Global and Regional Prevalence and Burden of Latent and Acute Toxoplasmosis in People Living With HIV: an Updated Systematic Review and Meta-analysis

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Abstract

Background: *Toxoplasma gondii* infection is one of the most prevalent opportunistic and life-threatening infections in people living with HIV (PLWH). Here, we undertook a meta-analysis to estimate the global prevalence of latent (LT) and acute (AT) toxoplasmosis in PLWH.

Methods: Eligible studies reporting the prevalence of LT or AT in PLWH were searched from January 1980 to July 2020, using PubMed/MEDLINE, Scopus, Web of Sciences, SciELO and Embase databases. We used a random effects model to calculate pooled prevalence estimates with 95% confidence intervals (CI) and evaluated overall burden of co-infection worldwide. Countries were categorised based on World Health Organization regions. Multiple subgroup and meta-regression analyses were performed.

Results: From 4,024 studies identified, 150 (involving 44,473 PLWH) and 65 (involving 17,705 PLWH) studies met the inclusion criteria, for LT and AT in PLWH, respectively. The overall prevalence rates of LT and AT in PLWH were 37.4% (95% CI, 33.4–4.4) and 1.3% (95%CI, 0.9–1.8%), respectively. We estimated that, worldwide, approximately 14.2 and 0.5 million PLWH are affected by LT and AT, respectively. The highest and lowest burden of LT and AT were seen in the African and Western Pacific regions, respectively. Moreover prevalence rates were highest in countries with low levels of income and human development indexes. We indicated that eating raw/undercooked meat, frequent contact with soil, low numbers of CD4+ T lymphocytes and older age were significant risk factors of toxoplasmosis in PLWH.

Conclusion: Our findings revealed that, a high number of PLWH are exposed to or infected with *T. gondii*. These findings suggest a need for more routine testing, care of, and treatment for *T. gondii* infection in all PLWH, and educating these patients about risk factors and preventive measures to reduce the burden of both latent and acute toxoplasmosis.

Introduction

Toxoplasma gondii infection or toxoplasmosis is one of the most prevalent opportunistic and life-threatening infections in people living with human immunodeficiency virus (PLWH) [1]. Toxoplasmic encephalitis (TE) is the second most common opportunistic infection of the central nervous system in PLWH, especially in patients with CD4 + T lymphocyte counts less than 200 cells per μL [2, 3]. In addition toxoplasmosis in PLWH can be a cause of other neurological symptoms (including epilepsy, disorientation, headache, drowsiness and hemiparesis,) and can result in clinical symptoms such as disseminated infection, pneumonitis, and retinochoroiditis [4, 5].

Primary *T. gondii* infection is acquired by ingestion of sporulated oocysts present in contaminated soil, water, and on contaminated fruits and vegetables; by ingestion of infectious stages in raw or undercooked meat from infected animals; by vertical transmission from an infected mother to the fetus; and rarely by blood transfusion or organ transplantation [6, 7, 8, 9, 10, 11]. Primary toxoplasmosis in PLWH can result in severe clinical symptoms, because overall antibody production in these patients is decreased due to immunodeficiency [12]. More commonly in PLWH, clinical toxoplasmosis results from the reactivation of a latent infection [5].

Generally detection of IgG antibodies to *T. gondii* indicates latent toxoplasmosis (LT); whereas the presence of anti-*Toxoplasma* IgG combined with detection of specific IgM, detection of low avidity serum anti-*Toxoplasma* IgG antibodies, or seroconversion from IgG negative to IgG positive status sequential tests could be marker of acute toxoplasmosis (AT) [10, 13, 14].

Estimating the burden of opportunistic infections and assessment of the related risk factors for PLWH will help to establish parameters for the effective use of specific prophylaxis [15]. Previous efforts to quantify toxoplasmosis in PLWH were limited to specific countries, geographical regions, or single-year estimates. One previous meta-analysis [14], included studies up to 2016 and estimated only LT, not AT, in PLWH; further it did not assess risk factors related to toxoplasmosis and prevalence. In the present study, we performed an updated systematic review of observational studies to better understand the epidemiology toxoplasmosis in PLWH at the global, regional, and national levels. The specific aims of this study were to: (1) estimate the prevalence and burden of LT in PLWH; (2) estimate the prevalence and burden of AT in PLWH; (3) evaluate the prevalence of latent and acute toxoplasmosis in PLWH based to socio-economic variables; (4) determine the change in prevalence rates over time; (5) estimate the prevalence of LT in PLWH in relation to CD4 + cell counts; and (6) determine associated risk factors of *Toxoplasma* infection in PLWH.

Methods

We followed the recommendations established by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement to perform this study [16]. All procedures including the literature search, assessing full texts, quality appraisal and data extraction were performed independently by trained researchers. Disagreements were resolved by discussion with the senior author (A.R.) and consensus.

Search strategy and selection criteria

A systematic review of the literature was performed using PubMed/MEDLINE, Scopus, Web of Sciences, SciELO and Embase to identify all peer-reviewed articles reporting data on the prevalence of LT or AT in PLWH from January 1980 to July 2020, without language and geographical restriction. We used relevant keywords for searching the databases (S1 Fig). The search strategy was discussed with a medical librarian for optimal inclusion sensitivity. To identify gray literature and missing studies, we searched Google Scholar database and also checked the reference list retrieved papers and relevant reviews. Inclusion criteria were: (i) observational studies that had data to estimate the prevalence of LT or AT in PLWH; (ii) studies that had sample size of more than 30 individuals; and (iii) studies that used serological assays to detect specific anti-*Toxoplasma* antibodies or antigens. Note that in case-control studies, data were extracted only for PLWH (i.e. cases). We excluded studies if they not meet the criteria; if they were not representative of the general population with HIV infection (e.g., patients with encephalitis especially whose with TE, psychiatric patients and drug users); if the diagnostic methods were unclear or used molecular assays; were comparative studies of diagnostic methods; if they included overlapping participation in multiple studies; or were experimental studies, if they were case-reports, case-series, reviews, systematic reviews or meta-analyses. With regard to AT, we applied definitions of acute toxoplasmosis [10], including: (a) low IgG

avidity; (b) *Toxoplasma* seropositivity for both IgG and IgM, or (c) seroconversion from a *Toxoplasma* IgG negative status to an IgG positive status.

Data extraction and quality assessment

We extracted the following variables from each study: first author's name, country, city, year of publication, study design, the number of participants, number of PLWH seropositive for LT or AT, and the type of diagnostic methods. Countries were grouped according to the WHO-defined regions [17], per capita income [18] and the human development index [HDI] [19]. Moreover, we extracted patient data on the number of CD4+ T cells (<200, 200-500, and > 500 cells/μL) and number of patients in distinct age groups (<20, 20–40, 41–60, >60), if available. In order to identify associated risk factors for toxoplasmosis in PLWH, we extracted data including place of residence (urban/rural), gender (male or female), close contact with dogs or cats, contact with soil, consumption of raw/undercooked meat, consumption of raw/unwashed vegetables, and drinking untreated water. To evaluate the methodological quality of included studies, we used the JBI (Joanna Briggs Institute) Prevalence Critical Appraisal Tool, as described by Munn et al [20].

Statistical analysis

Analyses were performed using Stata statistical software (v.16 Stata Corp., College Station, TX, USA). For each individual study, the prevalence rate was defined as the number of PLWH with LT or AT divided by the total number of PLWH screened. We used the variance of the study-specific prevalence estimates with the Freeman-Tukey double arcsine transformation before pooling the data using the DerSimonian-Laird random-effects meta-analysis model to minimise the effect of studies with extremely small or extremely large prevalence [21, 22]. The random-effects model was selected in anticipation of substantial variation in prevalence estimates of LT or AT across the included studies [23]. The between-studies heterogeneity was evaluated by Cochran's Q test and I^2 index. I^2 values of 25%, 50% and 75% represented low, medium and substantial heterogeneity, respectively [24]. To explore potential drivers of heterogeneity, several subgroup and meta-regression analyses were performed considering the following study features: (i) WHO region, (ii country, (iii) type of diagnostic method, (iv) type of study design, (v) country income level, and (vi) country HDI level. Moreover, to calculate the global burden of LT and AT in PLWH, we followed the method used in the most recently published meta-analysis on this subject [14] and used data from WHO showing the number of PLWH in 2018 [25]. We then multiplied this number by our calculated percentages of PLWH with LT or AT (with a 95% CI) at the global and national levels. We did not undertake an assessment of publication bias, as it is not relevant for prevalence studies [26]. A P value < 0.0 5 was considered statistically significant.

