PATHOGENS AND GLOBAL HEALTH, 2017
VOL. 111, NO. 1, 31–44
http://dx.doi.org/10.1080/20477724.2016.1273597

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Toxoplasmic encephalitis relapse rates with pyrimethamine-based therapy: systematic review and meta-analysis

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ABSTRACT

Toxoplasmic encephalitis (TE) is caused by *Toxoplasma gondii* infection and can be a life-threatening disease in immunocompromised patients. This study evaluated the rate of relapse associated with pyrimethamine-based maintenance therapy (i.e. secondary prophylaxis) in patients with human immunodeficiency virus (HIV) or AIDs treated prior to and after the common use (i.e. 1996) of highly active antiretroviral therapy (HAART) (pre-HAART and post-HAART, respectively). PubMed, Google Scholar, and Cochrane databases were searched to 6 June 2016 using search terms: pyrimethamine, Daraprim, Fansidar, Metakelfin, Fansimef, 5-(4-chlorophenyl)-6-ethyl-2,4-pyrimidinediamine, encephalitis, cerebral, toxoplasmosis, toxoplasmic, and *gondii*. Single-arm cohort, retrospective, and randomized studies were included. Twenty-six studies with 1,596 patients were included in the analysis; twenty pre-HAART (n = 1,228) studies and six post-HAART (n = 368) were performed. Pooled proportions test for pyrimethamine-based therapy from pre-HAART studies indicated a relapse rate of 19.2% and 18.9% from the fixed-effects and random-effects models, respectively. The relapse rate in the post-HAART studies was 11.1% (fixed and random effects). Continuous therapy was suggestive of lower incidence of relapse compared with intermittent therapy in the pre-HAART era (range, 18.7 to 17.3% vs. 20.9 to 25.6%, respectively). These findings indicate that the likelihood of relapse associated with pyrimethamine-based therepy in patients with HIV and TE decreased after the introduction of HAART to approximately 11%. The findings have important implications as relapse may affect a patient's disease severity and prognosis, increase utilization of health care resources, and result in additional health care expenditure.

KEYWORDS

Toxoplasmosis; Encephalitis; Toxoplasmis; Pyrimethamine; Human immunodeficiency virus; Meta-analysis; Relapse; Proportions

Introduction

Toxoplasmic encephalitis (TE) results from infection by *Toxoplasma gondii* (*T. gondii*), a ubiquitous obligate intracellular parasite with a worldwide prevalence that infects humans and other warm-blooded animals [1]. Approximately, one third of the population worldwide is chronically infected with *T. gondii* [2], *T. gondii* seroprevalence varies world wide. In the United States, it is estimated that 22.5% of the population 12 years and older are infected with the parasite [3]. It is estimated that 6.7% of people in Korea, 12.3% in China, 23.9% in Nigeria, 46% in Tanzania, and 47% in the rural areas of France are seropostive for *T. gondii* [4–8]. In Brazil, up to 50% of elementary school children and 50 to 80% of women of child-bearing age have antibodies to *T. gondii* [9]. *T. gondii* infection has two phases: active (acute) which is characterized by severe symptoms; and latent (dormant) which is typified by life-long persistence of cysts in tissues [10]. TE typically results from reactivation of the dormant organism [11].

TE is one of the most common opportunistic infections of the central nervous system (CNS) in patients with acquired immune deficiency syndrome (AIDS) worldwide, and in the United States between 10 and 40% of HIV-infected individuals have antibodies against *T. gondii* [12–14]. TE is a life-threatening disease, especially for immunocompromised patients, such as those with AIDS [13,15]. Encephalitis causes significant morbidity and mortality in patients with HIV, and toxoplasmosis was found to be the most common specified encephalitis-associated hospitalizations in patients with HIV [16].

The National Institutes of Health (NIH) Guidelines recommend the use of pyrimethamine, sulfadiazine, and leucovorin for the initial treatment of TE in HIV-infected pateints [17]. Pyrimethamine and sulfadiazine are thought to act synergistically to inhibit *T. gondii* proliferation and survival by blocking the folate metabolic pathway and consequently DNA synthesis [11]. Leucovorin is added to reduce potential adverse reactions associated with folic acid metabolism [11]. In case of allergy to sulfa

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Supplemental data for this article can be accessed here.

drugs, the recommended alternative treatment is a combination of pyrimethamine, clindamycin, and leucovorin [17]. Sulfa drug allergies are observed in about 5% of the population and up to 30% of HIV-infected patients [18].

The incidence of TE in patients infected with HIV is closely related to the progression of immune deficiency and a reduction in CD4 T lymphocyte cell counts. TE is rare in patients with CD4 cell counts >200 cells/μL, while the risk of TE is greatest in patients with CD4 counts <50 cells/μL [19]. It is recommended by the NIH/AIDS Guidelines to continue chronic maintenance treatment in patients who have responded to initial TE therapy until the person remains asymptomatic and their CD4 counts are >200 cells/μL after highly active anti-retroviral therapy (HAART) for for six months [17].

Despite treatment efforts, a percentage of patients receiving maintenance therapy for TE will experience a relapse [13]. Relapse of TE can have significant implications for patients who often develop new lesions in areas of the brain previously free of infection [20], and for providers and the health care system as a relapse can result in rehospitalization and/or change in therapy.

Previous meta-analyses have assessed the efficacy and safety of pyrimethamine for acute TE [21–23]; however, the incidence of relapse during maintenance therapy following resolution of acute TE has not been assessed [21–24]. Therefore, to gain greater insight into the risk of TE relapse, we performed a systematic review and meta-analysis to evaluate the incidence of relapse associated with pyrimethamine-based maintenance therapy (i.e. secondary prophylaxis) in persons with HIV/AIDS. We also investigated whether the likelihood of relapse changed following the introduction of HAART therapy in the mid-1990s. This was of interest because HAART has greatly reduced AIDS-related morbidity and mortality and decreased the incidence of opportunistic infections in HIV-infected patients [25]. The impact of HAART on the incidence of relapse of TE in patients with HIV is not clear. In order to incorporate the broadest scope of available evidence, the analysis protocol allowed for inclusion of studies of varying design, such as single-arm observational cohort, randomized, and retrospective studies.

