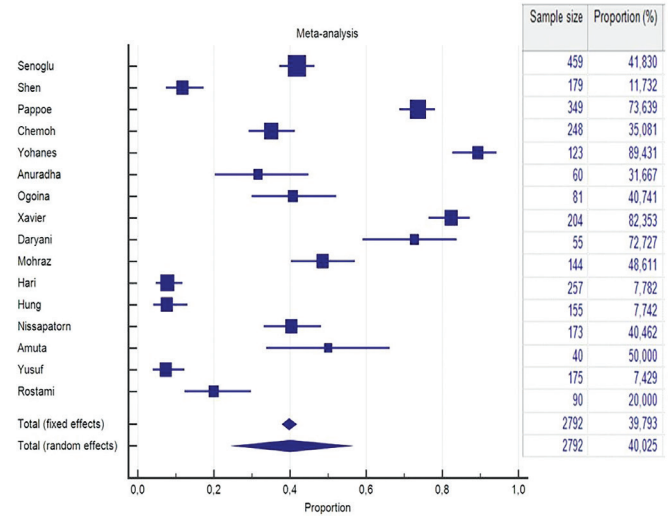

Figure 4. Meta-analysis graph of *T. gondii* seroprevalence in HIV-positive patients with CD4-counts ≥200 cells/mm^3 (Group 1)
HIV: Human ımmunodeficiency virus

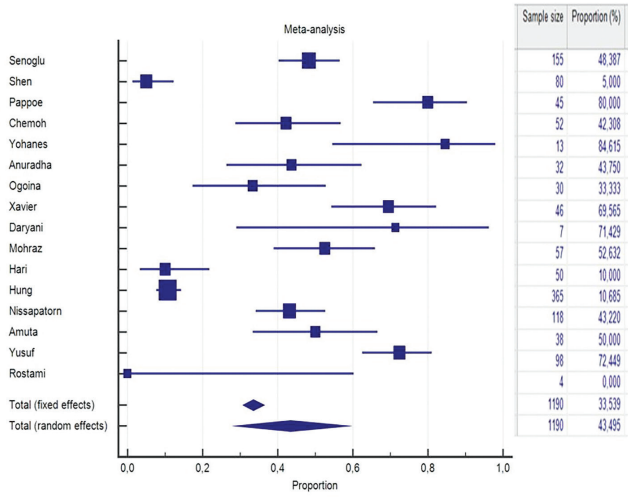

Figure 5. Meta-analysis graph of *T. gondii* seroprevalence in HIV-positive patients with CD4-counts <200 cells/mm^3 (Group 2)
HIV: Human immunodeficiency virus

DISCUSSION

In human-beings, seroprevalence of *T. gondii* infection could vary with the age-groups, geographic locations and also special populations (1). There are two populations of interest with regard to toxoplasmosis screening; pregnant women for congenital toxoplasmosis and immunocompromised populations. Since symptomatic toxoplasmosis in immunocompromised populations like those infected with HIV almost always occurs as a result of reactivation of chronic infection, screening Toxoplasma serology has an important role in the follow up of the infection causing immunosuppression in these populations (8). According to a meta-analysis including 25989 HIV-infected people in 74 studies from 34 countries, the pooled worldwide prevalence of *T. gondii* infection was estimated to be 35.8% (3). The prevalence was highest in North Africa and Middle East (60.7%), and it was higher in low-income countries (54.7%) compared with middle (34.2%) or high-income countries (26.3%). In another meta-analysis that compares the seroprevalence of *T. gondii* between AIDS/HIV patients and non-HIV-infected population, the seroprevalence of *T. gondii* was higher in AIDS/HIV group compared with control group (46.12% vs 36.56%) (odds ratio=1.55, 95%, confidence interval=1.19-2.04) (4).

