

Cotrimoxazole for Treatment of Cerebral Toxoplasmosis: An Observational Cohort Study during 1994–2006

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Abstract. Cotrimoxazole (trimethoprim/sulfamethoxazole [TMP-SMX]) is an alternative treatment for toxoplasmic encephalitis because it is inexpensive, well-tolerated, and as effective as pyrimethamine-sulfadiazine, which is the first-line drug regimen. We report results of a large cohort study of patients with acquired immunodeficiency syndrome who were treated for toxoplasmic encephalitis with cotrimoxazole. The mean follow-up period was more than three years. Our results confirm that cotrimoxazole is effective (85.5%), with a relatively low incidence of side effects (22%; 7.4% requiring treatment interruption). Relapse occurred in 30.1% of the patients at a mean \pm SD of 7.8 ± 16.2 months after the first episode. The only risk factor for relapse was poor treatment and/or prophylaxis adherence. Mortality was significantly higher ($P < 0.05$) before 1996 than after 1996 (the era of highly active antiretroviral therapy). There was a non-significant trend towards a higher rate of relapse among patients treated before 1996 ($P = 0.06$). Consequently, cotrimoxazole could be a first-line drug regimen for curative treatment and prophylaxis of toxoplasmic encephalitis.

INTRODUCTION

Despite highly active antiretroviral therapy (HAART), toxoplasmic encephalitis (TE) remains the most frequent neurologic opportunistic infection in patients with acquired immunodeficiency syndrome (AIDS). The prevalence of TE equals the prevalence of antibodies to *Toxoplasma gondii* and was estimated in the late 1980s to range from 3% to 10% in patients with AIDS in the United States and from 25% to 50% in patients with AIDS in Europe.¹ More recently, a cohort in Italy showed an overall prevalence of 26% in patients with AIDS.²

Since the early 1990s, the standard treatment for TE has been a combination of pyrimethamine-sulfadiazine (PYR-SULF), which is effective in 75%³ to 89%⁴ of cases. However, treatment with PYR-SULF has numerous limitations, including poor tolerability (particularly for sulfadiazine), the large number of pills needed, unavailability in some countries, high cost, and lack of an intravenous form. Alternative therapies such as the pyrimethamine-clindamycin (PYR-CLIN) and trimethoprim-sulfamethoxazole (TMP-SMX or cotrimoxazole [CTX]) have been used. Cotrimoxazole appears to be a promising drug because it is inexpensive and widely available. Its efficacy has been shown in animal models and in primary prophylaxis in humans. This drug is available in a parenteral form, and its diffusion into the central nervous system is excellent. Uncontrolled studies show a clinical improvement in 71–100% of cases. The largest study was a retrospective study of 71 patients in Italy, in which 62 patients (87%) showed improvement and only 7 had to stop taking CTX because of side effects.⁵

Only three randomized studies have compared these treatments. Dannemann and others³ and Katlama and others⁶ compared PYR-SULF and PYR-CLIN,^{3,6} and Torre and others⁷ compared PYR-SULF and CTX.⁷ None of these studies showed a significant difference in efficacy.⁸ However, Torre

and others observed better tolerability with CTX than with PYR-SULF.⁷ Because of the poor tolerability of PYR-SULF and given the good results of studies in Italy, CTX has been prescribed as first-line treatment for TE in Martinique since 1994. We report the results of a large cohort study conducted during 1994–2006.

PATIENTS AND METHODS

AIDS patients with a first episode of TE who came to the Fort de France University Hospital in Martinique, French West Indies, from January 1994 through December 2006, were enrolled in an observational study. Inclusion criteria were seropositivity for HIV, symptoms of TE (fever, headache, or neurologic manifestations), computed tomography (CT) findings compatible with TE, and consent to be treated with CTX. A total of 112 patients were included, but 29 patients had to be excluded because they had also received another treatment (even if for only one day). A total of 83 patients were studied. All patients had a CT scan on admission and two weeks later. All the patients were tested for IgG antibodies to *Toxoplasma* spp. No brain biopsies were performed.