Methods

Search strategy`

The study was performed in accordance with PRISMA [26], and the protocol can be found in Supplemental Material. PubMed, Google Scholar and Cochrane databases were searched up to 6 June 2016 using the following search terms: pyrimethamine, Daraprim, Fansidar, Metakelfin, Fansimef, 5-(4-chlorophenyl)-6-ethyl-2,4-pyrimidinediamine, encephalitis, cerebral, toxoplasmosis, toxoplasmic, *gondii*. Eligible studies included randomized controlled studies, observational prospective studies, and retrospective longitudinal studies. Studies had to report relapse of TE during maintenance therapy in patients with AIDS or HIV. All studies had to be published in peer-reviewed journals in English, Spanish, Portugueuse, or French. Studies that only provided relapse rates during acute treatment were rejected. Review articles, letters, comments, editorials, case reports, proceedings, personal communications, and preclinical studies were also excluded. Study eligibility for inclusion was determined by two independent reviewers, and in cases of uncertainty, a third reviewer was consulted.

Data extraction

Double data extraction was performed on all included studies to ensure data consistency. Discrepencies in extracted data between the two independent reviewers were resolved by a third reviewer. Non-English studies were reviewed by native speakers, and validated by a second reviewer for extracted data using Google Translator. The following data were extracted from the studies when reported: first author, publication year, study design, acute and maintence treatment regimens, number of patients, incidence of relapse, and duration of follow-up. For studies with insufficient reported data, we attempted to contact authors to obtain complete data. Studies were classified as being pre-HAART or post-HAART based on a cut-off date of 1996 for the conduct of the study (not publication date). The year 1996 is when the use of HAART therapy became widely available and dramatically decreased mortality of patients with AIDS (from 29.4/100 person years in 1995 to 8.8 per 100 person-years in the second quarter of 1997) [25]. HAART status was verified by patient baseline characteristics and current treatments reported, although not all patients treated in the HAART period were receiving antiretroviral therapy. The abstracts were screened and data were extracted by the authors MPC and EG.

Quality assessment

The quality of the included studies was evaluated using Study Quality Assessment Tools of the National Heart, Lung, and Blood Institute of the NIH for quality assessment of observational cohort, cross-sectional, before–after (pre-post) studies with no control group, and case series studies [27].

Statistical analysis

Pooled proportions meta-analysis

The primary outcome was rate of relapse during pyrimethamine-based maintenance therapy. The secondary outcome was rate of relapse with continuous (daily) or intermittent (two to three times per week) pyrimethamine-based therapy. For each outcome, rates in each study were transformed using the Freeman-Tukey

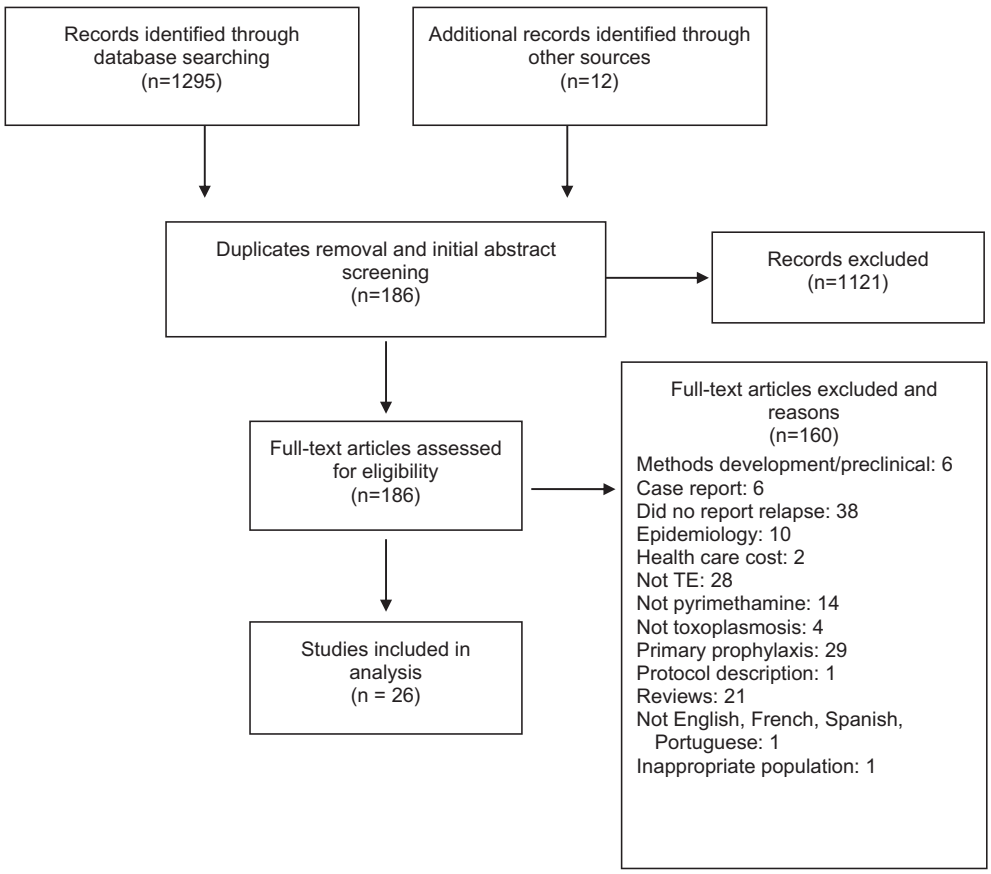

Figure 1. Search flow diagram.

double arcsine method. This transformation stabilizes the variance estimates, which is important for proportions close to 0 or 1 [28]. Rates were then pooled using both fixed-effect and random-effects meta-analysis models. The fixed-effect model was performed using the inverse variance method and the random-effects model using the DerSimonian and Laird method, with the estimate of heterogeneity taken from the inverse variance model [29]. Heterogeneity across studies was assessed by quantifying I^2 inconsistency scores [30]. I^2 describes the percentage variation across studies attributed to heterogeneity rather than chance. Low I^2 values (≤50%) suggest limited heterogeneity between studies, and I^2 values >50 to 75% indicate moderate heterogeneity. Values >75% suggest high heterogeneity and the need to consider estimates from random-effects models [30]. The analysis was performed using StatsDirect (Altrincham, UK) statistical program version 2.8.0 (27 October 2013). For ease of interpretating, the reported proportions were converted to percentages. Because the studies are non-comparative, we assessed active treatment arms independently; therefore, no comparative statistics were performed and only the combined relapse rate is reported.