Results

Study characteristics

From 4024 citations, 150 studies (155 datasets), involving 44,473 PLWH, met the inclusion criteria for eligibility in a quantitative analysis of the prevalence of HIV–LT co-infection. Moreover, 65 studies, involving 17,705 PLWH, had data for HIV-AT co-infection (S2 Fig). Considering WHO regions, most studies were from

Africa (45 for LT and 15 for AT), then the Eastern Mediterranean (23 for LT and 15 for AT); the fewest were in South America (nine for LT and four for AT). Supplementary Table 1 summarizes the characteristics of, and references to, included studies as well as geographic location of each.

Global prevalence of LT in PLWH

For the 155 data sets in 49 countries, 14,913 of 44,473 PLWH were diagnosed as having LT, resulting in an overall, pooled global prevalence of 37.4% (95% CI, 33.4–4.4) (Table 1; Fig. 1A), with evidence of heterogeneity among studies (I^2 = 98.7%, P < 0.001). In WHO-regions, the pooled prevalences (in descending order, with a 95% CI) were 46.2% (37.7–54.7%) in Africa, 46.2% (29.6–62.6%) in South America, 45.8% (36.3–55.5%) in the Eastern Mediterranean region, 41.1% (33.0–49.4%) in Europe, 29.9% (22.0–38.3%) in South-East Asia, 25.5% (19.2–32.4%) in North America and 18.4% (12.4–25.3%) in the Western Pacific. For countries with two or more eligible studies, Ethiopia (80.5%), Ghana (70.6%), and Cameroon (54.5%) in Africa; Iran (45.7%) in the Middle East; France (72.5%) and Austria (57.3%) in Europe; Brazil (48.8%) in America and Indonesia (38.5%), Thailand (37.5%) and Malaysia (36.1%) in East Asia exhibited some of the highest seroprevalence rates (Table 1 and Fig. 1A). Moreover, we estimated that approximately 14,174,600 (12,658,600–15,690,600) PLWH worldwide were seropositive for LT. Our estimates demonstrated that countries in the African region, which has a large proportion of PLWH, also has the largest number of people with LT 11,873,400 (9,688,900–14,057,900), accounting for approximately 84% of cases of HIV-LT coinfection worldwide. Additional details pertaining to the prevalence and burden of LT in PLWH in WHO-regions and individual countries are given in Table 1 and Fig. 1A.

Table 1
Global, regional and national pooled prevalence of latent toxoplasmosis (LT) among people living with HIV (PLWH) (results from 155 datasets performed in 48 countries).

WHO regions/ country	Number datasets	Number of PLWH screened (total)	Number of PLWH with LT	Pooled prevalence (95% CI)	Estimated number of PLWH individuals*	Estimated number of PLWH with LT
Global	**155**	**44473**	**14913**	**37.4 (33.4–41.4)**	**37,900,000**	**14,174,600 (12,658,600–15,690,600)**
South Americas	**9**	**2905**	**1270**	**46.2 (23.6–69.6)**	**1,900,000**	**877,800 (448,400–1,322,400)**
Brazil	8	650	1203	48.8 (23.5–74.5)	900,000	439,200 (211,500–670,500)
Chile	1	255	67	26.3 (21.0–32.1)	71000	18,673 (14,910–22,791)
African region	**49**	**9504**	**3967**	**46.2 (37.7–54.70)**	**25,700,000**	**11,873,400 (9,688,900–14,057,900)**
Ethiopia	12	1778	1396	80.5 (66.3–91.6)	690,000	555,450 (457,740–632,040)
Nigeria	12	2149	709	30.3 (19.2–42.7)	1,900,000	575,700 (364,800–811,300)
Burkina Faso	5	2548	691	30.7 (25.5–36.2)	96,000	29,472 (24,480–34,752)
Cameroon	3	293	167	54.5 (37.5–71.1)	540,000	294,300 (202,500–383,940)
Ghana	2	519	365	70.6 (66.6–74.4)	330,000	232,980 (219,780–245,520)
Uganda	2	316	134	42.3 (36.9–47.8)	1,400,000	592,200 (516,600–669,200)

Abbreviations: NA: not applicable

WHO regions are sorted according to prevalence rates

Countries are sorted according to number of studies included

WHO regions/ country	Number datasets	Number of PLWH screened (total)	Number of PLWH with LT	Pooled prevalence (95% CI)	Estimated number of PLWH individuals*	Estimated number of PLWH with LT
South Africa	2	407	62	13.5 (10.3–17.0)	7,700,000	1,039,000 (793,100–1,309,000)
Zambia	2	256	14	5.2 (2.7–8.4)	1,200,000	62,400 (32,400–100,800)
Mozambique	2	258	110	42.5 (36.5–47.7)	2,200,000	935,000 (803,000–1,049,400)
Tanzania	1	38	26	68.4 (51.3–82.5)	1,600,000	1,094,400 (820,800–1,320,000)
Canary island (Spain)	1	157	56	35.7 (28.2–43.7)	140,000	49,000 (39,480–61,180)
Botswana	1	46	3	6.5 (1.4–17.9)	370,000	24,050 (5,180–66,230)
Togo	1	56	14	25.0 (14.4–38.4)	110,000	27,500 (15,840–42,240)
Congo	1	375	75	22.0 (19.1–26.4)	89,000	19,580 (16,999–23,496)
Congo (Democratic Republic of the)	1	38	28	73.6 (52.5–94.6)	450,000	331,200 (236,250–425,700)
Central African Republic	1	270	117	43.3 (37.3–49.5)	110,000	47,630 (41,030–54,450)
Eastern Mediterranean	**23**	**3151**	**1271**	**45.8 (36.3–55.5)**	**400,000**	**183,200 (145,200–222,000)**
Iran	19	2886	1148	45.7 (35.3–56.3)	61,000	27,877 (21,533–34,343)

Abbreviations: NA: not applicable

WHO regions are sorted according to prevalence rates

Countries are sorted according to number of studies included

WHO regions/ country	Number datasets	Number of PLWH screened (total)	Number of PLWH with LT	Pooled prevalence (95% CI)	Estimated number of PLWH individuals*	Estimated number of PLWH with LT
Saudi Arabia	1	50	15	30.0 (17.9–44.6)	13,000	39,00 (2,327–5,798)
Bahrain	1	76	16	21.1 (12.5–31.9)	260	55 (32–83)
Morocco	1	95	59	62.1 (51.6–71.9)	21,000	13,041 (10,836–15,099)
Sudan	1	44	33	75.0 (59.7–86.8)	59000	44,250 (35,223–51,212)
European region	**20**	**8786**	**4109**	**41.1 (33.0–49.4)**	**2,500,000**	**1,027,500 (825,000–1,235,000)**
Spain	4	1707	562	30.7 (9.4–57.7)	150,000	46,050 (14,100–86,550)
Turkey	2	788	352	45.2 (41.7–48.7)	14,800	6,690 (6,172–7,207)
United Kingdom	2	609	164	26.9 (23.4–30.5)	101,600	27,330 (23,774–30,988)
France	2	1715	1237	72.5 (70.3–74.6)	180,000	130,500 (126,540–134,280)
Austria	2	659	377	57.3 (53.5–61.1)	9000	5,157 (4,815–5,499)
Romania	2	224	69	30.5 (24.6–36.8)	18,000	5,490 (4,428–6,624)
Czech Republic	2	1302	20	40.0 (37.4–42.7)	4400	1,760 (1645–1879)

Abbreviations: NA: not applicable

WHO regions are sorted according to prevalence rates

Countries are sorted according to number of studies included

WHO regions/ country	Number datasets	Number of PLWH screened (total)	Number of PLWH with LT	Pooled prevalence (95% CI)	Estimated number of PLWH individuals*	Estimated number of PLWH with LT
Croatia	1	166	86	51.8 (43.9–59.6)	1600	829 (702–953)
Germany	1	183	64	35.0 (28.1–42.4)	87,000	30,450 (24,447–36,888)
Denmark	1	503	223	44.3 (39.9–48.8)	6,200	2746 (2,474–3,025)
Switzerland	1	715	360	50.3 (46.6–54.1)	20,000	10,060 (9,320–10,820)
Serbia	1	288	127	44.1 (38.3–50.0)	3000	1,323 (1,149–1,500)
North America and the Caribbean	**12**	**7202**	**1150**	**25.5 (19.2–32.4)**	**1,700,000**	**433,500 (326,400–550,800)**
USA	8	5862	889	18.3 (13.3–23.9)	1,100,000	201,300 (146,300–262,900)
Mexico	2	187	91	10.6 (8.8–12.6)	230,000	24,380 (20,240–25,980)
Canada	1	1074	14	48.7 (41.5–55.9)	63,000	30,681 (26,148–35,217)
Cuba	1	79	56	70.9 (59.6–80.6)	31,000	21,979 (18,476–24,986)
South-East Asian Region	**18**	**5232**	**1582**	**29.8 (22.0–38.3)**	**3,800,000**	**1,132,400 (836,000–1,455,400)**
India	10	2773	532	24.1 (16.8–32.2)	2,200,000	530,200 (369,600–708,400)