Patients were treated with a TMP plus SMX at a fixed ratio of 1:5 given orally (intravenously in case of coma). If treatment was initially given intravenously, the transition to oral therapy was made with the same dose after clinical improvement (3–5 days). The initial dosage of TMP-SMX was 10–50 mg/kg/day, or 15–75 mg/kg/day if vigilance was altered until clinical improvement (usually 3–5 days), then 7.5–37.5 mg/kg/day. After 4–6 weeks, curative treatment of TE was stopped and TMP-SMX (160/800 mg once a day) was given for secondary prophylaxis. Adverse reactions were exhaustively reported, whether or not CTX therapy was stopped.

Improvements were defined clinically and by CT scan. Clinical improvement corresponded to more than a 50% improvement in neurologic findings after two weeks of treatment. Improvement on a CT scan corresponded to more than a 50% decrease in the size or number of brain lesions after two weeks of treatment. If patients were clinically improved but did not show improvement by CT scan, they were considered to have treatment failure.

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Effectiveness of CTX was defined by a clinical improvement and by treatment completion. Inefficacy of CTX was recorded when there was no clinical improvement or when CTX had to be stopped because of side effect, even at the end of initial treatment or when the patients were improved. These definitions of improvement and efficacy were used to distinguish the doctors' viewpoint (clinical and radiologic improvement) and from patients' viewpoint (clinical improvement and tolerability).

Proportions are expressed as percentages and as ratios because some clinical and radiologic data were lacking. All statistical analyses were performed using SPSS version 13.0 software (SPSS Inc., Chicago, IL). Categorical variables were compared using the chi-square test or Fisher's exact test, and non-categorical variables were compared using the Wilcoxon rank sum test for variables were not normally distributed. Probabilities of survival and relapse were estimated by the Kaplan-Meier method. The log rank test was used to compare differences between patients treated before and after 1996. Data are expressed as means and standard deviation.

RESULTS

Characteristics of patients when TE was diagnosed are summarized in Table 1. All patients were positive for IgG antibodies to *Toxoplasma* spp. A total of 74.7% (62 of 83) were positive before diagnosis of TE or at the time of diagnosis of TE and 25.3% (21 of 83) were positive within one month after onset of TE. Steroid therapy was prescribed to 14 patients. Improvement was observed in 77 (92.8%) of 83 patients. Side effects appeared in 18 patients (22%) but only 6 (7.4%) patients had to stop taking CTX. Side effects are summarized in Table 2. Cotrimoxazole was effective in 71 patients (85.5%).

Among six patients who did not show improvement after receiving CTX, one was lost to follow-up (he left the hospital on the day of admission), one committed suicide one month after admission (CT scan showed an improvement), two died of *Pneumocystis carinii* pneumonia 4 days and 21 days after admission, one died of bacterial pneumonia 8 days after

TABLE 1
Baseline characteristics of 83 patients positive for human immunodeficiency virus (HIV) treated with cotrimoxazole for toxoplasmic encephalitis (TE)*

Characteristics	Values
Males, no. (%)	56 (67.5)
Mean ± SD age, years	39.8 ± 11.0
Mean ± SD duration of HIV infection, months	52.4 ± 55.5
Mean ± SD duration of AIDS, months	4.0 ± 14.4
Risk factor for HIV, no. (%)	
Heterosexual	56 (67.5)
MSM	21 (25.3)
Intravenous drug abuse	2 (2.4)
Transfusion	1 (1.2)
Unknown	3 (3.6)
TE as a feature of HIV infection (%)	26 (31.3)
Primary prophylaxis for toxoplasmosis (%)	20 (24.1)
No. of abscesses on CT scan, 1/< 5/> 5 (%)	14/39/9 of 62 (22.6/62.9/4.5)
Mean ± SD CD4 lymphocyte count/mL*	51.3 ± 50.2

*AIDS = acquired immunodeficiency syndrome; MSM = men who have sex with men; CT = computed tomography.

TABLE 2

Side effects in patients treated with cotrimoxazole for toxoplasmic encephalitis in patients infected with human immunodeficiency virus (HIV)

Side effect	No. of patients	No. who stopped treatment
Rash	7	4
Neutropenia	6	0
Pancreatitis	2	2
Liver toxic effect	1	0
Renal toxic effect	1	0
Thrombocytopenia	1	0

admission, and one patient died of wasting two months after admission. Among the six patients who had to stop taking CTX, four had toxiderma and two had pancreatitis. However, they improved clinically and radiologically and were cured of TE. At the end of the study, four of these six patients had died, but the time from admission to death was not different between those who stopped taking CTX and those who did not (mean ± SD = 12.3 ± 10.0 months versus 22.7 ± 27.8 months; *P* not significant), and the duration of follow-up after toxoplasmosis was not different between those who stopped taking CTX and those who did not (11.3 ± 10.0 months versus 22.0 ± 28.0 months; *P* not significant).