Bias of the results was evaluated by the funnel plot and the Egger's test [31,32]. In the absence of bias, the graph is a symmetrical inverted funnel, and if there is bias, the funnel plot will appear asymmetrical [31,32]. Reporting bias was assessed for the pre-HAART analysis, but not the post-HAART analysis as the minumum studies for this analysis should be >10; below this value, the test power is usually too low to distinguish chance from real asymmetry [33].

Results

Search results

Of 1,307 studies initially identified, 1,121 were excluded following the 'removal of duplicates and an initial abstract screen (Figure 1). After full-text review, an additional 160 were removed for only describing methodology or a study protocol, being a pre-clinical study, being a case report, not reporting relapse rates, being an epidemiology or health care cost study, not evaluating TE, not administering pyrimethamine-based regimens, not investigating toxoplasmosis, describing finding for primary prophylaxis of TE, being a review article, not being published in English, French, Spanish, or Portugeuse, or evaluting an inappropriate patient population.

Study characteristics

Twenty-six studies were included in the analysis with 1,596 patients (Tables 1 and 2). Twenty reported findings from studies that were performed up to 1996 ($n = 1,228$) (Table 1) [34–51], and six described results of studies performed after 1996 ($n = 368$) (Table 2) [52–57].

Table 1. Summary of study characteristics performed until 1996.

Author	Study Design	Demographics	Pyrimethamine-based therapy		No. patients evaluated for relapse, *n*	Relapse, *n*(%)	Follow-up
			Acute	Maintenance			
Randomized studies							
Katlama (1996)	Randomized prospective open-label	*N* = 299 *PC* (*n* = 152) Male:133 (88%) Mean age: 34 yrs *PS* (*n* = 147) Male: 129 (88%) Mean age: 33 yrs	*PS* PYR (50 mg daily) plus SDZ (4 g daily in four divided doses) plus folinic acid (min 50 mg/wk) *PC* PYR (50 mg daily) plus clindamycin (2.4 g daily in four divided doses) plus folinic acid (min 50 mg/wk) Acute therapy was given for six weeks.	*PS* PYR (25 mg/day) plus SDZ (500 mg four times/day) plus folinic acid 50 mg weekly *PC* PYR (25 mg/day) plus CLI (300 mg four times/day) plus folinic acid 50 mg weekly Maintenance therapy was life-long.	PS: 83 PC: 92	PS: 17 (20.5%) PC: 35 (38.0%)	89 to >130 weeks
Podzamczer (1995)	Randomized open-label	*N* = 105 *Daily*: (*n* = 60) Male: 40 (66.7%) Age: 34 yrs *Twice weekly*: (*n* = 45) Male: 34 (75.6%) Age: 32 yrs	n.a.	*Daily PS* PYR (25 mg/day) plus SDZ (500 mg four times per day) and folinic acid (15 mg/day). *Intermittent PS* PYR (25 mg/day) twice weekly plus SDZ (500 mg four times per day) and folinic acid (15 mg/day).	105	Total: 11 (10.4%) *Intermittent*: 19.5 per 100 patient-yrs *Daily*: 4.4 per 100 patient-yrs	median 11 months
Torre (1998)	Randomized, prospective, pilot	*N* = 77 *PS* (*n* = 37) Male: 29 (78.4%) Mean age: 32.4 yrs *TMP-SMX* (*n* = 40) Male: 28 (70%) Mean age: 34.0 yrs	*PS* PYR (50 mg/day) plus SDZ (60 mg/kg/day) plus folinic acid (10 mg/day) *TMP-SMX* TMP (10 mg/kg/day BID) plus SMX (50 mg/kg/d BID) TX was for 30 days	Same regimens as above but at half of the original dosage given for three months	PS: *n* = 35 TMP–SMX: *n* = 37	PS: 0 TMP-SMX: 1 (2.7%)	3 months
Prospective studies							
Bouree (1997)	Prospective observational	*N* = 60 Male: 46 (76.7) Mean age: 40 yrs.	*PS* PYR (100 mg/day) plus SDZ (6 g/day) plus folinic acid (50 mg/day)	*PS* PYR (100 mg/day) plus SDZ (6 g/day) plus folinic acid (50 mg/day)	60	11 (18.3%)	7 years
Canessa (1992)	Prospective	*N* = 24 Male: 19 (79.2%) Age, range: 23–53 yrs	*TMP-SMX* TMP-SMX (40 mg/kg/day) or TMP-SMX (120 mg/kg/day) Folinic acid (15 mg/day) was also given TX duration 25 day	*PYR±SMP* Sulfamethoxpyrazine (500 mg) plus PYR (25 mg) twice weekly	24	4 (17%)	n.r.
Leport (1987)	Prospective observational	*N* = 12 Male: 11 (91.7%) Age, range: 20–47 yrs	*PS* PYR (average 50 mg [range 15–100 mg) plus SDZ (average 4 g (range 2–6 g), for 30 days. Folinic acid (range, 5 to 50 mg/day) was also administered. The 12th patient died during TX	Same as acute	12	0	n.r.

