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CASE REPORT

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Treatment of toxoplasmic encephalitis with the combination of clindamycin plus azithromycin in an HIV-infected patient: A case report

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Abstract

The existence of alternative oral therapies could help clinicians to treat toxoplasmic encephalitis (TE) in the HIV patients. The combination of azithromycin and clindamycin may serve as an effective treatment for TE in HIV-infected patients.

KEYWORDS

azithromycin, clindamycin, HIV, thrombocytopenia, toxoplasmic encephalitis, trimethoprim-sulfamethoxazole

1 | INTRODUCTION

Standard treatment of toxoplasmic encephalitis (TE) has several limitations, including potential toxicity, the burden of pills, cost, low availability, and lack of a parenteral formulation; therefore, alternative treatment options are needed. We present a case of successful treatment of TE with an experimental drug regimen consisting of azithromycin and clindamycin.

Toxoplasmosis is a common infection of the central nervous system in patients with human immunodeficiency virus (HIV) infection who are not receiving proper prophylaxis.[1,2] *Toxoplasma gondii* (*T. gondii*) infections commonly occur in HIV-infected patients with CD4 T-cell counts below 100 cells/μL.[3]

The main clinical manifestations of toxoplasmosis in these individuals are encephalitis, chorioretinitis, pneumonitis, or disseminated infection that usually have subacute onset with focal neurological presentations such as headache and altered sensorium.[4] Nonfocal manifestations, including nonspecific headache and neuropsychiatric symptoms, may also be seen.[5]

Presumptive diagnosis includes compatible clinical manifestations and at least one brain mass lesion on neuroimaging. Isolation of cysts and trophozoites in a biopsy specimen is required for a definitive diagnosis of TE.[6] Ring-enhancing hypodense brain lesion, usually associated with edema, may be seen on magnetic resonance imaging (MRI).[4] Due to mass effect, lumbar puncture (LP) is often contraindicated, although the cerebrospinal fluid (CSF) analysis usually is nonspecific. Serum antitoxoplasma immunoglobulin (IgG) antibodies are often reported positive in the vast majority of patients with TE. CSF polymerase chain reaction (PCR) is highly specific for the diagnosis of TE, but it has low sensitivity.[7] Brain biopsy is usually done in patients with negative serology and patients who have an inadequate response to therapy.[2,8]

Treatment of TE in HIV-infected patients includes antimicrobial therapy against *T. gondii*, as well as antiretroviral therapy (ART) for the immune system recovery. The preferred initial therapy for TE consists of the combination of pyrimethamine, sulfadiazine, and leucovorin.[2,9] The use of leucovorin decreases the risk of hematologic adverse effects

TABLE 1 Treatment regimens for toxoplasmosis

Preferred regimen	Pyrimethamine 200 mg orally once then 50 mg (Body weight ≤ 60 kg) or 75 mg (body weight > 60 kg) + sulfadiazine 1000 mg (body weight ≤ 60 kg) to 1500 mg (Body weight > 60 kg) every 6 h + leucovorin (Folinic acid) 10-25 mg orally daily (up to 50 mg once or twice daily)
Potential alternative regimens	Pyrimethamine (same as doses listed in preferred regimen) + clindamycin 600 mg intravenously or orally every 6 h + leucovorin (same as doses listed in preferred regimen)
	Trimethoprim-sulfamethoxazole (TMP-SMX) TMP 5 mg/kg and SMX 25 mg/kg orally or intravenously twice daily
	Pyrimethamine (same as doses listed in preferred regimen) + atovaquone 1500 mg orally twice daily + leucovorin (same as doses listed in preferred regimen)
	Atovaquone 1500 mg orally twice daily + sulfadiazine (same as doses listed in preferred regimen)
	Atovaquone 1500 mg orally twice daily
	Azithromycin + pyrimethamine + leucovorin
	Pyrimethamine + clarithromycin + leucovorin
	Pyrimethamine + dapsone + leucovorin
	Clindamycin + 5-fluorouracil
	Doxycycline or minocycline + either pyrimethamine plus leucovorin, sulfadiazine, or clarithromycin (doses ≤ 500 mg twice daily)
	Clindamycin + azithromycin

of pyrimethamine.[10] The preferred alternative regimen in patients who have contraindications or do not have a satisfactory response to first-line therapy is the combination of pyrimethamine, clindamycin, and leucovorin [9,11,12] (Table 1).