In HIV-infected population, the risk of toxoplasmosis increases depending on the immunosuppressive status of the patients. Sensitized CD4$^+$ T lymphocytes are cytotoxic for *T. gondii* infected cells, and CD4$^+$ T cells are unable to suppress the latent infection due to immuno-deficiency in HIV-infected patients (9). Although cerebral toxoplasmosis occurs most commonly in HIV-infected patients having CD4-counts below 100 cells/mm^3; rare cases are reported among patients having CD4-counts up to 200 cells/mm^3 (6,10). Also, threshold CD4-count-level of 200 cells/mm^3 is important because maintenance therapy of toxoplasmosis should be continued in all patients until immune reconstitution is achieved which is defined as persistent CD4-count of more than 200 cells/mm^3 for at least six months (11). Besides very wide ranging seroprevalence rates in different studies and populations in literature, some studies show higher *T. gondii* prevalence rates in HIV-infected population having low CD4-counts, whereas, some show higher prevalence in population with high CD4-counts. In this meta-analysis, we aimed to compare seroprevalence rates of *T. gondii* in HIV-infected population worldwide according to threshold of 200 cells/mm^3 by means of revealing the actual *T. gondii* seroprevalence rates in both subgroups with low and high CD4.

In the present meta-analysis, we included 16 studies which present *T. gondii* seroprevalence in HIV/AIDS population and which also have subgroups with low and high CD4 counts according to threshold of 200 cells/mm^3 (12-27). The major finding of this meta-analysis was that the seroprevalence of *T. gondii* was higher in AIDS/HIV patients with CD4 counts below 200 cells/mm^3 compared with those higher. In six of 16 studies included in the meta-analysis, *T. gondii* seroprevalence was higher in patients with CD4 counts above 200 cells/mm^3 than those with below 200 cells/mm^3. However, it was higher in patients with CD4 counts below 200 cells/mm^3 than those with above 200 cells/mm^3 in nine studies, and the seroprevalence rate was 50% to 50% in two groups in one study.

Heterogeneity test results showed strong heterogeneity among the studies, and strong heterogeneity indicated that the validity of the meta-analysis was impaired as the results in the included studies were inconsistent. When the prevalence rates in the included studies evaluated, and the funnel plot graph were analyzed; references 13, 22, 23 and 26 with lower prevalence rates and references 14, 16, 19 and 20 with higher prevalence rates revealed the most distant results from the meta-analyzed prevalence rate in group 1 (CD4≥200 cells/mm^3). Also in group 1 (CD4 ≥200 cells/mm^3), references 13 and 23 with lower prevalence rates and references 14, 19 and 26 with higher prevalence rates revealed the most distant results from the meta-analyzed prevalence rate. No remarkable differences in *T. gondii* seroprevalence rates in HIV/AIDS patients in relation to countries or regions were noticed according to the results in meta-analysis. Even studies from same countries reported inconsistent results (18,20,21,25-27).

The study has some limitations. First, we had to use a random-effect model results in the meta-analysis because of strong heterogeneity, however, the conclusions in the random-effect model are known to be more conservative than fix-effect. Second, it was revealed that the *T. gondii* seroprevalence was higher in low-income countries compared with middle or high-income countries (3); we did not find any studies from high-income countries like North American or European countries that met the inclusion criteria. Thus, this must be taken into consideration while generalizing the results worldwide.

CONCLUSION

Our meta-analysis results revealed the overall seroprevalence of *T. gondii* was higher in the HIV-infected population with CD4-counts <200 cells/mm^3 compared with CD4-counts ≥200 cells/mm^3. We concluded that HIV/AIDS patients with low CD4 counts have higher epidemiological risk of toxoplasmosis as well as immunological risk. To the best of our knowledge, this is the first meta-analysis evaluating the seroprevalence of *T. gondii* in AIDS/HIV population by comparing the seroprevalance of *T. gondii* in subgroups formed according to CD4 counts. Further studies and analyses conducted by including data from high-income countries and with larger samples are still needed to determine the precise

influence of CD4 counts on *T. gondii* seroprevalence in AIDS/HIV patients.

* Ethics

Ethics Committee Approval: Since it was meta-analysis it was not approved.

Informed Consent: Since it was meta-analysis it was not approved.

Peer-review: Internally peer-reviewed.

* Authorship Contributions

Concept: E.Y., R.A.Ç., Design: E.Y., R.A.Ç., Data Collection or Processing: E.Y., R.A.Ç., Analysis or Interpretation: E.Y., R.A.Ç., Literature Search: E.Y., R.A.Ç., Writing: E.Y., R.A.Ç.

Conflict of Interest: No conflict of interest was declared by the authors.

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