Relapse occurred in 25 patients (30.1%), and 11 patients (13.3%) had more than one relapse, for a total of 40 relapses in the cohort. The mean ± SD interval between the first episode and the first relapse was 7.8 ± 16.2 months, and the overall interval between two episodes or relapse was 8.5 ± 14.7 months.

In patients with relapses, the mean ± SD CD4 cell count was 35.6 ± 31.5 cells/mm³. Cotrimoxazole was used to treat 81.6% (31 of 38) of the relapses and treatment was effective in 90.9% (30 of 33) (95% confidence interval [CI] = 81.1–100). Side effects occurred in 17.1% (6 of 35) of the patients (95% CI = 4.6–29.6), but only required treatment discontinuation in 6.3% (2 of 32) of the patients (95% CI = 0–14.7). Cotrimoxazole was effective on 92.9% (26 of 28) of the relapses (95% CI = 83.4–100) and other treatments were effective in 80% (4 of 5) of the cases (95% CI = 44.9–100) (*P* not significant). The rates of adverse events were 13.8% (4 of 29) (95% CI = 1.2–26.4) with CTX and 33.3% (2 of 6) (95% CI = 0–71.0) with other treatments (*P* not significant). Treatment had to be interrupted in 3.7% (1 of 27) (95% CI = 0–10.6) of the patients treated with CTX and 20% (1 of 5) (95% CI = 0–52.0) of the patients who received other treatments cases (*P* not significant). Receiving a treatment other than CTX was associated with a higher rate of death during treatment (33.3%, 3 of 9) ([95% CI = 2.1–64.1) then being treated with CTX (3.2%, 1 of 31) (95% CI = 0–9.4) (*P* = 0.03). Factors associated with efficacy of CTX and relapse are shown in Tables 3 and 4 and Figure 1.

Historical, biological, and clinical factors were not associated with a higher risk of CTX inefficacy. Altered vigilance on admission was significantly associated with a lower risk of relapse. Moreover, patients with relapse had significantly shorter treatment periods than patients with no relapse (34.8 ± 14.1 versus 50.3 ± 19.1 days; *P* = 0.01).

The first episode of TE was the presenting feature of HIV infection in 26 (31.3%) of the 83 patients. Twenty patients (24.1%) were receiving CTX primary prophylaxis for TE. On admission, these 20 patients were asked about their adherence to CTX, and 18 (90%) of 20 said they had stopped taking the

TABLE 3

Factors associated with efficacy of cotrimoxazole (CTX) treatment for toxoplasmic encephalitis (TE) in patients infected with human immunodeficiency virus (HIV)*

Factors	CTX efficient (n = 71)	CTX inefficient (n = 12)	P
Age, years	39.9 ± 10.6	40.9 ± 13.3	NS
Duration of HIV infection, months	55.4 ± 56.5	37.4 ± 48.4	NS
Duration of AIDS, months	4.6 ± 15.5	0.6 ± 1.5	NS
Sex ratio, M:F	49:22	7:5	NS
Risk factor for HIV/ heterosexual/homosexual/ IV drug use/transfusion/ unknown	6/20/2/1/2	10/1/0/0/1	NS
TE as a feature of HIV infection	28.2 (20/71)	54.6 (6/11)	NS
Primary prophylaxis for toxoplasmosis	23.9 (17/71)	25.0 (3/12)	NS
Initial CD4 cell count/mL	53.8 ± 52.2	33.7 ± 28.3	NS
Steroid use	14.1 (10/71)	33.3 (4/12)	NS
Initial hospitalization in intensive care unit	11.3 (8/71)	25.0 (3/12)	NS
Vigilance altered	62.3 (33/53)	63.6 (7/11)	NS
Localization signs	85.2 (46/54)	63.6 (7/11)	NS
Meningeal syndrome	23.5 (12/51)	18.2 (2/11)	NS
Signs of toxoplasmosis on CT scan	98.3 (59/60)	100 (11/11)	NS
> 1 abscess on CT scan	80.4 (41/51)	63.6 (7/11)	NS
No improvement on J15 CT scan	6.5 (3/46)	12.5 (1/8)	NS

*Values are the mean ± SD, number, or % (no. positive/no. tested). AIDS = acquired immunodeficiency syndrome; IV = intravenous; CT = computed tomography.

drug. After the first episode, all patients who had not died or were lost to follow-up were given CTX prophylaxis. Among the 20 evaluable of 25 patients who relapsed, 16 (80%) were non-adherent, 3 (15%) were adherent, and 1 (5%) was underdosed ($P < 0.001$).