Orefice (1992)	Prospective, observational	*N* = 15 Male: 12 (80%) *PSC* (*n* = 5) *PS* (*n* = 10)	*PSC* PYR (50 mg/day) plus SDZ (4 g/day) plus CLI (1200 mg/day) plus folinic acid *PS* PYR (50 mg/day) plus SDZ (4 g/day) plus folinic acid TX was for 4–6 weeks	PYR (25 mg/day) plus SDZ (2 g/day)	15	3 (20%)	n.r.
Ruf (1991)	Prospective, observational	*N* = 51 *Three-drug regimen* (*PC* ± *SPY*) (*n* = 25) *Two-drug regimen* (*PC*) (*n* = 26)	*Three-drug regimen* (*PC* ± *SPY*) PYR (1.5 mg/kg/day) plus CLI (2400 mg/day) plus SPY (9 × 10^6 IU/day) *Two-drug regimen (PC)* PYR (50 mg/day for body weight <65 kg or 75 mg/day for body weight >65 kg) plus CLI (2400 mg/day) Both TX arms received folinic acid 45 mg/day (although some patients only received drug after myelosuppression became apparent) TX was for three weeks	*PYR* ± *SDX* (*Fansidar*) PYR (15 mg) plus SDX (500 mg) plus folinic acid (15 mg) twice a week.	39	4 (10%)	Median 13 months
Ruf (1993)	Prospective, open-label	*N* = 56 Male: 48 (85.7%) Median age: 39 yrs	*PC* PYR (50 mg/day body weight <65 kg or 75 mg/day body weight >65 kg) plus CLI (2400 mg/day) plus LEU 30 mg/day.	*PYR* ± *SDX* (*Fansidar*) 25 mg PYR/SDX 500 mg plus LEU (15–30 mg) twice a week	56	4 (7.1%)	n.r.
Retrospective studies							
Altes (1989)	Retrospective	*N* = 70; 13 with TE	*PS* PYR (50–100 mg) plus SDZ (4–6 g) and folinic acid (15–45 mg) daily.	PYR 25 mg/day	13	7 (54%)	n.r.
Dannemann (1988)	Retrospective, case review	*N* = 15 Mean age:47 yrs *CLI* (*n* = 9) *PC* (*n* = 6)	*CLI* Various IV dosages of CLI (–) from 1200–4.8 g/day given from every 6-8 h) *PC* Various IV dosages of CLI (–from 1200–4.8 g/day given every 6-8 h) with PYR (25–100 mg/day) Folinic acid (5–10 mg/day) was administered to 11 patients TX length variable across patients (range 3 to 300 days)	*PC* PYR (25–75 mg/day plus CLI (300 to 900 every 6-8 h) or PYR (75 mg every other day) plus CLI 450 mg every 6 h) *PYR* PYR (25–100 mg/day) *CLI* CLI (300–450 mg every 6 h or 900 every 8 h) *SPY* SPY (500 mg every 8 h)	PC: 4 PYR: 4 CLI: 3 SPY: 1	PC: 1 (25%) PYR: 1 (25%) CLI: 3 (100%) SPY: 0	Mean 7.5 months
de Gans (1992)	Retrospective	*N* = 38 Male: 37 (97.7%) Median age: 38.5	*PS* PYR (25–75 mg/day) plus SDZ (2–6 mg/day) plus folinic acid (15 mg/day) Acute treatment was for six weeks.	PYR (25 or 50 mg/day) plus folinic acid (15 mg/day)	38	12 (31.6%)	n.r.

(*Continued*)

Table 1. (*Continued*).

Author	Study Design	Demographics	Pyrimethamine-based therapy		No. patients evaluated for relapse, *n*	Relapse, *n*(%)	Follow-up
			Acute	Maintenance			
Ferrer (1996)	Retrospective	*N* = 63 Male: 46 (73%) Mean age for both: 21–65 years *PS* (*n* = 49) *PC* (*n* = 14)	*PS* PYR (50–75 mg/day) plus SDZ (4 g/day) plus folinic acid (15 mg/day) QID PO for 4–6 weeks *PC* (*n* = 14) PYR (50–75 mg/day) plus folinic acid (15 mg/day) QID PO for 4–6 weeks plus CLI (600 mg/q6 h) PO or IV Pts w/ intracranial hypertension and perilesional edema: Dexamethasone (12- 16 mg/day)	*PS* PYR (25 mg/day) plus SDZ (2 g/day) *PC* PYR (25 mg/day) plus CLI (1200 mg/day)	63	Total: 19 (30.2%) PS: 12 PC: 7	n.r.
Foppa (1991)	Retrospective	*N* = 14 Male: 13 (92.9%) Age, range: 29–39 yrs	*PC* PYR (100 mg loading dose, followed by 50 mg/d) plus CLI (600–900 mg orally TID) plus folinic acid (15 mg/day) for 6–8 weeks Duration of acute therapy was from 6 to 8 weeks	*PC* PYR (25 mg/d) plus CLI (300 mg QID or 450 mg TID) plus folinic acid (15 mg/day)	14	0	Mean 7.7 months
Gonza-lez-Clemente (1990)	Retrospective	*N* = 57	*PS* PYR 5–100 mg for one day followed by 25–50 mg/day, SDZ 75 mg/kg/day divided into four doses, plus folinic acid (10–20 mg/day) *PC* If patient had sulfa allergy, clindamycin (600 mg/every 6 h) was substituted for SDZ. Acute treatment was for 3 to 6 weeks	*PS* PYR 5–100 mg for one day followed by 25–50 mg/day, SDZ 75 mg/kg/day divided into four doses, plus folinic acid (10–20 mg/day) two days per week (Tuesday and Friday) *PC* If patient had sulfa allergy, clindamycin (600 mg/every 6 h) was substituted for SDZ	PS: *n* = 15 PC: *n* = 10	PS: 0 PC: 4 (40%)	PS: Median 12.3 months PC: Median 13.3 months
Leport (1988)	Retrospective chart review	*N* = 35 Male: 33 (94.3%) Mean age: 37.0 yrs	*PS* PYR (loading doses 100–200 mg for first 1–2 days, followed by 50–100 mg/day) plus SDZ (2–6 g/day) plus folinic acid (5–50 mg/day)	*PS* PYR (25–50 mg/day) plus SDZ (1–4 g/day) plus folinic acid (5–50 mg/day)	24	6 (25%)	Mean 6 months
Leport (1991)	Retrospective	*N* = 35	n.a.	*PS* (*n* = 13)[a] PYR (25–100 mg/day) plus SDZ (2–4 g/day) *PC* (*n* = 20)[a] PYR (25–100 mg/day) plus CLI (450–1200 mg/day) *PYR* (*n* = 11)[a] PYR 50–100 mg/day	35	Total: 6 (17%) PC: 4 PYR: 1 PS: 1	Mean 13 months
Pedrol (1990)	Retrospective	*N* = 43 Male: 35 (81.4%)	*PS* PYR 50–75 mg loading dose, followed by 25 mg/day plus SDZ 75 mg/day plus folinic acid (10–20 mg/day) Acute treatment was for 3 weeks	*PS* Same as acute dosage but given only 2 days/wk (Tues and Fri)	12	6 (50.0%)	10.3–13.7 months
Ragnaud (1993)	Retrospective	*N* = 73 Sex ratio: 2.8:1 Mean age: 36.2 yrs	*PS* PYR (100–200 mg/day for 1–3 days followed by 75 mg/day) plus SDZ (4–8 g/day) plus folinic acid (10–50 mg/day)	*PS* PYR 50 mg / day plus SDZ 2 to 3 g / day *PC* PYR 50 mg/day plus CLI 1.2 g/day	60	12 (20%)	8 months

Renold (1992)	Retrospective chart review	*N* = 86 Male: 69 (80%) Mean age: 36.4 yrs	*PS* *PC* Acute treatment was defined as antitoxoplasma drugs received within 42 days of diagnosis	*PS* *PC* Maintenance therapy was calculated from the 42nd day following diagnosis to death, loss to follow-up, relapse, or December 31, 1990, or whichever came first.	82	16 (19.5%)	n.r.	