Abbreviations: NA: not applicable

WHO regions are sorted according to prevalence rates

Countries are sorted according to number of studies included

WHO regions/ country	Number datasets	Number of PLWH screened (total)	Number of PLWH with LT	Pooled prevalence (95% CI)	Estimated number of PLWH individuals*	Estimated number of PLWH with LT
Indonesia	4	1131	447	38.5 (32.2–45.0)	640,000	246,400 (206,080–288,000)
Thailand	3	1328	603	37.5 (20.8–56.0)	480,000	180,000 (99,840–268,800)
Western Pacific Region	**24**	**7630**	**1530**	**18.4 (12.4–25.3)**	**1,900,000**	**349,600 (235,600–480,700)**
China	10	3768	598	12.2 (5.5–20.9)	900000	109,800 (49,500–188,100)
Malaysia	6	1507	511	36.1 (18.4–56.1)	87,000	31,407 (16,008–48,807)
Japan	4	680	67	9.9 (6.4–14.0)	30,000	2,970 (1,920–4,200)
Taiwan	1	550	56	10.2 (7.8–13.0)	48,000	4,896 (3,744–6,240)
South-Korea	1	173	7	4.0 (1.6–8.2)	45,000	1,800 (720–3,690)
Singapore	1	771	183	23.7 (20.8–26.9)	7900	1,872 (1,643–2,125)
Papua New Guinea	1	181	108	59.7 (52.1–66.9)	45,000	26,865 (23,445–30,105)
Abbreviations: NA: not applicable						
WHO regions are sorted according to prevalence rates						
Countries are sorted according to number of studies included						

Subgroup and meta-regression analyses according to socio-demographic and study characteristics

In subgroup analyses, with respect to income level and HDI, the highest prevalence of LT was in low-income countries (58.2%, 46.2–69.8%) and the lowest prevalence was in high-income countries (28.0%, 21.3–35.2%). The pooled prevalence of LT in PLWH in countries with low, medium, high and very high levels of

HDI were 51.9% (42.8–60.8%), 29.3% (20.9–38.4%), 38.0% (22.6–33.1%), and 27.6% (22.6–33.1%), respectively (Table 2). Meta-regression analyses revealed a significant decreasing trend in prevalence in countries with increasing per capita income (C = -2.97^{e-06}; P-value = 0.004) and HDI levels (C = -0.473; P-value < 0.001) (Fig. 2A and B). Studies that were performed after 2005 showed slightly higher prevalence rates than other periods, although this increasing trend (1980–2020) was non-significant in meta-regression analysis (C = 0.0016; P value = 0.46) (Table 2 and Fig. 2C). In subgroup analyses, according to type of study, the highest and lowest prevalence rates were estimated in case-control (40.4%, 30.7–50.6%) and retrospective cohorts (26.5%, 17.1–37.2%), respectively. Subgroup analysis based on diagnostic methods revealed the lowest (30.5%, 14.9–48.9%) and highest (57.2%, 47.0–67.1%) prevalences in studies that used the Sabin-Feldman (SFT) and immunofluorescence (IFAT) methods, respectively. The prevalence rate in studies using ELISA, the most commonly used method, was 35.5% (31.1–40.1%). More subgroup analyses and details are given in Table 2. With respect to age, prevalence rates of LT in PLWH < 20, 20–40, 40–60 and > 60 years were (13.8%, 11.8–15.7%), (39.5%, 38.7–40.4%), (46.3%, 44.9–47.7%) and (43.7%, 37.1–50.3%), respectively (Table 3). With respect to the number of CD4 + lymphocytes in patients, prevalence rates of LT in PLWH with CD4 + counts of < 200, 200–500 and > 500 were (18.4%, 16.8–20.0%), (33.8%, 32.6–34.9%) and (21.9%, 20.5–23.3%), respectively (Table 3).

Table 2
Prevalence of latent toxoplasmosis (LT) and acute toxoplasmosis (AT) in people living with HIV (PLWH) according to *a priori* defined subgroups

Variable/subgroups	Number datasets		Number of PLWH screened (total)		Number of PLWH with LT	Pooled prevalence (95% CI)	Number of PLWH with AT	Pooled prevalence (95% CI)
	LT	AT	LT	AT				
Income								
Low	27	5	5950	973	2675	58.2 (46.2–69.8)	8	0.4 (0.0–1.9)
Lower middle	35	13	7168	3389	2350	34.5 (27.0–42.3)	72	1.8 (0.7–3.2)
Upper middle	55	28	13980	5764	4682	36.0 (29.2–43.1)	105	1.4 (0.7–2.3)
High	38	20	17375	7579	5206	28.0 (21.3–35.2)	104	1.2 (0.6–1.9)
HDI								
Low	42	8	7969	1307	3533	51.9 (42.8–60.8)	23	1.4 (0.1–3.7)
Medium	22	12	5556	3462	1554	29.3 (20.9–38.4)	64	1.5 (0.6–2.6)
High	47	25	13405	6858	45269	38.0 (22.6–33.1)	109	1.3 (0.6–2.2)
Very high	44	21	17543	6078	4557	27.6 (22.6–33.1)	93	1.3 (0.7–2.0)
Type of study								
Cross sectional	95	44	24576	8739	7941	38.7 (33.6–44.0)	148	1.2 (0.7–1.8)
Case-control	32	10	5204	1895	2059	40.4 (30.7–50.6)	36	2.6 (0.8–5.0)
Prospective cohort	9	4	3534	1591	1151	36.6 (19.1–56.1)	34	2.1 (1.1–3.4)

Variable/subgroups	Number datasets		Number of PLWH screened (total)		Number of PLWH with LT	Pooled prevalence (95% CI)	Number of PLWH with AT	Pooled prevalence (95% CI)
	LT	AT	LT	AT				
Retrospective cohort	19	8	11159	5480	3762	26.5 (17.1–37.2)	71	1.0 (0.3–1.0)
Acute toxoplasmosis criteria								
IgG & IgM	NA	50	NA	9872	NA	NA	166	1.2 (0.7–1.8)
Seroconversion	NA	12	NA	6715	NA	NA	88	1.2 (0.8–1.7)
IgG avidity	NA	2	NA	961	NA	NA	28	1.7 (1.0–2.7)
Antigen detection	NA	2	NA	157	NA	NA	7	3.5 (1.0–7.2)
Year								
< 2000	35	17	11920	5894	4282	37.5 (29.4–46.0)	82	1.2 (0.6–1.9)
2000–2005	14	3	6366	1095	1823	26.2 (17.3–36.2)	6	0.5 (0.0–1.6)
2006–2010	17	4	2893	726	803	28.7 (15.7–43.8)	5	0.4 (0.0–1.2)
2011–2015	49	16	12386	4212	4475	45.3 (37.4–53.3)	90	1.7 (0.7–3.2)
2016–2020	40	26	10908	5688	3530	35.6 (27.8–43.9)	106	1.5 (0.7–2.5)
Sample size								
≤ 99	45	20	2987	1338	1269	41.5 (33.7–49.6)	55	2.9 (1.2–5.1)
100–300	65	27	11526	4782	4807	43.1 (36.3–50.1)	77	1.0 (0.4–1.8)

Variable/subgroups	Number datasets		Number of PLWH screened (total)		Number of PLWH with LT	Pooled prevalence (95% CI)	Number of PLWH with AT	Pooled prevalence (95% CI)
	LT	AT	LT	AT				
301–500	22	10	8372	4016	2067	22.0 (14.5–30.7)	72	1.6 (1.0–2.4)
501–1000	16	7	11132	4651	3530	29.9 (19.7–41.1)	57	0.9 (0.3–2.0)
> 1000	7	2	10456	2918	3241	29.8 (14.7–47.7)	28	1.0 (0.6–1.3)
Risk of bias (total number of item with "yes" answers per study)								
Low	118	50	42227	16736	13984	36.1 (31.6–40.6)	249	1.2 (0.8–1.6)
Moderate	37	16	2246	969	967	41.8 (33.4–41.4)	40	2.8 (1.0–5.4)
Method								
ELISA	125	NA	35286	NA	11736	35.5 (31.1–40.1)	NA	NA
IFAT	9	NA	2828	NA	1486	57.2 (47.0–67.1)	NA	NA
LAT	5	NA	658	NA	395	61.9 (40.9–80.8)	NA	NA
MEIA	5	NA	1631	NA	321	30.1 (14.3–48.8)	NA	NA
SFT	6	NA	3199	NA	706	30.5 (14.9–48.9)	NA	NA
Other (MAT, CFT, ELFA, DAT)	5	NA	871	NA	269	40.2 (15.4–68.0)	NA	NA