Trimethoprim-sulfamethoxazole (TMP-SMX) is frequently considered as a first-line treatment option for TE in many countries, especially in settings where pyrimethamine is unavailable or when an injectable regimen is required[9] (Table 1). Moreover, TMP-SMX is largely used in resource-limited settings, given its low cost.[13] Other alternative drug regimens[9,32] are listed in Table 1. These alternative regimens have not been studied enough and should be used in special conditions.

Here, an HIV-infected case of toxoplasmic encephalitis who was successfully treated with clindamycin plus azithromycin is reported.

2 | CASE PRESENTATION

A 35-year-old man was hospitalized for a 2-week history of loss of consciousness, disorientation, and unsteady gait. Other initial symptoms included weakness, lethargy, anorexia, and 2-month history of episodic productive cough. His past medical history was notable for HIV infection and pulmonary tuberculosis. He was taking methadone as opioid maintenance therapy. The patient's adherence to antiretroviral drugs, including tenofovir disoproxil fumarate/ emtricitabine plus efavirenz, was poor, and he did not take them regularly.

The physical examination was significant for oropharyngeal candidiasis and decreased strength of upper and lower limbs (upper 4/5, left lower 2/5, and right lower 1/5). The patient's vital signs were normal, and the oxygen saturation was 94 percent on room air. Auscultation of the lung revealed bibasilar crackles.

The initial brain MRI, T2-weighted scan, and coronal view revealed round hyposignal, ring-enhancing lesions in the thalamus and left basal ganglia, massive brain edema, and midline shift to right (Figure 1A). In the axial view, fluid-attenuated inversion recovery (FLAIR) sequence, ring-like lesions were reported in the right hemisphere of the cerebellum (Figure 1B). All of these were highly suggestive of TE. Findings on chest CT scan were bibasilar consolidation and tree-in-bud lesions. Multiple lymphadenopathies were detected on the abdominopelvic ultrasound that suggesting disseminated tuberculosis.

Baseline laboratory data on admission were WBC = 4.8×10^9 cells/L (neutrophils 4.5×10^9 cells/L and lymphocyte 0.23×10^9 cells/L), hemoglobin = 98 gram/L, and platelets count = 93×10^9 cells/L. Other laboratory tests such as metabolic profile, kidney, and liver function parameters were within the normal range. The last CD4 cell count was 25 cells/μL. The patient's platelet count was 214×10^9 cells/L at 3 months before hospitalization (day −90, Figure 2).

Due to the local endemic area for tuberculosis (TB), based on the radiologic findings on chest CT scan and patient's history of tuberculosis, an antituberculous regimen consisting of isoniazid, rifampin, ethambutol, and pyrazinamide was administered. The clinical manifestations and radiographic findings were highly suggestive of TE; therefore, therapy against *T. gondii* was considered. Due to pyrimethamine shortage, intravenous TMP-SMX (15 mg/kg/day as TMP component, divided in three equal doses) was initiated in the emergency department at a higher dose, because