[a]*n* indicates number of courses. Forty-four treatment courses were evaluated in 35 patients.
BID: twice daily; CLI, clindamycin; IV, intravenous; LEU, leucovorin; n.a., not applicable; n.r., not reported; PC, pyrimethamine plus clindamycin; PK, pharmacokinetic; PS, pyrimethamine plus sulfadiazine; PSC: pyrimethamine plus sulfadiazine, plus clindamycin; PYR, pyrimethamine; QID, four times/day; SDX, sulfadoxine; SDZ, sulfadiazine; SMP, sulphamethoxpyrazine; SMX, sulfamethoxazole; SPY, spiramycin; TMP, trimethoprim; TMP-SMX, trimethoprim-sulfamethoxazole (co-trimoxazole); TX, treatment.

Study designs differed across both pre- and post-HAART studies. The pre-HAART studies included three randomized, six prospective, and 11 retrospective studies (Table 1), and the post-HAART studies included two randomized, two prospective, and two retrospective studies (Table 2). All studies included patients with AIDS or infected with HIV and who had received maintenance therapy for TE.

Among the studies, the pyrimethamine-based treatment regimens were heterogeneous, both for acute and maintenance therapy (Tables 1 and 2). In the pre- and post-HAART groups, the most common therapy both for acute and maintenance therapy was the combination of pyrimethamine and sulfadiazine. Other investigated pyrimethamine-based regimens included clindamycin, sulphamethopyrazine, sulfadoxine, clarithromycin, and atovaquone. Four studies in the pre-HAART group [41,42,45,47] and two in the post-HAART group [52,55] administered pyrimethamine alone for maintenance therapy. Most studies co-administered folinic acid (leucovorin) with pyrimethamine for acute therapy; only four did not report co-administering folinic acid with pyrimethamine – three in the pre-HAART group [35,58,59] and one in the post-HAART group [52]. Of the included studies, 11 did not report co-administering folinic acid with pyrimethamine during maintenance therapy [34,35,38,41,45,47,49,51,52,54,60].

The follow-up for pre-HAART studies ranged from 3 months to 7 years and for the post-HAART studies from 4 to 22 months. For the pre-HAART studies, the rate of relapse ranged from 0 to 67% and for the post-HAART studies ranged from 0 to 12.9%.

Quality assessment

The majority of included studies obtained scores of medium–to-low quality due the varied trial designs. Despite the overall quality assessment, the relapse data reported were of sufficient quality for inclusion in the proportions analysis.

Meta-analysis

The pooled proportions test for pyrimethamine-based therapy in pre-HAART studies indicated a relapse rate of 19.2% and 18.9% from the fixed-effects and random-effects models, respectively (Table 3 and Figure 2 and Figure 3). In the post-HAART period, the pooled proportions relapse rate was 11.1%, and was the same from both the fixed- and random-effect models due to limited heterogeneity in the data ($I^2 = 0\%$) (Table 3 and Figure 4).

Six studies reported relapse rates of patients who received intermittent pyrimethamine-based therapy (two to three times per week); five pre-HAART [40,43,45,49,61] and one post-HAART [56]. We evaluated the rate of relapse in these studies compared with studies with continuous (daily) dosing. The relapse

Table 2. Summary of study characteristics after 1996.

Author	Study design	Demographics	Pyrimethamine-based therapy		No. patients evaluated for relapse, *n*	Relapse, *n*(%)	Follow-up
			Acute	Maintenance			
Randomized studies							
Chirgwin (2002)	Randomized, open-label, phase 2	*N* = 39 *ATO±PYR* (*n* = 28) Male: 22 (79%) Median age: 35 yrs *ATO±SDZ* (*n* = 12) Male: 10 (83%) Median age: 37 yrs	*ATO ± PYR* ATO (1500 mg BID) plus PYR (200 mg loading dose, followed by 75 mg/day) plus LEU 10 mg daily *ATO ± SDZ* ATO (1500 mg BID) plus SDZ (1500 mg QID) plus LEU 10 mg/day. Acute treatment was administered for six weeks	42 weeks after acute treatment with same treatment regimen as acute therapy	15	1 (6.7%)	48 weeks
Podzamczer (2000)	Randomized open-label	*N* = 124 *Daily* (*n* = 58) Male/female ratio: 3.5 Age: 35.7 yrs *Thrice weekly* (*n* = 66) Male/female ratio:5.0 Age: 34.9 yrs.	n.a.	*PS Daily Regimen*:PYR (25 mg/day) plus SDZ (1 g BID) plus folinic acid (15 mg/day) *PS Three times/wk regimen*: PYR (50 mg/day) plus (SDZ: 1 g BID) plus folinic acid (15 mg)/day	124	Total: 16 (12.9%) *Daily*: 14.9 episodes per 100 patient yrs *Intermittent*: 14.1 episodes per 100 patient yrs	Median 11 months
Prospective studies							
Langmann (2004)	Prospective	*N* = 6 (3 received secondary prophylaxis) Age, range: 35–59 yrs	n.a.	PYR: 50 mg/day or 37.5 mg/day depending on body weight plus folinic acid (7.5 mg/day)	3	0	Mean 22 ± 13 months
Vidal (2005)	Prospective longitudinal	*N* = 55 Male: 33 (60%) Mean age: 36 yrs	*PS* PYR + SDZ + folinic acid	*PS* PYR + SDZ + folinic acid	46	2 (4%)	One year from diagnosis
Retrospective study							
Arendt (1999)	Retrospective	*N* = 106 Male: 101 (95.3%) Mean age: 40.4 yrs *P ± SND* (*n* = 98) *PC* (*n* = 6)	*P ± SND* PYR (75 mg/day) plus sulfonamides (2 g/day) or clindamycin (2400 mg/day). *PC* PYR (75 mg/day) plus clindamycin (2400 mg/day).	PYR: 75 mg/day	106	13 (12%)	n.r.
Davarpanah (2007)	Retrospective	*N* = 38 Male: 30 (78.9%) Age: 38 yrs	*PS* PYR + SDZ + leucovorin	*PS* PYR + SDZ	4	0	n.r.