Table 3
Risk factors associated with *Toxoplasma gondii* seropositivity among people living with HIV (PLWH)

Variables (number of studies)	Number of PLWH	Number (%) of seropositive	Pooled prevalence (95% CI)	OR (95% CI)	Heterogeneity	Publication bias *P* value |t|
					I^2 (%)	
Gender (34)					89.1	0.25
Female	5806	2106	35.16 (34.28, 36.03)	1		
Male	7826	2363	29.44 (28.60, 30.28)	0.78 (0.55–1.12)		
Residence (9)					36.9	0.44
Urban	1472	820	59.73 (57.61, 61.84)	1		
Rural	283	166	67.29 (63.16, 71.42)	1.45 (0.76–2.75)		
Close contact with dog (3)					90.1	0.98
No	531	141	17.47 (14.89, 20.05)	1		
Yes	235	56	16.36 (12.46, 20.26)	2.69 (0.55–13.18)		
Close contact with cats (15)					84.0	0.31
No	1753	919	76.52 (74.94, 78.10)	1		
Yes	1039	611	75.39 (73.13, 77.64)	1.79 (0.91–3.50)		
Contact with soil (5)					67.2	0.5
No	442	219	46.84 (43.18, 50.49)	1		

df: degrees of freedom.

Variables (number of studies)	Number of PLWH	Number (%) of seropositive	Pooled prevalence (95% CI)	OR (95% CI)	Heterogeneity	Publication bias *P* value |t|
					I^2 (%)	
Yes	316	236	83.92 (80.26, 87.58)	3.01 (1.50–6.04)		
Consumption of raw meat (15)					78.5	0.88
No	1626	892	68.09 (66.65, 69.53)	1		
Yes	1016	699	85.28 (83.54, 87.02)	2.01 (1.19–3.39)		
Consumption of raw/unwashed vegetable (8)					13.7	0.26
No	493	411	88.79 (86.14, 91.43)	1		
Yes	756	653	95.28 (93.82, 96.74)	1.04 (0.68–1.6)		
Drinking untreated water (5)					45.5	0.19
No	835	612	82.19 (79.95, 84.44)	1		
Yes	298	207	83.64 (80.24, 87.03)	1.19 (0.67–2.11)		
Number of CD4 (29)						
≥ 500	1733	440	18.48 (16.88, 20.09)	1		
200–500	3625	1201	33.82 (32.68, 34.97)	1.71 (1.08–2.72)	50.9	0.71

df: degrees of freedom.

Variables (number of studies)	Number of PLWH	Number (%) of seropositive	Pooled prevalence (95% CI)	OR (95% CI)	Heterogeneity	Publication bias *P* value |t|
					I^2 (%)	
< 200	2511	700	21.97 (20.57, 23.36)	1.04 (0.79–1.37)	77.2	0.51
Age (36)						
< 20	1064	181	13.81 (11.86, 15.77)	1		
20–40	6824	2393	39.59 (38.70, 40.47)	1.63 (1.15–2.61)	42.3	0.06
40–60	2968	1295	46.33 (44.93, 47.74)	2.49 (1.62–3.82)	54.2	0.09
> 60	181	75	43.78 (37.19, 50.36)	2.39 (1.56–3.66)	0.0	0.48
df: degrees of freedom.						

Risk factors for prevalence of latent Toxoplasmosis

With respect to risk factors associated with LT, our results showed that PLWH who consumed raw/undercooked meat (Odds Ratio [OR], 2.01; 95% CI, 1.19–3.9) and those who were in frequent contact with soil (OR, 3.01; 95% CI, 1.5–6.04) were more likely to be seropositive compared with other PLWH (S3 and S4 Figs). Moreover prevalence rates with significantly higher in PLWH who were older in age and had lower CD4 + lymphocyte counts. PLWH in ages 20–40 (OR, 1.63; 95% CI, 1.15–2.61), 40–60 (OR, 2.49; 95% CI, 1.62–3.82) and > 60 (OR, 2.39; 95% CI, 1.56–3.66) (S5-7 Figs) and those with number of CD4 200–500 (OR, 1.71; 95% CI, 1.08–2.72) and lower than 200 (OR, 1.04; 95% CI, 0.79–1.37) were more likely to be seropositive as compared with other PLWH (S8-9 Figs). With respect to other risk factors associated with LT, our results showed that female patients, those who lived in rural areas, those who were cat or dog owners, and those who consumed raw/unwashed vegetables or consumed untreated water were at more, but non-significant greater, risk to acquire infection. More details are given in Table 3 and S10-15 Figs. In Egger's test we did not identify any significant publication bias (Table 3).

Global prevalence of acute Toxoplasmosis

The global prevalence of AT in PLWH, when data for all 65 datasets representing 32 countries were pooled, was 1.3% (95%CI, 0.9–1.8%; 289/17,705). The heterogeneity between studies was significant (I^2 = 79.1%, *P*

< 0.001). With respect to WHO-epidemiological regions, the highest prevalence rates were found in South America (2.0%; 0.1–5.4%), and then the Eastern Mediterranean region (1.8%; 0.7–3.3%), and the lowest prevalence rate was found in the European region (0.6%; 0.2–1.3%). The pooled prevalence rates in other WHO regions were: 1.6% (0.5–3.1%) in North America, 1.3% (0.9–1.8%) in South-East Asia, 1.2% (0.2–2.6%) in the Western Pacific and 0.9% (0.2–1.2%) in Africa (Table 4 and Fig. 1B). Moreover, we estimated that approximately 492,700 (341,100–682,200) PLWH worldwide were affected by AT. Our estimates demonstrated that countries in the African region, has the largest number of PLWH with AT (231,300; 51,400–308,400), accounting for approximately 47% of cases of HIV-AT co-infection worldwide. Additional details pertaining to the prevalence and burden of AT in PLWH in WHO-regions and individual countries are given in Table 4 and Fig. 1B.

Table 4
Global, regional and national pooled prevalence of acute toxoplasmosis (AT) among people living with HIV (PLWH) (results from 65 studies performed in 31 countries).

WHO regions/ country	Number datasets	Number of PLWH screened (total)	Number of PLWH with AT	Pooled prevalence (95% CI)	Estimated number of PLWH individuals*	Estimated number of PLWH with AT
Global	**65**	**17705**	**289**	**1.3 (0.9–1.8)**	**37,900,000**	**492,700 (341,100–682,200)**
South Americas	**4**	**863**	**20**	**2.0 (0.1–5.4)**	**1,900,000**	**38,000 (1900–102,600)**
Brazil	4	863	20	2.0 (0.1–5.4)	900,000	38,000 (1900–102,600)
African region	**15**	**2505**	**32**	**0.9 (0.2–1.2)**	**25,700,000**	**231,300 (51,400–308,400)**
Ethiopia	1	150	0	1.1 (0.2–2.4)	690,000	7,590 (1,380–16,560)
Nigeria	1	111	1	0.9 (0.1–4.9)	1,900,000	17,100 (1900–93,100)
Burkina Faso	2	497	0	0.1 (0.0–0.4)	96,000	96 (0-384)
Cameroon	2	223	14	5.4 (2.7–8.9)	540,000	29,160 (14,580–48,060)
Ghana	2	519	1	0.1 (0.0–0.8)	330,000	330 (0–2,640)
South Africa	2	407	7	1.4 (0.4–2.9)	7,700,000	107,800 (30,800–223,300)
Zambia	1	69	0	0.1 (0.0–5.2)	1,200,000	1,200 (0–62,400)
Canary island (Spain)	1	157	1	0.6 (0.0–3.5)	140,000	840 (0–4900)

Abbreviations: NA: not applicable

WHO regions are sorted according to prevalence rates

Countries are sorted according to number of studies included

WHO regions/ country	Number datasets	Number of PLWH screened (total)	Number of PLWH with AT	Pooled prevalence (95% CI)	Estimated number of PLWH individuals*	Estimated number of PLWH with AT
Botswana	1	46	0	0.1 (0.0–7.7)	370,000	370 (0–28,490)
Togo	1	56	2	3.6 (0.4–12.3)	110,000	3,960 (440–13,530)
Eastern Mediterranean	**15**	**2125**	**51**	**1.8 (0.7–3.3)**	**400,000**	**7,200 (2,800–13,200)**
Iran	13	1999	42	1.5 (0.6–2.7)	61,000	915 (366–1,647)
Saudi Arabia	1	50	9	18.0 (8.6–31.4)	13,000	2,340 (1,118–4,082)
Bahrain	1	76	0	0.1 (0.0–4.7)	260	2 (0-12.2)
European region	**15**	**6447**	**67**	**0.6 (0.2–1.3)**	**2,500,000**	**15,000 (5,000–32,500)**
Spain	1	63	6	9.5 (3.6–19.6)	150,000	14,250 (5,400–29,400)
Turkey	2	788	0	0.1 (0.0–0.2)	14,800	15 (0–29.6)
United Kingdom	1	500	7	1.4 (0.6–2.9)	101,600	1,422 (609–2,946)
France	2	1715	14	0.3 (0.0–0.7)	180,000	540 (0–1,260)
Romania	2	224	2	0.1 (0.0–1.0)	18,000	18 (0–180)
Czech Republic	2	1302	14	0.8 (0.3–1.4)	4400	35 (13–61)
Croatia	1	166	2	1.2 (0.1–4.3)	1600	19 (2–69)