As the prognosis of HIV-infected patients improved drastically when HAART became available in April 1996, we studied the effect of HAART on the prognosis of TE in our cohort. Survival and relapse were compared between patients admitted before and after 1996, the year when all patients who needed HAART were effectively treated. Mortality was significantly higher in patients who had their first episode of TE before 1996 (hazard ratio = 1.94, 95% CI = 1.02–4.93, $P < 0.05$, by log rank test). However, early mortality (within a year after TE) was not different ($P = 0.2$) before (13 of 19, 68.4%) and after 1996 (7 of 15, 46.7%). No difference was found ($P = 0.4$) with respect to mortality within one month after TE. There was a non-significant trend towards a higher rate of relapse among patients treated before 1996 (hazard ratio = 2.09, 95% CI = 0.96–6.30, $P = 0.06$, by log rank test).

As of December 31, 2006, 34 (41%) patients had died, 8 (9.6%) were lost to follow-up, and 3 (3.6%) were being managed in another hospital. The mean ± SD follow-up period after toxoplasmosis was 36.1 ± 36.9 months in the whole cohort and 20.9 ± 26.1 months for the patients who died. Seventeen (50%) of the deaths were related to HIV. Other causes of death were stroke, hepatitis, suicide, septic shock, and undetermined. Among the 38 patients who survived, 35 (92.1%) were receiving HAART, two (5.3%) had their treatment interrupted, and one had not yet been treated. Twenty-five patients (65.8%) had undetectable viral load (< 50 copies/mL) and 26 (68.4%) had stopped their prophylaxis with CTX.

TABLE 4

Factors associated with relapse in treatment with cotrimoxazole (CTX) for toxoplasmic encephalitis (TE) in patients infected with human immunodeficiency virus (HIV)*

Factors	No relapse (n = 58) %	Relapse (n = 25) %	P
Age, years	40.7 ± 11.0	37.8 ± 10.9	NS
Duration of HIV infection, months	49.3 ± 54.6	59.4 ± 58.1	NS
Duration of AIDS, months	4.4 ± 16.2	2.9 ± 9.4	NS
Sex ratio, M:F	40:18	16:9	NS
Risk factor for HIV/ heterosexual/homosexual/ IV drug use/transfusion/ unknown	38/15/2/1/2	18/6/0/0/1	NS
TE as a feature of HIV infection	32.8 (19/58)	28.0 (7/25)	NS
Primary prophylaxis for toxoplasmosis	20.7 (12/58)	32.0 (8/25)	NS
Initial CD4 counts/mL	55.9 ± 57.1	41.2 ± 27.3	NS
Steroid use	13.8 (8/58)	24.0 (6/25)	NS
Initial hospitalization in intensive care unit	10.3 (6/58)	20 (5/25)	NS
Vigilance altered	70.2 (33/47)	41.2 (7/17)	0.034
Localization signs	81.3 (39/48)	82.4 (14/17)	NS
Meningeal syndrome	23.9 (11/46)	18.8 (3/16)	NS
Signs of toxoplasmosis on CT scan	98.0 (49/50)	100 (21/21)	NS
> 1 abscess on CT scan	80.4 (37/46)	68.8 (11/16)	NS
No improvement on J15 CT scan	9.8 (4/41)	0.0 (0/13)	NS

*Values are the mean ± SD, number, or % (no. positive/no. tested). AIDS = acquired immunodeficiency syndrome; IV = intravenous; CT = computed tomography.