ATO, atovaquone; LEU, leucovorin; n.a., not applicable; n.r., not reported; PC, pyrimethamine plus clindamycin; PS, pyrimethamine plus sulfadiazine; P + SND, pyrimethamine plus a sulfonamide; PYR, pyrimethamine; SDZ, sulfadiazine.

Table 3. Pyrimethamine-based maintenance therapy: relapse rates in pre-HAART and post-HAART period.

	Proportions Fixed-effect	Proportions Random-effect	I^2
Pre-HAART	0.192 (95% CI = 0.167 to 0.218)	0.189 (95% CI = 0.137 to 0.247)	76.4% (95% CI = 62.8 to 83.5%)
Post-HAART	0.111 (95% CI = 0.078 to 0.149)	0.111 (95% CI = 0.078 to 0.149)	0% (95% CI = 0 to 61%)
Intermittent Pre-HAART	0.209 (95% CI = 0.139 to 0.287)	0.256 (95% CI = 0.104 to 0.445)	72.9% (95% CI = 17.9 to 86.7%)
Intermittent Post-HAART[a]	–	–	
Continuous Pre-HAART	0.187 (95% CI = 0.161 to 0.214)	0.173 (95% CI = 0.119 to 0.234)	77.5% (95% CI = 64.4 to 84.3%)
Continuous Post-HAART	0.105 (95% CI = 0.069 to 0.146)	0.105 (95% CI = 0.069 to 0.146)	0% (95% CI = 0 to 61%)

[a]Analysis was not performed as only one study in the post-HAART timeframe evaluated intermittent pyrimethamine-based therapy.
CI, confidence interval; I^2, inconsistency.

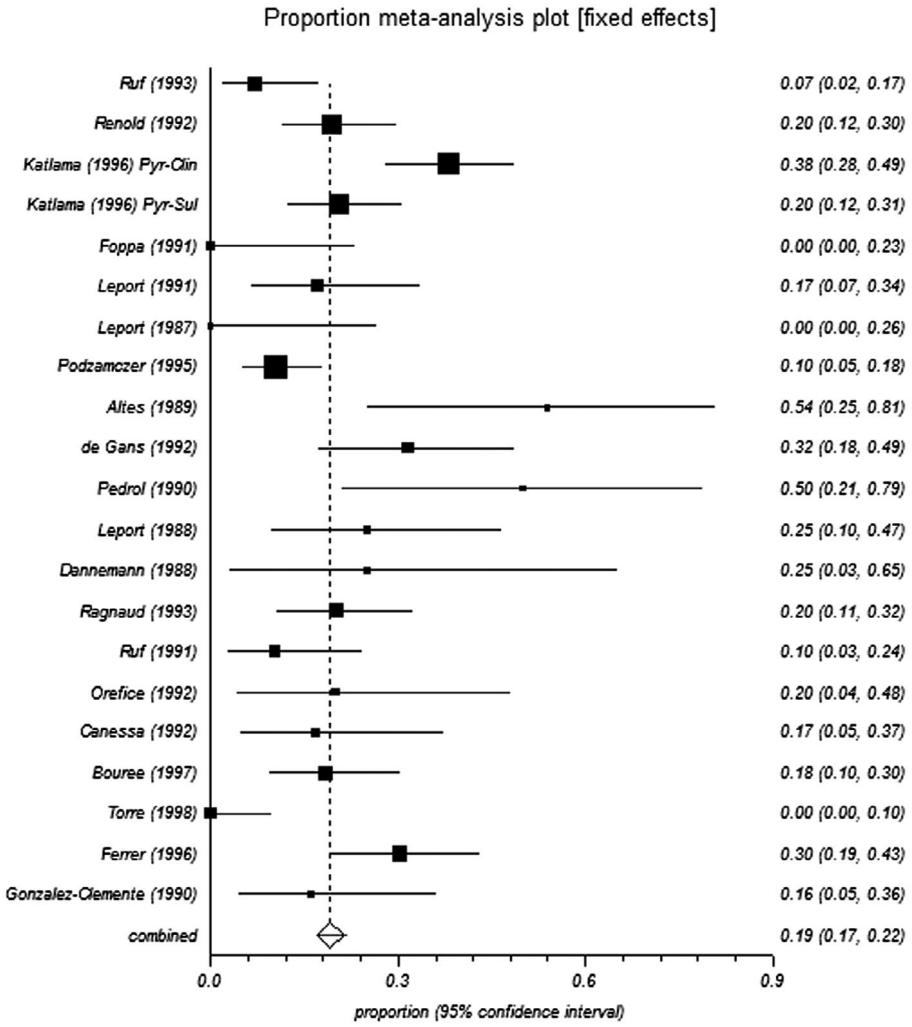

Figure 2. Forest plot of fixed for analysis of pre-HAART studies.

rate with intermittent pyrimethamine-based therapies in pre-HAART studies was 20.9% from the fixed-effect and 25.6% from the random-effect models, and for continous therapy was 18.7–17.3%, respectively (Table 3). The rates for continuous therapy for post-HAART were 10.5%. Intermittent therapy was not analyzed in the post-HAART studies as only one study [56] evaluated this type of treatment regimen.

Analysis of reporting bias

Funnel plot analysis was performed for the pre-HAART studies (Figure 5). The analysis indicated the presence of reporting bias as indicated by significant funnel plot asymmetry (Eggar bias: 3.12386 (95% CI = 1.196098 to 5.051621); $P = 0.0031$).