Abbreviations: NA: not applicable

WHO regions are sorted according to prevalence rates

Countries are sorted according to number of studies included

WHO regions/ country	Number datasets	Number of PLWH screened (total)	Number of PLWH with AT	Pooled prevalence (95% CI)	Estimated number of PLWH individuals*	Estimated number of PLWH with AT
Germany	1	183	6	3.3 (1.2–7.0)	87,000	2,871 (1,044–6,090)
Denmark	1	503	4	0.8 (0.2–2.0)	6,200	49 (12–124)
Switzerland	1	715	12	1.7 (0.9–2.9)	20,000	340 (180–580)
Serbia	1	288	0	0.1 (0.0–1.3)	3000	3 (0–39)
North America and the Caribbean	**5**	**1729**	**28**	**1.6 (0.5–3.1)**	**1,700,000**	**27,200 (8,500–52,700)**
USA	4	1637	27	1.7 (0.5–3.6)	1,100,000	18,700 (5,500–39,600)
Mexico	1	92	1	1.1 (0.1–5.9)	230,000	2,530 (230–13,570)
South-East Asian Region	**9**	**3605**	**85**	**1.3 (0.9–1.8)**	**3,800,000**	**49,400 (34,200–68,400)**
India	5	1730	27	1.6 (0.4–3.4)	2,200,000	35,200 (8,800–74,800)
Indonesia	3	737	29	3.9 (2.5–5.4)	640,000	24,960 (16,000–34,560)
Thailand	2	1138	29	1.5 (0.8–2.3)	480,000	7,200 (3,840–11,040)
Western Pacific Region	**3**	**441**	**6**	**1.2 (0.2–2.6)**	**1,900,000**	**22,800 (3,800–49,400)**
China	1	259	3	1.2 (0.2–3.3)	900000	10,800 (1,800–29,700)

Abbreviations: NA: not applicable

WHO regions are sorted according to prevalence rates

Countries are sorted according to number of studies included

WHO regions/ country	Number datasets	Number of PLWH screened (total)	Number of PLWH with AT	Pooled prevalence (95% CI)	Estimated number of PLWH individuals*	Estimated number of PLWH with AT
Malaysia	2	182	3	1.5 (0.1–4.1)	87,000	1,305 (87–3,567)
Abbreviations: NA: not applicable						
WHO regions are sorted according to prevalence rates						
Countries are sorted according to number of studies included						

Subgroup and meta-regression analyses according to socio-demographic and study characteristics

In subgroup analyses, when the pooled prevalence was stratified according to the income-level of a country, the highest prevalence rates of AT were estimated for countries with lower-middle income-levels (1.8%, 0.7–3.2%) and the lowest for those with low income-levels (0.4%, 0.0–1.9%). Based on HDI level, the highest prevalence rates were seen in countries with low HDI-levels (1.4%, 0.1–1.3%) and the lowest prevalence rates in countries with high HDI-levels (1.3%, 0.7–2.0%) (Table 2). Moreover meta-regression analyses revealed a non-significant decreasing trend in prevalence in countries with increasing per capita income (C = -0.00082; P-value = 0.88) and HDI levels (C = -0.0056; P-value = 0.92) in a country (Fig. 2D and E). Sub-group analysis on year of study showed higher prevalence rates after 2010. This increasing trend was non-significant in meta-regression analysis (*C* = 0.0002; *P*-value = 0.7) (Fig. 2F). In subgroup analyses, according to type of study, the highest prevalence rates were estimated in the case-control (2.6%, 0.8–5.0%), and then in prospective cohort (2.6%, 0.8–5.0%) studies, and the lowest prevalence rates were estimated in retrospective cohorts (1.0%, 0.3–2.0%). Subgroup analysis based on diagnostic methods showed that prevalence rates were similar when studies used both IgG-IgM tests (1.2%, 0.7–1.8%) and seroconversion (1.2%, 0.8–1.7%). More subgroup analyses and details are given in Table 2.

Discussion

This systematic review and meta-analysis is the first global assessment of the prevalence of AT and the most comprehensive assessment of the prevalence of LT among HIV-infected people. Our findings highlight the high prevalence and burden of LT (37.4%, approximately 14.2 million people) and AT (1.3%, approximately 0.5 million people) in PLWH. Estimates reported here are similar to the prevalence rates for LT and AT observed in recent meta-analyses that we have conducted among pregnant women [10, 11], and also corroborate a general assumption that one-third of humans are infected with *Toxoplasma* [27]. Our estimate for LT (37.4%) is slightly higher than a previous meta-analysis by Wang et al. (35.8%) in the same population [14], although they included only 74 studies (49% of those included in our meta-analysis) and 25,989 HIV-infected people (approximately 58% of individuals in our meta-analysis) [14].

In the present study, the overall prevalence and burden of LT and AT varied across regions, with the highest prevalence in African and South-American countries and the lowest prevalence in the Western Pacific region. These findings are in agreement with previous global studies in pregnant women [10, 11]. In a study by Wang et al. among PLWH, the prevalence of LT was highest in countries located at sub-Saharan Africa, Latin America and the Caribbean regions [14]. The variability in prevalence in these different regions could be related to differences in climate (e.g. temperature and humidity) [10, 28], the degree of contamination of the environment (e.g., soil and water) with cat feces and *T. gondii* oocysts, cultural or culinary habits, particularly the consumption of semi-cooked or raw meat [7, 9], infectivity of the diversity of *T. gondii* genotypes present, accessibility to public health and sanitary services, control measures for stray cats, income and HDI status of a country [10, 11]. A detailed explanation about effects of these variables on the prevalence of toxoplasmosis in different populations is available in previous publications [10, 11, 27].

Considering risk factors for exposure to *T. gondii*, our analyses found that eating raw/undercooked meat, frequent contact with soil, older age, and low number of CD4 + lymphocytes were associated with increased seropositivity for LT. The risk factors for acquisition of toxoplasmosis are well documented and have been reviewed in previous studies [29, 30, 31, 32, 33]. Consumption of raw/undercooked meat is assumed to be a major source of *T. gondii* infection, however, as a risk factor, this depends on the kind of meat consumed and local culinary habits of meat preparation; for example in China who used duck and beef meat had higher seropositivity for *T. gondii* infection compared to those who used other kinds of meat including pork, lamb and chicken [34]. Lamb and pork are major dietary risk factors in European and American countries and lamb is a major risk factor in Middle Eastern countries [30, 31, 35, 36]. Contact with soil is an important source of exposure to infectious oocysts [37, 38, 39, 40, 41, 42, 43, 44, 45, 46]. We identified an increasing prevalence with age, which can be explained by the fact that risk of *Toxoplasma* infection is constant over time and older PLWH have had a longer period of time for exposure to *Toxoplasma* [7, 47]. This observation is in agreement with our previous study in pregnant women [11]. Our findings indicated that another, and maybe most important risk factor for toxoplasmosis in PLWH, is a low number of CD4 + lymphocytes. It is well known that decline in CD4 + T cells is the main reason for reactivation of latent infection in PLWH and can lead to severe toxoplasmosis and TE in these patients [48, 49].

The findings from this study must be interpreted in consideration of certain limitations. First, and common to systematic reviews, we found a high statistical heterogeneity between studies, which could not be explained by the subgroup and meta-regression analyses; the major sources of heterogeneity might result from the study characteristics including differences in study design, geographical distribution, sample size, publication year, and detection methods, including differences in the performance of these methods and differences in cut-off values for test-positivity. Second, most studies in the literature have used serological methods to detect latent or acute toxoplasmosis in PLWH; serological methods are unreliable in PLWH due to profound immunodeficiency. While bioassays (in mice or cats) are considered as the gold standard for the definitive diagnosis of toxoplasmosis, these methods are not applicable in humans. Moreover due to variation in the sensitivity and specificity (and, thus, positive and negative predictive values) of serological methods, the findings from the present study might underestimate or overestimate the prevalence of latent or active toxoplasmosis in PLWH. In addition our estimates of acute toxoplasmosis might not be the true prevalence, since relatively few studies were included; we did not include studies using data on DNA, due to

a paucity of such data and the fact that the majority of molecular studies were done in HIV patients suspected to TE or pulmonary toxoplasmosis. Thus, the estimated rates reported here must be considered as apparent prevalence rates of latent or acute toxoplasmosis in PLWH. We lastly acknowledge that despite our comprehensive systematic search, the eligible studies and data were not available for many countries and some regions of the world were not appropriately covered, which may hinder the translatability of our results at a global scale.