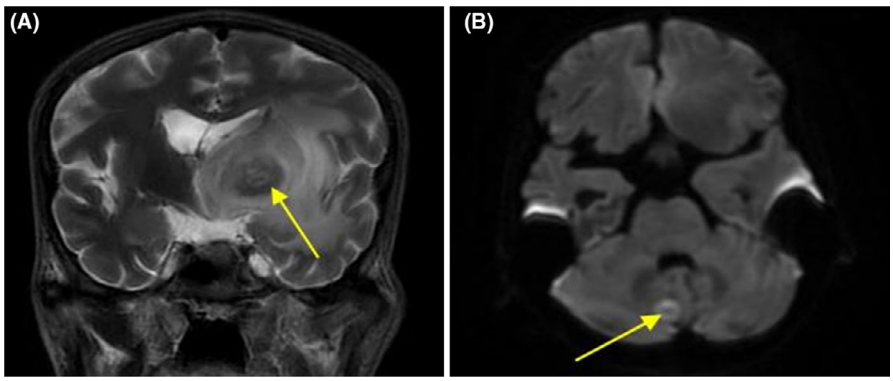

FIGURE 1 A, T2-weighted scan, coronal view at baseline showing round hyposignal, ring-enhancing lesions in the thalamus and left basal ganglia (arrow), massive brain edema, and midline shift to right. B, axial view, fluid-attenuated inversion recovery (FLAIR) sequence at baseline showing ring-like lesions in the right hemisphere of the cerebellum (arrow)

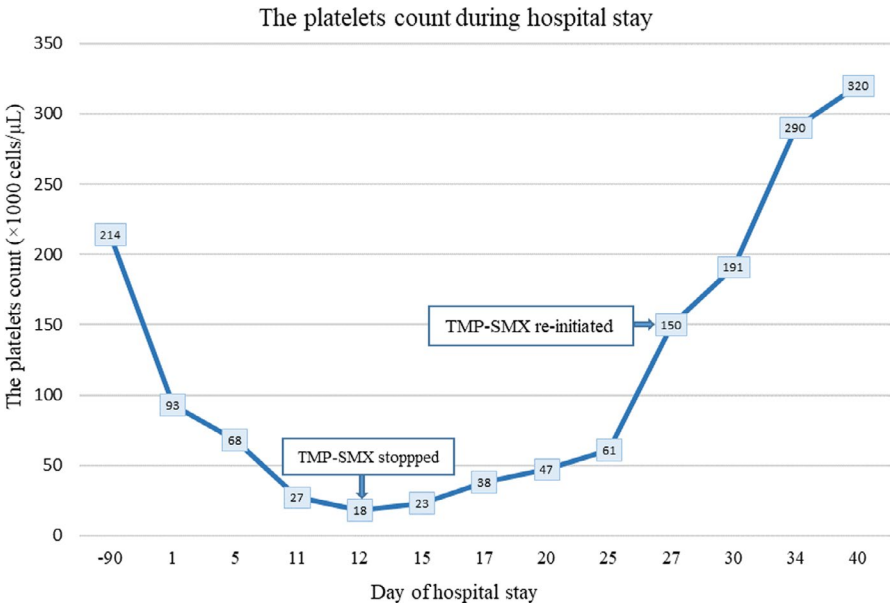

FIGURE 2 The platelets count trend during hospital stay

of simultaneous *pneumocystis jiroveci* pneumonia (PJP) suspicion. Fluconazole 100 mg/day orally was initiated for treatment of oropharyngeal candidiasis. Dexamethasone was considered as adjuvant therapy for the reported brain edema and midline shift on MRI.

The patient's platelet count on the day of TMP-SMX initiation was 93×10^9 cells/L. After 5 days of treatment with TMP-SMX, the platelet count began to decline and reached 18×10^9 cells/L at day 12 of TMP-SMX therapy, as illustrated in Figure 2. Lactate dehydrogenase (LDH) and mean corpuscular volume (MCV) were mildly elevated, and folate level was 3 ng/mL (reference range 4.95-19 ng/mL). Other laboratory tests including coagulation profile were within the normal range. No purpura or mucosal hemorrhage was noted.