Discussion

This systematic review and meta-analysis assessed the incidence of TE relapse following pyrimethamine-based therapy in patients with HIV or AIDS. The anlysis found that the incidence of relapse was higher in pre-HAART (19.2% for fixed effect model and 18.9% for random effect model) compared with post-HAART (11.1% for both fixed- and random-effect models). The drop in the incidence of relapse with the use of HAART therapy is consistent with the impact of HAART on the immune

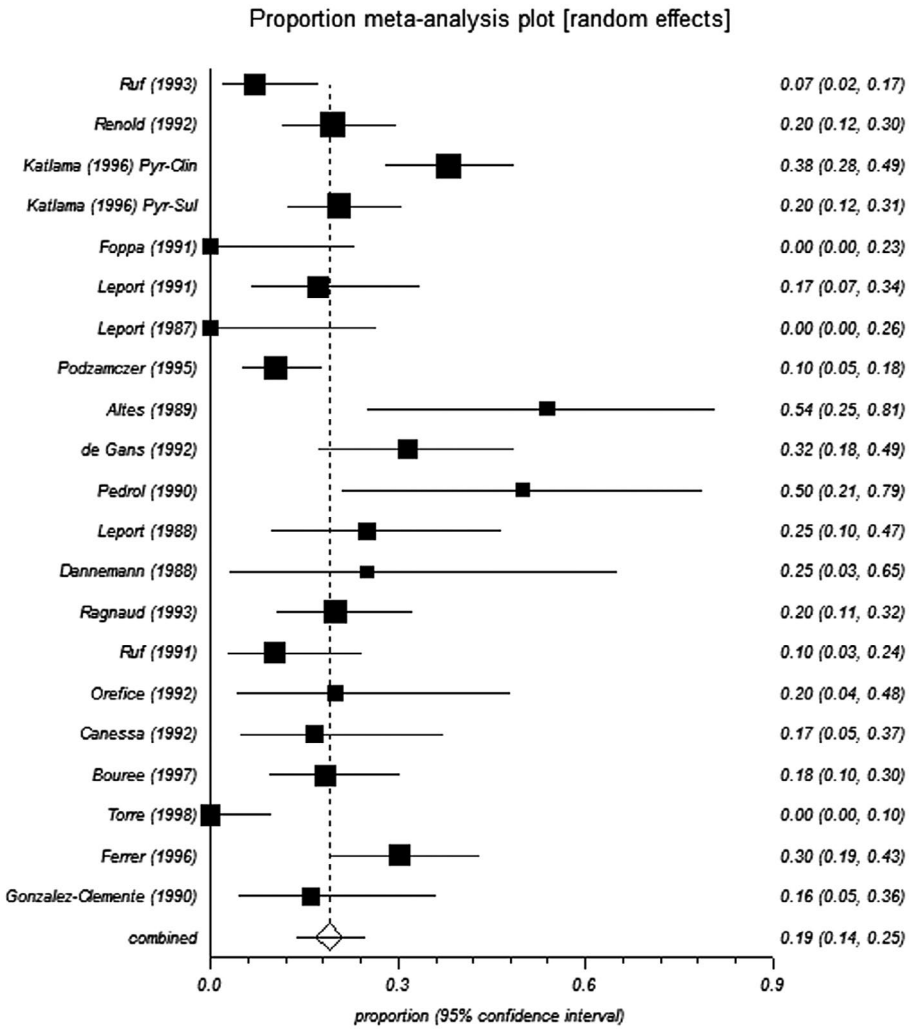

Figure 3. Forest plot of random effect model for analysis of pre-HAART studies.

status of patients with HIV or AIDs. To our knowledge, this is the first meta-analysis to evaluate the rate of relapse of TE in HIV-infected or AIDS patients, and specifically illustrates the benefits of HAART therapy for preventing relapse.

Relapse during maintenance therapy may result from a number of causes including treatment efficacy, dosing regimen, patient characteristics, and treatment adherence. The importance of the dosing regimen is indicated by our results that sugggest intermittent therapy administered two to three times per week was associated with a higher relapse rate compared with continuous therapy, and supports the NIH Guidelines of daily dosing of pyrimethamine plus sulfadiazine for maintenance treatment [17].

The analysis described here focused on pyrimethamine-based therapy for the prevention of relapse due to the extensive history of the use of pyrimethamine in the clinic and the significant number of observational and retrospective clinical studies that have evaluated the effect of pyrimethamine-based therapy in treating TE. Much less-published information is available regarding the use of other off-label treatments for TE, such as the trimethoprim–sulfamethoxazole (TMP-SMX) combination. A similar search identified only five studies that evaluated TMP-SMX for maintenance therapy and reported relapse of HIV-infected patients with TE [48,62–65], four of which were performed post-1996 [62–65]. Across the five studies, the rate of TE relapse ranged from 3 to 39%.

Evidence from randomized controlled trials serve as the gold-standard for studies to be included in meta-analyses to reduce bias in the results. However, challenges exist in applying randomized control trial results to the real-world clinical setting due to differences between subjects recruited and the types of patients encountered in clinical practice [66]. We included both prospective observational and retrospective studies due to the shortage of available randomized studies with pyrimethamine relative to the number of other study designs in TE. The inclusion of these studies in our analysis broadens the range of evidence and may improve the generalizability of the findings. This approach is consistent with other health service researchers who have included observational study designs in meta-analyses, and has been applied in other disease areas [67,68].

The analysis described here has several limitations that are worth considering. Significant heterogeneity