Conclusion

In conclusion, our findings revealed that, globally, more than one third of PLWH are exposed to, or infected with. *Toxoplasma*. International guidelines recommend toxoplasmosis screening for all PLWH and also prophylactic measures (e.g. co-trimoxazole) should be implemented for all *T. gondii*-seropositive PLWH with < 100 CD4 + cells/μL. This approach is currently not well implemented in many countries.

In our study, the prevalence rates was higher in less developed countries and regions; therefore these countries, in particular, should promote routine testing, care, and treatment for *T. gondii* infection in all PLWH.

We also determined potential risk factors related to toxoplasosis in PLWH. *T. gondii*-seronegative PLWH should be aware and educated about these risk factors and related preventive measures to reduce the risk of health problems arising from both latent and acute toxoplasmosis.

Declarations

Compliance with ethical standards

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Conflict interest

The authors declare no conflict of interest.

Ethical approval

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Informed consent

not applicable

Authors' contributions

A.R., S.A.S and M.S conceived the study. A.R., A.T., and S.A.S. conducted the searches and collected data. A.R., M.S., and S.M.R. analysed and interpreted the data sets. A.R., and R.G. drafted and edited the manuscript. All authors commented on, or edited drafts and approved the final version of the manuscript.

Availability of data and material

All data are available in main manuscript and supplementary files. Further data would be provided by corresponding author if requested.

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Figures

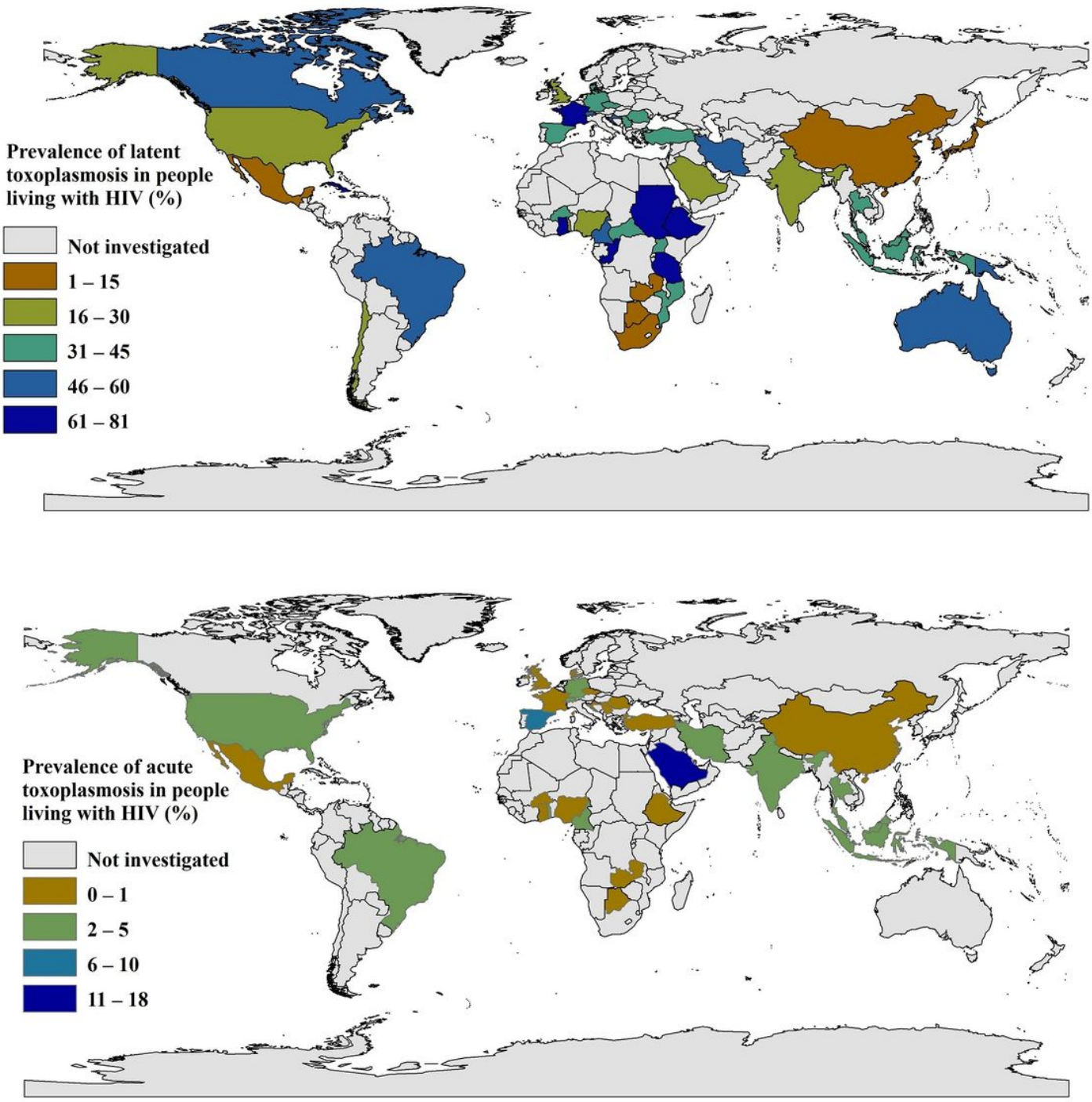
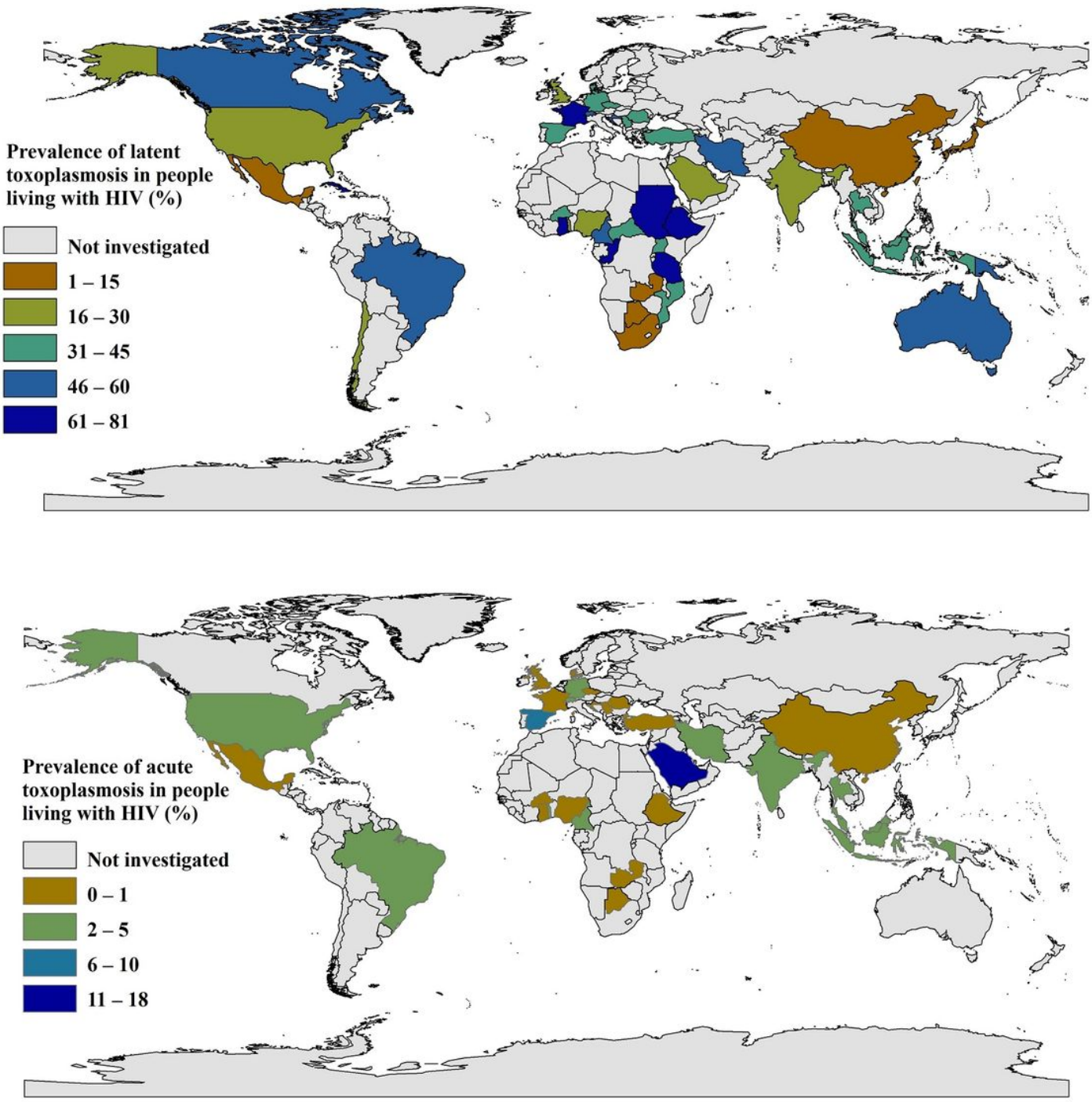


Figure 1

Prevalence of latent (A) and acute (B) toxoplasmosis in people living with HIV in different countries using geographic information system (GIS). Note: The designations employed and the presentation of the material on this map do not imply the expression of any opinion whatsoever on the part of Research Square concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. This map has been provided by the authors.