Thrombocytopenia is one of the well-known hematologic side effects of TMP-SMX. TMP-SMX was discontinued, evaluation for other possible causes was performed, and unnecessary medications were withdrawn or replaced by alternative agents. Base on the folate level and elevated MCV, folic acid supplementation was also considered. The informed consent was obtained from a legally authorized representative. After that, the combination drug regimen consisted of clindamycin 900 mg intravenously three times per day plus azithromycin 1000 mg daily was considered for treatment of TE, and the patient was monitored on a regular basis. The platelet count was stable in the range of 20-40 $\times 10^9$ cells/L and then showed an upward trend. After 12 and 15 days of treatment with clindamycin and azithromycin, the platelet count was 61×10^9 cells/L and 150×10^9 cells/L, respectively (Figure 2).

After 18 days of treatment with clindamycin and azithromycin, a follow-up brain MRI was obtained. As it has been shown in Figure 3, lesions in the basal ganglia and cerebellum disappeared. The edema and mass effect around the left deep temporal lesion markedly decreased. At this time, the level of consciousness improved and other baseline clinical findings such as gait disturbance, disorientation, dysarthria, sphincter dysfunction, and decreased force of the upper and lower limbs disappeared. No adverse effects were observed during the therapy. It was postulated that the dramatic radiological and clinical responses were attributed to the experimental drug regimen including clindamycin and azithromycin.

As the clinical and laboratory parameters were stable, the drug regimen was changed to oral TMP-SMX in the dosing

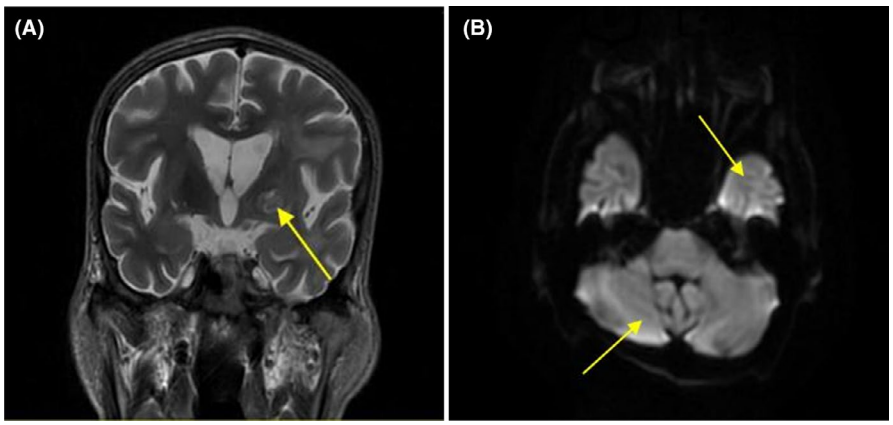

FIGURE 3 A, T2-weighted scan, coronal view at day 20 of therapy showing disappearance of lesions in the thalamus and left basal ganglia basal ganglia (arrow). B, axial view, fluid-attenuated inversion recovery (FLAIR) sequence at day 20 of therapy showing disappearance of lesions in the cerebellum (arrow) and markedly decrease in edema and mass effect around the left deep temporal (arrow)

range usually used for TE (5 mg/kg per dose of TMP or 25 mg/kg per dose of SMX, twice daily). The platelet count was closely monitored, and fortunately, no episode of thrombocytopenia has occurred. The patient was discharged and then referred to the HIV clinic for follow-up visits. After 6 weeks, the dose of TMP-SMX was changed to the maintenance dose[9] without any complication.

3 | DISCUSSION

Opportunistic CNS infections such as cryptococcal meningitis, TE, and tuberculous meningitis are considered as significant causes of morbidity and mortality in HIV-infected patients. Until the 1980s, toxoplasmic encephalitis was rare; thereafter, the incidence of TE noticeably increased following the AIDS pandemic.[2]

Therapy against TE is usually begun with a combination of pyrimethamine, sulfadiazine, and leucovorin for 6 weeks until the clinical symptoms and radiological findings are resolved.[3] TMP-SMX is an alternative, but it may cause some troublesome adverse effects, including hypersensitivity reactions, neurological adverse effects, hyperkalemia, and hematologic toxicity.[14]