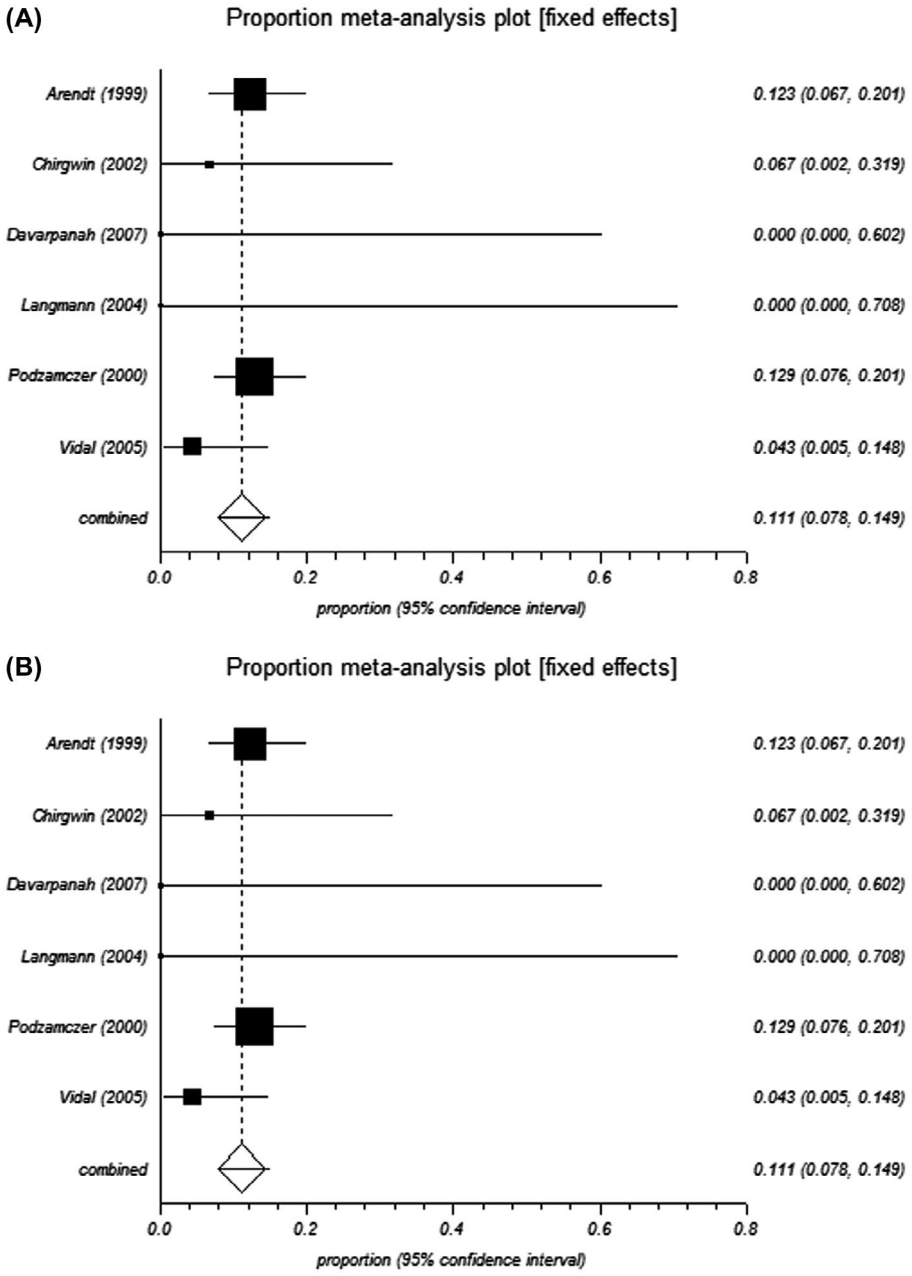

Figure 4. Forest plot of (A) fixed and (B) random effect model for analysis of post-HAART studies.

across studies was present with respect to study design, dosing regimen, and defintion of relapse, and the majority of studies were of mediumto-low quality. Also, the size of the patient population for the post-HAART analysis was small. Furthermore, not all patients were receiving HAART therapy for various reasons, and the results were not presented by HAART precluding an assessment of how this would influence results. Although, based on the analysis described here it is likely to have diminished effectiveness and increased likelihood of relapse. Reporting bias was also present which may have confounded the results. In addition, duration of follow-up varied between studies which could influence the rate of relapse. It is also important to emphasize that the proportions reported here are independently evaluated; therefore, it was not feasible to infer whether differences in relapse rates reported here are significantly different.

This study comprehensively evaluated the relapse rate of TE in patients with HIV or AIDS who received pyrimethamine-based maintenance therapy. The findings indicate that the incidence of relapse decreased after the introduction of HAART. The reduction in relapse following the introduction of HAART is consistent with the ability of HAART to control HIV infection. In addition, this study suggests that daily pyrimethamine-based maintenance therapy is likely more efficacious in preventing TE relapse compared with intermittent therapy. These findings have important medical and cost implications as relapse may affect a patient's prognosis and healthcare resource utilization, and result in additional healthcare expenditure.

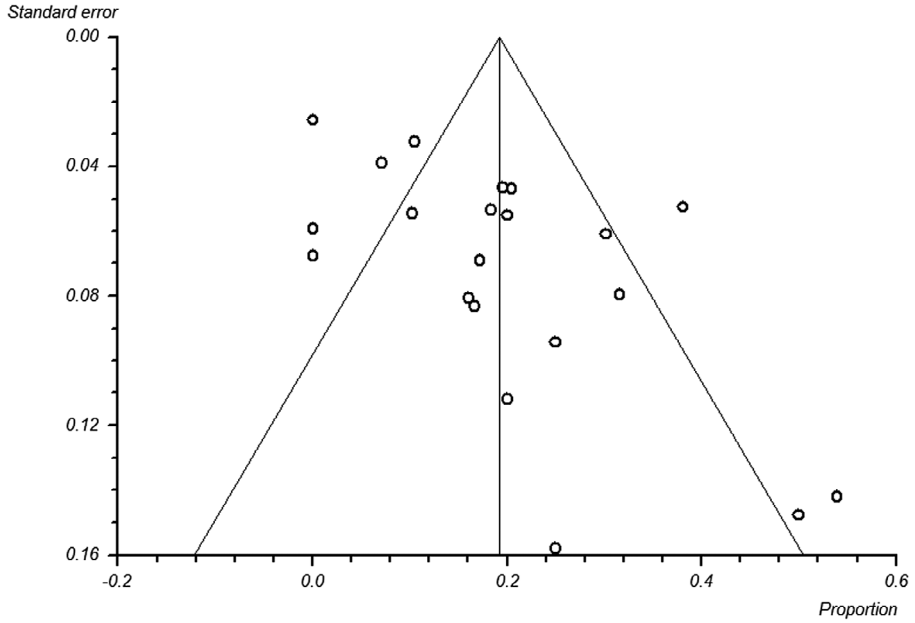

Figure 5. Funnel plot analysis of reporting bias.

Acknowledgment

The authors would like to thank Melissa Giraldo for assisting with the literature search, and Julio Casoy, MD and Rubben Ben-Harari, PhD for critically reading and reviewing the manuscript.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

This work was supported by Turing Pharmaceuticals.

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