DISCUSSION

We studied TE in a large cohort of AIDS patients treated with CTX. Although this was an observational retrospective study, it confirms the efficacy and tolerability of CTX in this treatment. Cotrimoxazole was effective in 71 (85.5%) of 83 patients in the intention-to-treat analysis, which is consistent with the 28 (70%) of 40 reported by Torre and others.⁷ Partial or complete resolution was obtained with PYR-SULF in three randomized studies: 16 of 33 (48.5%) reported by Dannemann and others,³ 117 of 147 (80%) reported by Katlama and others,⁶ and 26 of 37 (70%) reported by Torre and others.⁷ It should be emphasized that none of these studies classified cross-overs as failures. Patients who switched to the second treatment because the first treatment was not effective or well-tolerated were considered to have had a successful initial treatment if cured, favoring the less effective or less well tolerated treatment. This conclusion suggests that results if intention-to-treat are lower than indicated, particularly if one considers that one-third of the patients switched to the other treatment.^{3,6}

The only randomized controlled study of CTX compared 40 patients receiving CTX (10–50 mg/kg of TMP-SMX) with 37 patients treated with PYR-SULF (50–60 mg/kg/day).⁷ PYR-SULF and CTX were equivalent with respect to clinical (85.7% versus 83.7%) and radiologic efficacy (69.6% versus 72.9%). However, tolerability was significantly better in the CTX group (5 events versus 14 events in the PYR-SULF group).

A wide range of doses of CTX are reported to be effective for treatment of TE (6.6–20 mg/kg/day of TMP), with a constant TMP:SMX ratio of 1:5.^{7,9–11} Our study confirms that a low-dose regimen is effective for treatment of patients with TE. Moreover, CTX bioavailability is approximately 100% in

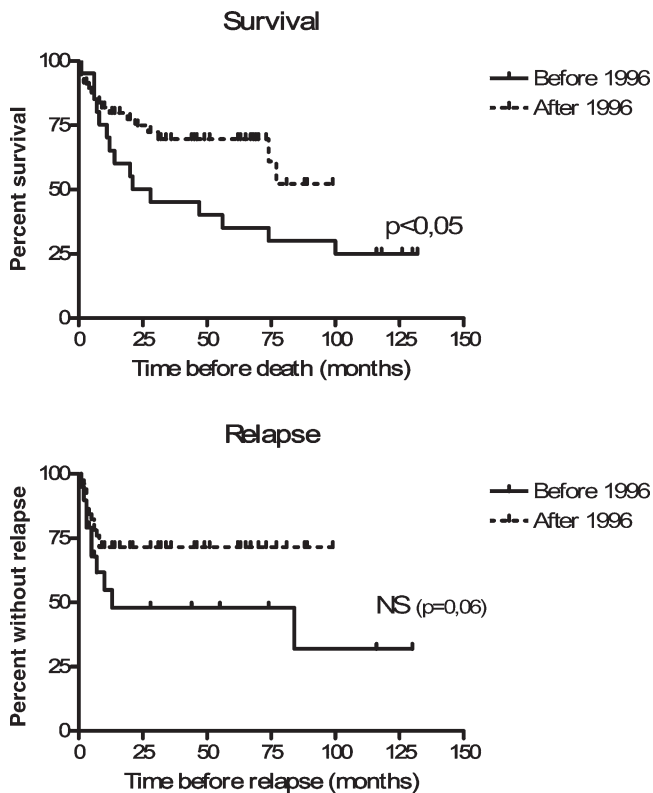


FIGURE 1. Survival and lack of relapse in patients treated for toxoplasmic encephalitis before or after 1996, Martinique, French West Indies, by log rank test.

critical and non-critical AIDS patients, and areas under the curve are similar with the intravenous and oral forms of CTX.¹² In contrast, Winstanley and others observed marked variations in pharmacokinetics of pyrimethamine, with serum levels less than the therapeutic range in some critically ill patients, which suggested that drug monitoring may be necessary.¹³

Our study also shows that the prognosis is not impaired when CTX is poorly tolerated or has to be discontinued. Numerous studies also suggest that there are less adverse effects with CTX than with other treatments. Torre and others observed significantly fewer adverse effects in the CTX group than in the PYR-SULF group, but difference in serious adverse effects was not significant.⁷ Our rates of side effects were relatively low (22%, 7.4% requiring treatment interruption), and are consistent with those of other studies of CTX. Francis and others reported no side effects in 20 patients,¹¹ and Torre and others⁷ reported side effects in 22 (31%) of 71 patients, but only 7 (10%) required CTX to be discontinued. A recent study comparing TE treatment with CTX ($n = 25$) and PYR-SULF ($n = 18$) showed a trend ($P = 0.06$) towards more frequent renal impairment in the PYR-SULF group.¹⁴

Surprisingly, altered vigilance on admission was significantly associated with a lower risk of relapse. Patients with altered vigilance may have received parenteral therapy longer, with a longer hospital stay or a longer period of curative treatment, thus introducing a confounding bias. We failed to find a significant association with the length of parenteral therapy because of a lack of precise data, but the significantly shorter length of treatment in patients with relapse supports this hypothesis. If parenteral therapy or curative treatment is shorter in patients

with normal vigilance and a high risk of relapse, this finding could increase the risk of non-compliance.