Thrombocytopenia is one of the known side effects of TMP-SMX, but its exact mechanism is not yet recognized. Immune-mediated thrombocytopenia due to drug-induced autoantibodies has been suggested[15]; however, it also may be attributed to folate deficiency.[14] Sulfamethoxazole inhibits bacterial synthesis of dihydrofolic acid, and trimethoprim blocks the production of tetrahydrofolic acid from dihydrofolic acid by inhibiting dihydrofolate reductase.[16] So, this combination could lead to bone marrow suppression, folate deficiency, megaloblastic anemia, and thrombocytopenia. Also, TMP-SMX can cause antibody-mediated destruction of platelets.[15] Presence of severe thrombocytopenia (platelet count $<20 \times 10^9$ cells/L) increases the likelihood of drug-induced thrombocytopenia (DITP). The rate of TMP/SMX-induced thrombocytopenia may be high as 38 per million users per week.[17] Furthermore, for the first-time administration of the drug, approximately 5-7 days of exposure is typically required to produce sensitization and onset of thrombocytopenia.[17] Most episodes resolved spontaneously without treatment, but fatal hemorrhages may occur when the platelet count falls to less than 10×10^9 cells/L.[15] The main treatment strategy in the TMP-SMX-induced thrombocytopenia is drug discontinuation, but corticosteroid, intravenous immunoglobulin (IVIg), and platelet transfusion may be helpful in special cases.[18]

Several adverse effects with the standard regimens for treatment of toxoplasmosis have been reported [19,20]; however, there is little knowledge regarding alternatives drugs. Clindamycin, a lincomycin antibiotic, inhibits *T. gondii* by an unknown mechanism that may involve the pathogen organelle apicoplast.[21] Clindamycin was effective in an experimental mouse model of toxoplasmosis.[22] Yapar et al reported a case of TE was treated with clindamycin alone.[23] Successful treatment of HIV-infected patients with toxoplasmic encephalitis treated with clindamycin has been reported.[20,24] Even in low concentration, clindamycin could inhibit *T. gondii* in vivo.[21]

Although the efficacy of clindamycin as monotherapy against TE has been reported,[23] its use has not been assessed in clinical studies yet. Therefore, the use of clindamycin for the treatment of TE is recommended in combination with other drugs such as pyrimethamine.[25] Due to high molecular weight, clindamycin poorly penetrates into the CNS; however, the therapeutic level could be obtained using the higher doses.[26]

Clarithromycin and azithromycin as macrolide antibiotics are active against *T. gondii*.[27] Moreover, azithromycin attains therapeutic concentration in the inflamed central nervous due to *T. gondii* infection.[28] Azithromycin in combination with pyrimethamine has been used for the treatment of TE.[29,30] Pyrimethamine may enhance the activity of azithromycin against *T. gondii*.[3] The safety and efficacy of oral azithromycin plus pyrimethamine have been shown in a dose-escalation study.[29]

Azithromycin has also administrated as a monotherapy regimen of active, nonvision-threatening toxoplasmic

retinochoroiditis. Compared with the sulfadiazine plus pyrimethamine regimen, it has acceptable efficacy and a favorable safety profile.[31] Successful treatment of a case of TE by the combination of azithromycin (1200 mg per day) and clindamycin (2400 mg per day) has been reported.[32]

There were some challenges in the treatment of TE in our case. Due to pyrimethamine shortage, TMP-SMX was administered. The decrease in platelet count was seen after 5 days of TMP-SMX therapy. At this time, platelets count began to decrease, and after about 12 days, platelets count was 18×10^9 cells/L. DITP was suspected, and TMP-SMX was discontinued. The Naranjo scale was applied to establish the probability of causality ([33]). The analysis of the cases with the Naranjo scale showed a possible causality for TMP-SMX-induced thrombocytopenia (Naranjo Score = 4). Other potential causes of thrombocytopenia in the case were anti-TB drugs, underlying diseases, hematologic disorders, and folate or B12 deficiency. TMP-SMX rechallenge in our case was successful without any episode of thrombocytopenia over a 6-week follow-up period. As mentioned previously, the platelet count was stable and then began to increase after about 11 days of TMP-SMX discontinuation, which further supports TMP-SMX-induced thrombocytopenia. Based on this thrombocytopenia pattern and the half-life of IgG and IgM, antibody-mediated DITP associated with TMP-SMX was postulated.