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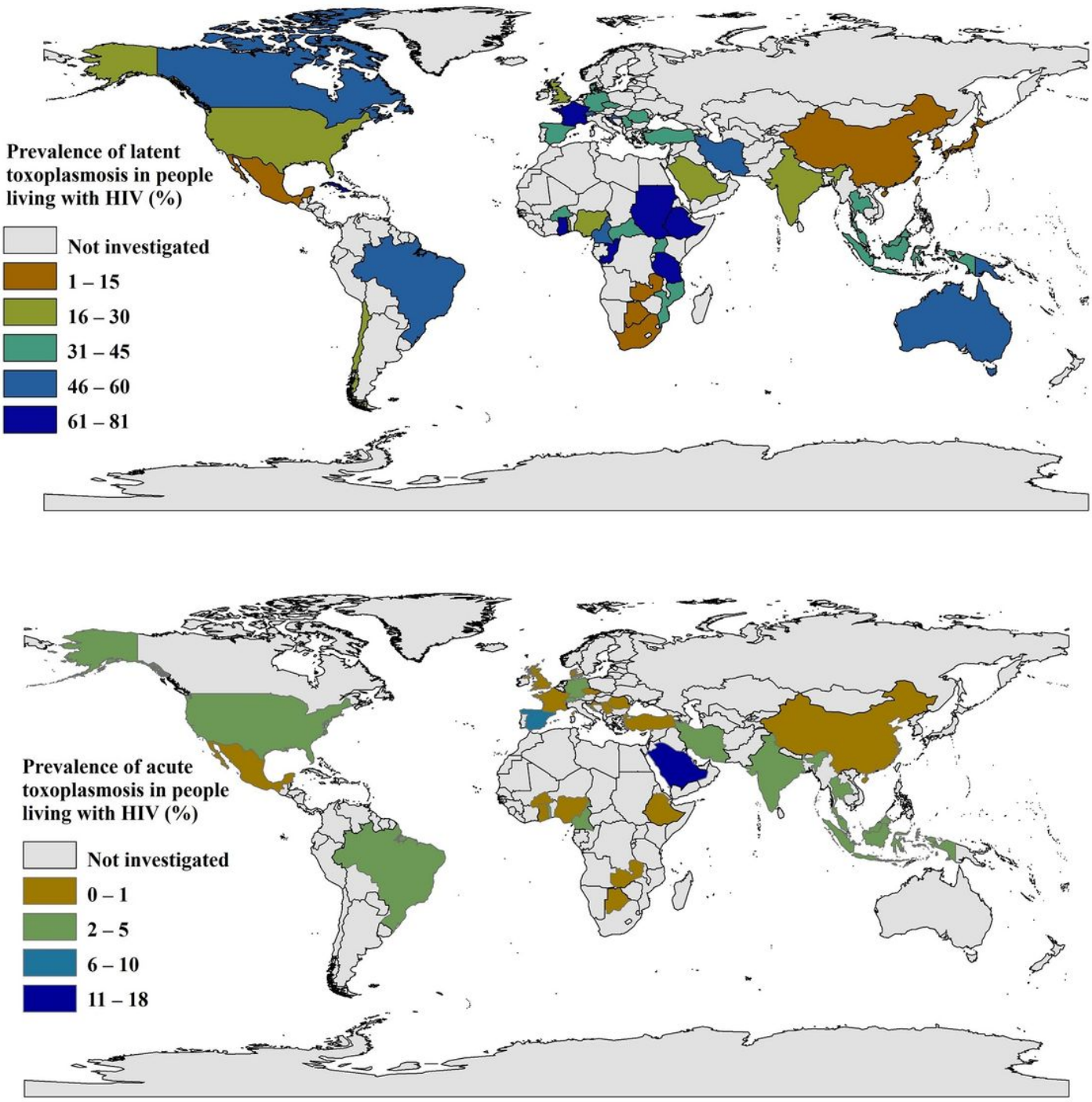

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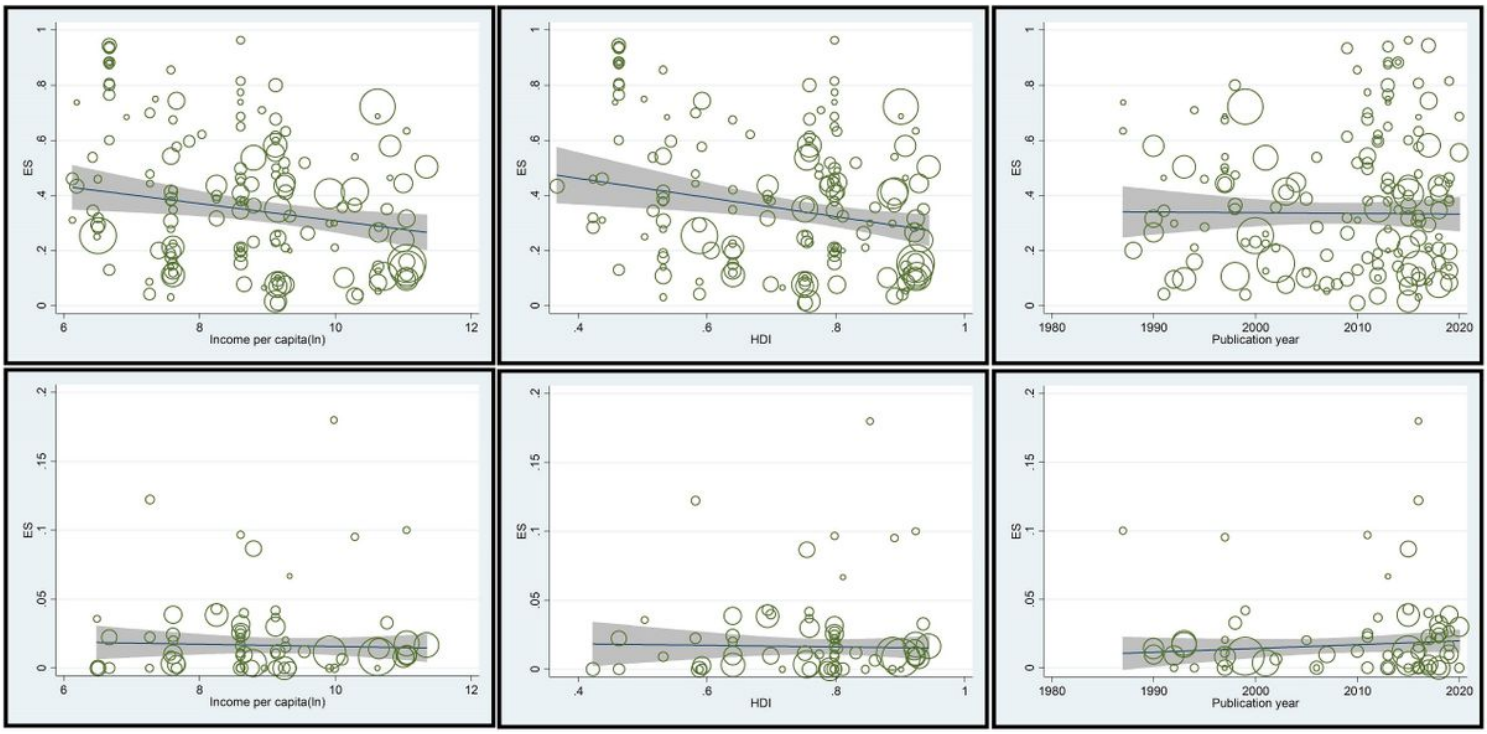


Figure 2

Meta-regression analyses of the prevalence of latent and acute toxoplasmosis in people living with HIV according to (A) a country's income level, showing a statistically significant downward trend in prevalence of LT in countries with higher income levels; (B) human development index (HDI), showing a statistically significant downward trend in prevalence of LT in countries with higher HDIs; (C) time period (1980-2019), showing a nonstatistically significant upward trend in prevalence of LT in more recent years; (D) a country's income level, showing a nonstatistically significant downward trend in prevalence of AT in countries with higher income levels; (E) HDI, showing a nonstatistically significant downward trend in prevalence of AT in countries with higher HDIs; (F) time period (1980-2019), showing a nonstatistically significant upward trend in prevalence of AT in more recent years.