The mean follow-up of more than three years, the longest for a study of treatment with TE, enables detailed evaluation of long-term outcome (this long follow-up also explains the relatively high rate of relapse). One of the main results was that the only risk factor for relapse was poor adherence to treatment or prophylaxis. The survival curves show that the introduction of HAART influenced mortality but not the risk of relapse. Our data highlight the lack of influence of HAART on early mortality caused by TE. The non-significant trend towards a higher rate of relapse among patients admitted before April 1996 suggests that poor adherence is more important risk factor for relapse than is the absence of HAART. The relatively high rate of poor adherence could also be linked to the low economic status of our population. Finally, our study shows that CTX is still effective for treating relapses, even when it has been prescribed for prophylaxis.

Secondary prophylaxis with CTX has already been shown to be effective after treatment with PYR-SULF.¹⁵ It is noteworthy that sulfadiazine intolerance, which is common, is not predictive of CTX intolerance.¹⁵ A large cohort study compared risk factors for toxoplasmic encephalitis before (19,598 patients) and during (17,016 patients) the era of HAART.¹⁶ Whatever the period, patients receiving CTX prophylaxis had a lower risk of TE (adjusted relative hazard ratios = 0.6 and 0.5, respectively, for the first and second period; $P < 0.001$).

Because CTX is inexpensive, effective, well-tolerated, and widely available in developing countries, it should be the first choice for curative treatment and prophylaxis of TE. This drug has already been shown to be useful in Côte d'Ivoire, where it lowered the rate of severe clinical events (death or hospital admission) in HIV-infected patients⁷ and mortality in HIV-infected patients with tuberculosis.¹⁸ Cotrimoxazole has been recommended as a first-line treatment of TE in South Africa since 2003.

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REFERENCES

- Luft BJ, Hafner R, Korzun AH, Leport C, Antoniskis D, Bosler EM, Bourland DD III, Uttamchandani R, Fuhrer J, Jacobson J, 1993. Toxoplasmic encephalitis in patients with the acquired immunodeficiency syndrome. Members of the ACTG 077p/ANRS 009 Study Team. *N Engl J Med* 329: 995-1000.
- Antinori A, Larussa D, Cingolani A, Lorenzini P, Bossolasco S, Finazzi MG, Bongiovanni M, Guaraldi G, Grisetti S, Vigo B, Gigli B, Mariano A, Dalle Nogare ER, De Marco M, Moretti F, Corsi P, Abrescia N, Rellecati P, Castagna A, Mussini C, Ammassari A, Cinque P, d'Arminio Monforte A, 2004. Prevalence, associated factors, and prognostic determinants of AIDS-related toxoplasmic encephalitis in the era of advanced highly active antiretroviral therapy. *Clin Infect Dis* 39: 1681-1691.
- Dannemann B, McCutchan JA, Israelski D, Antoniskis D, Leport C, Luft B, Nussbaum J, Clumeck N, Morlat P, Chiu J, 1992.