4 | CONCLUSION

In conclusion, discontinuation and, in selected cases, rechallenging is an effective approach in TMP-SMX-induced DITP. With closely clinical and radiological monitoring, clindamycin combined with azithromycin could be used as an alternative therapy as first-line therapies with a favorable efficacy and safety profile in an HIV-positive patient with TE.

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Nothing.

CONFLICT OF INTEREST
None declared.

AUTHOR CONTRIBUTIONS
KM and HK: Wrote the original format of the article. HK and SJ: Edited, reviewed, and provided guidance and helpful feedback on the draft. All authors contributed to patient management and prepared the final version of the manuscript.

ETHICAL APPROVAL
Informed consent was obtained from the patient for this report.

DATA AVAILABILITY STATEMENT
All data generated or analyzed during this study are available as part of the article, and no additional source data are required.

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REFERENCES
1. Porter SB, Sande MA. Toxoplasmosis of the central nervous system in the acquired immunodeficiency syndrome. *N Engl J Med*. 1992;327(23):1643-1648.
2. Bowen LN, Smith B, Reich D, et al. HIV-associated opportunistic CNS infections: pathophysiology, diagnosis and treatment. *Nat Rev Neurol*. 2016;12(11):662-674.
3. Dunay IR, Gajurel K, Dhakal R, Liesenfeld O, Montoya JG. Treatment of toxoplasmosis: historical perspective, animal models, and current clinical practice. *Clin Microbiol Rev*. 2018;31(4):e00057-17.
4. Basavaraju A. Toxoplasmosis in HIV infection: an overview. *Trop Parasitol*. 2016;6(2):129-135.
5. Flegr J. Neurological and neuropsychiatric consequences of chronic Toxoplasma infection. *Curr Clin Micro Rpt*. 2015;2(4):163-172.
6. Kaplan JE, Benson C, Holmes KK, et al. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations From CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR Recomm Rep*. 2009;58(4):1-207.
7. Saylor D. Neurologic complications of human immunodeficiency virus infection. *Continuum (Minneap Minn)*. 2018;24(5):1397-1421.
8. Mathews C, Barba D, Fullerton SC. Early biopsy versus empiric treatment with delayed biopsy of non-responders in suspected HIV-associated cerebral toxoplasmosis: a decision analysis. *AIDS*. 1995;9(11):1243-1250.
9. Panel on Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV. Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-infected Adults and Adolescents: Recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf. Accessed July 6, 2020.
10. Van Delden C, Hirschel B. Folinic acid supplements to pyrimethamine-sulfadiazine for toxoplasma encephalitis are associated with better outcome. *J Infect Dis*. 1996;173(5):1294-1295.
11. Torre D, Casari S, Speranza F, et al. Randomized trial of trimethoprim-sulfamethoxazole versus pyrimethamine-sulfadiazine for therapy of toxoplasmic encephalitis in patients with AIDS. *Antimicrob Agents Chemother*. 1998;42(6):1346-1349.
12. Béraud G, Pierre-François S, Foltzer A, et al. Cotrimoxazole for treatment of cerebral toxoplasmosis: an observational cohort study during 1994-2006. *Am J Trop Med Hyg*. 2009;80(4):583-587.
13. Dedicoat M, Livesley N. Management of toxoplasmic encephalitis in HIV-infected adults (with an emphasis on resource-poor settings). *Cochrane Database Syst Rev*. 2006;19(3):CD005420.
14. Ho JMW, Juurlink DN. Considerations when prescribing trimethoprim-sulfamethoxazole. *CMAJ*. 2011;183(16):1851-1858.