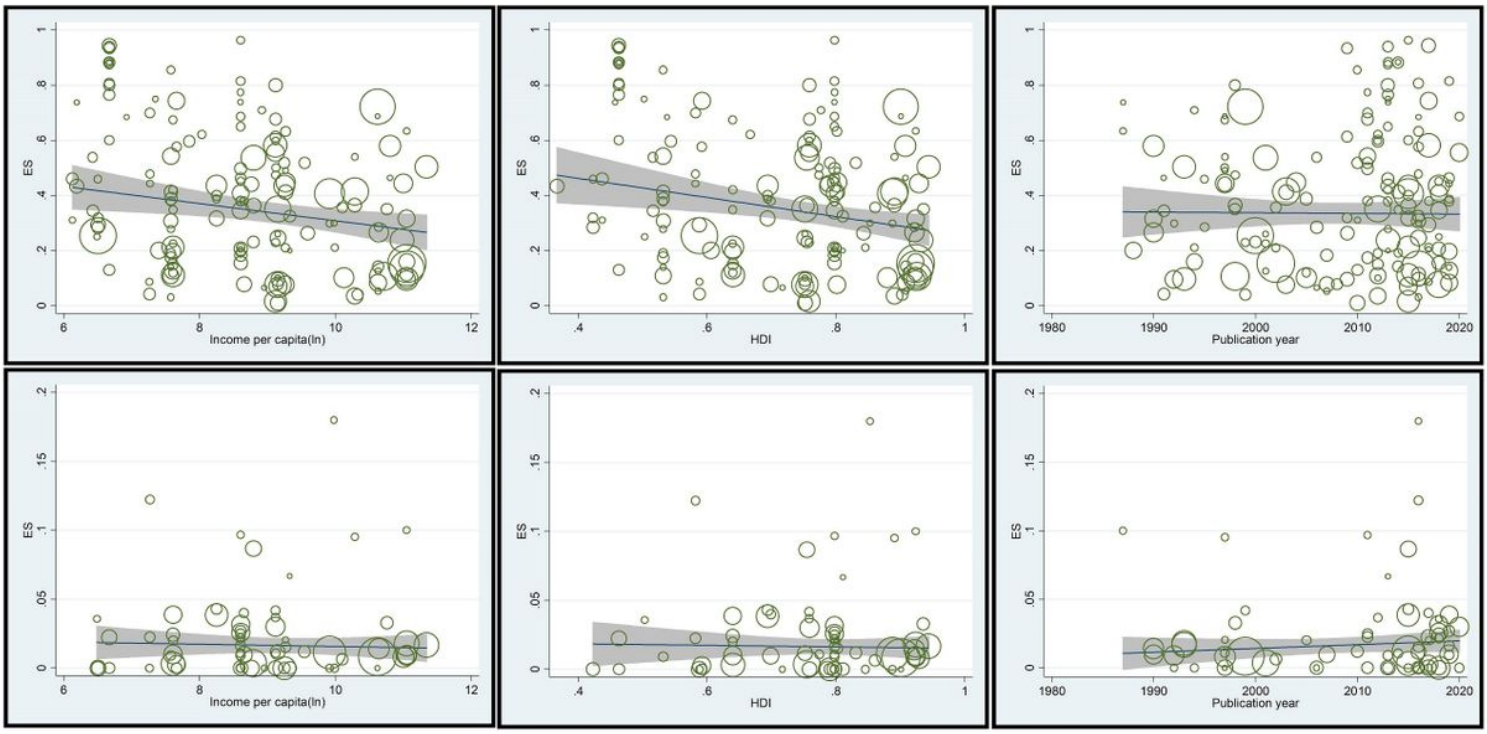
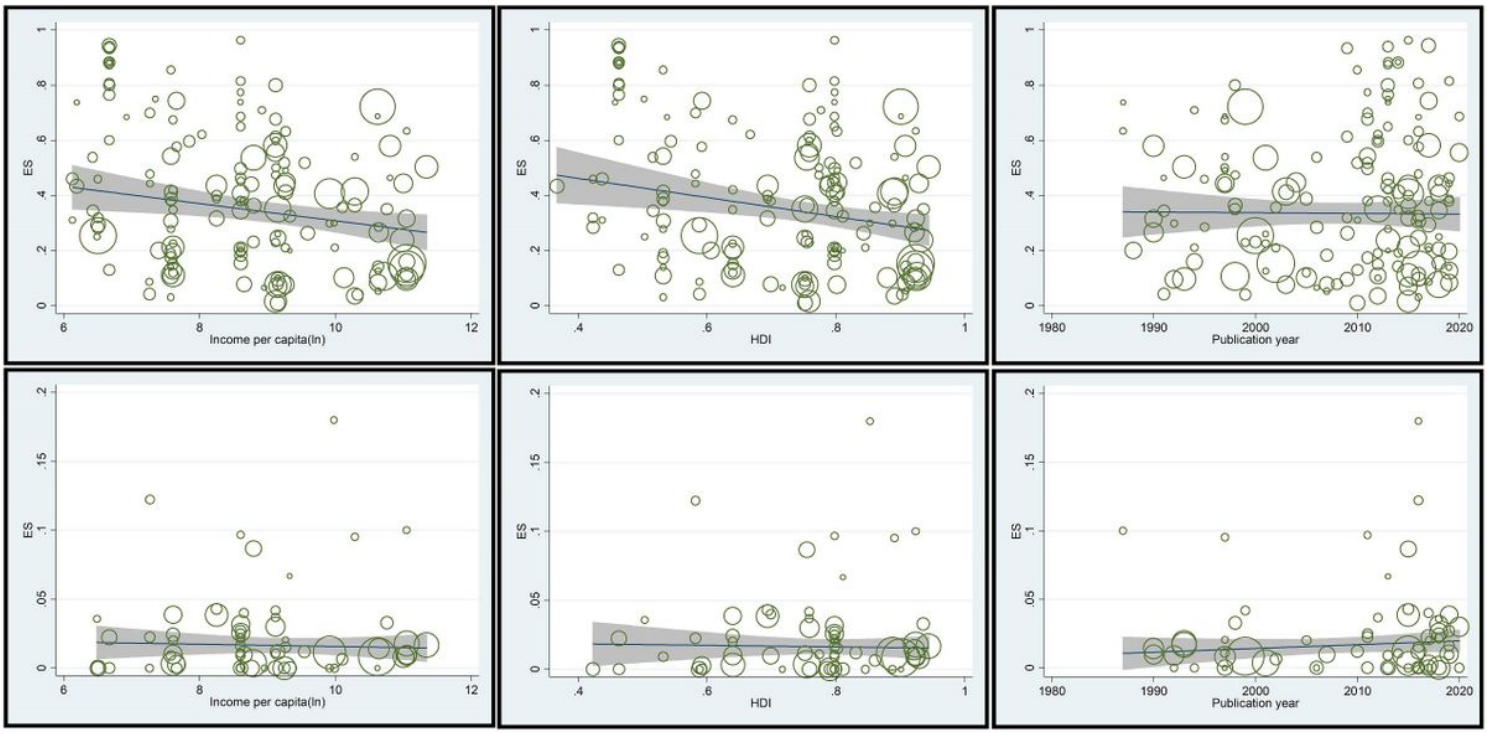


Figure 2

Meta-regression analyses of the prevalence of latent and acute toxoplasmosis in people living with HIV according to (A) a country's income level, showing a statistically significant downward trend in prevalence of LT in countries with higher income levels; (B) human development index (HDI), showing a statistically significant downward trend in prevalence of LT in countries with higher HDIs; (C) time period (1980-2019), showing a nonstatistically significant upward trend in prevalence of LT in more recent years; (D) a country's income level, showing a nonstatistically significant downward trend in prevalence of AT in countries with higher income levels; (E) HDI, showing a nonstatistically significant downward trend in prevalence of AT in countries with higher HDIs; (F) time period (1980-2019), showing a nonstatistically significant upward trend in prevalence of AT in more recent years.



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