- Treatment of toxoplasmic encephalitis in patients with AIDS. A randomized trial comparing pyrimethamine plus clindamycin to pyrimethamine plus sulfadiazine. The California Collaborative Treatment Group. *Ann Intern Med* 116: 33–43.
4. Leport C, Raffi F, Matheron S, Katlama C, Regnier B, Saimot AG, Marche C, Vedrenne C, Vilde JL, 1988. Treatment of central nervous system toxoplasmosis with pyrimethamine/sulfadiazine combination in 35 patients with the acquired immunodeficiency syndrome. Efficacy of long-term continuous therapy. *Am J Med* 84: 94–100.
 5. Torre D, Speranza F, Martegani R, Zeroli C, Banfi M, Airoidi M, 1998. A retrospective study of treatment of cerebral toxoplasmosis in AIDS patients with trimethoprim-sulphamethoxazole. *J Infect* 37: 15–18.
 6. Katlama C, De Wit S, O'Doherty E, Van Glabeke M, Clumeck N, 1996. Pyrimethamine-clindamycin vs. pyrimethamine-sulfadiazine as acute and long-term therapy for toxoplasmic encephalitis in patients with AIDS. *Clin Infect Dis* 22: 268–275.
 7. Torre D, Casari S, Speranza F, Donisi A, Gregis G, Poggio A, Ranieri S, Orani A, Angarano G, Chiodo F, Fiori G, Carosi G, 1998. Randomized trial of trimethoprim-sulfamethoxazole versus pyrimethamine-sulfadiazine for therapy of toxoplasmic encephalitis in patients with AIDS. Italian Collaborative Study Group. *Antimicrob Agents Chemother* 42: 1346–1349.
 8. Dedicoat M, Livesley N, 2006. Management of toxoplasmic encephalitis in HIV-infected adults (with an emphasis on resource-poor settings). *Cochrane Database Syst Rev* 3: CD005420.
 9. Canessa A, Del Bono V, De Leo P, Piersantelli N, Terragna A, 1992. Cotrimoxazole therapy of *Toxoplasma gondii* encephalitis in AIDS patients. *Eur J Clin Microbiol Infect Dis* 11: 125–130.
 10. Solbreux P, Sonnet J, Zech F, 1990. A retrospective study about the use of cotrimoxazole as diagnostic support and treatment of suspected cerebral toxoplasmosis in AIDS. *Acta Clin Belg* 45: 85–96.
 11. Francis P, Patel VB, Bill PL, Bhigjee AI, 2004. Oral trimethoprim-sulfamethoxazole in the treatment of cerebral toxoplasmosis in AIDS patients—a prospective study. *S Afr Med J* 94: 51–53.
 12. Chin TW, Vandenbroucke A, Fong IW, 1995. Pharmacokinetics of trimethoprim-sulfamethoxazole in critically ill and non-critically ill AIDS patients. *Antimicrob Agents Chemother* 39: 28–33.
 13. Winstanley P, Khoo S, Szwandt S, Edwards G, Wilkins E, Tija J, Coker R, McKane W, Beeching N, Watkin S, 1995. Marked variation in pyrimethamine disposition in AIDS patients treated for cerebral toxoplasmosis. *J Antimicrob Chemother* 36: 435–439.
 14. Arens J, Barnes K, Crowley N, Maartens G, 2007. Treating AIDS-associated cerebral toxoplasmosis: pyrimethamine plus sulfadiazine compared with cotrimoxazole, and outcome with adjunctive glucocorticoids. *S Afr Med J* 97: 956–958.
 15. Duval X, Pajot O, Le Moing V, Longuet P, Ecobichon JL, Mentre F, Leport C, Vilde JL, 2004. Maintenance therapy with cotrimoxazole for toxoplasmic encephalitis in the era of highly active antiretroviral therapy. *AIDS* 18: 1342–1344.
 16. Abgrall S, Rabaud C, Costagliola D, 2001. Incidence and risk factors for toxoplasmic encephalitis in human immunodeficiency virus-infected patients before and during the highly active antiretroviral therapy era. *Clin Infect Dis* 33: 1747–1755.
 17. Anglaret X, Chene G, Attia A, Toure S, Lafont S, Combe P, Manlan K, N'Dri-Yoman T, Salamon R, 1999. Early chemoprophylaxis with trimethoprim-sulphamethoxazole for HIV-1-infected adults in Abidjan, Côte d'Ivoire: a randomised trial. Cotrimo-CI Study Group. *Lancet* 353: 1463–1468.
 18. Wiktor SZ, Sassan-Morokro M, Grant AD, Abouya L, Karon JM, Maurice C, Djomand G, Ackah A, Domoua K, Kadio A, Yapi A, Combe P, Tossou O, Roels TH, Lackritz EM, Coulibaly D, De Cock KM, Coulibaly IM, Greenberg AE, 1999. Efficacy of trimethoprim-sulphamethoxazole prophylaxis to decrease morbidity and mortality in HIV-1-infected patients with tuberculosis in Abidjan, Côte d'Ivoire: a randomised controlled trial. *Lancet* 353: 1469–1475.