15. Prueksaritanond S, Barbaryan A, Ali AM, Mirrakhimov AE. An uncommon cause of gastrointestinal bleeding in an 84-year-old female. *Case Rep Hematol*. 2013;2013:940271.
16. Masters PA, O'Bryan TA, Zurlo J, Miller DQ, Joshi N. Trimethoprim-sulfamethoxazole revisited. *Arch Intern Med*. 2003;163(4):402-410.
17. Aster RH, Bougie DW. Drug-induced immune thrombocytopenia. *N Engl J Med*. 2007;357(6):580-587.
18. Gaudel P, Qavi AH, Basak P. Life-threatening thrombocytopenia secondary to trimethoprim/sulfamethoxazole. *Cureus*. 2017;9(12):e1963.
19. Hernandez AV, Thota P, Pellegrino D, et al. A systematic review and meta-analysis of the relative efficacy and safety of treatment regimens for HIV-associated cerebral toxoplasmosis: is trimethoprim-sulfamethoxazole a real option? *HIV Med*. 2017;18(2):115-124.
20. Katlama C, De Wit S, O'Doherty E, Van Glabeke M, Clumeck N. Pyrimethamine-clindamycin vs. pyrimethamine-sulfadiazine as acute and long-term therapy for toxoplasmic encephalitis in patients with AIDS. *Clin Infect Dis*. 1996;22(2):268-275.
21. Fichera ME, Bhopale MK, Roos DS. In vitro assays elucidate peculiar kinetics of clindamycin action against Toxoplasma gondii. *Antimicrob Agents Chemother*. 1995;39(7):1530-1537.
22. Araujo FG, Remington JS. Effect of clindamycin on acute and chronic toxoplasmosis in mice. *Antimicrob Agents Chemother*. 1974;5(6):647-651.
23. Yapar N, Erdenizmenli M, Oguz VA, et al. Cerebral toxoplasmosis treated with clindamycin alone in an HIV-positive patient allergic to sulfonamides. *Int J Infect Dis*. 2005;9(1):64-66.
24. Madi D, Achappa B, Rao S, Ramapuram JT, Mahalingam S. Successful treatment of cerebral toxoplasmosis with clindamycin: a case report. *Oman Med J*. 2012;27(5):411-412.
25. Rajapakse S, Chrishan Shivanthan M, Samaranayake N, Rodrigo C, Deepika Fernando S. Antibiotics for human toxoplasmosis: a systematic review of randomized trials. *Pathog Glob Health*. 2013;107(4):162-169.
26. Nau R, Sörgel F, Eiffert H. Penetration of drugs through the blood-cerebrospinal fluid/blood-brain barrier for treatment of central nervous system infections. *Clin Microbiol Rev*. 2010;23(4):858-883.
27. Neville AJ, Zach SJ, Wang X, et al. Clinically available medicines demonstrating anti-toxoplasma activity. *Antimicrob Agents Chemother*. 2015;59(12):7161-7169.
28. Araujo FG, Guptill DR, Remington JS. Azithromycin, a macrolide antibiotic with potent activity against toxoplasma gondii. *Antimicrob Agents Chemother*. 1988;32(5):755-757.
29. Jacobson JM, Hafner R, Remington J, et al. Dose-escalation, phase I/II study of azithromycin and pyrimethamine for the treatment of toxoplasmic encephalitis in AIDS. *AIDS*. 2001;15(5):583-589.
30. Saba J, Morlat P, Raffi F, et al. Pyrimethamine plus azithromycin for treatment of acute toxoplasmic encephalitis in patients with AIDS. *Eur J Clin Microbiol Infect Dis*. 1993;12(11):853-856.
31. Balaskas K, Vaudaux J, Boillat-Blanco N, et al. Azithromycin versus sulfadiazine and pyrimethamine for non-vision-threatening toxoplasmic retinochoroiditis: a pilot study. *Med Sci Monit*. 2012;18(5):CR296-CR302.
32. Shiojiri D, Kinai E, Teruya K, et al. Combination of clindamycin and azithromycin as alternative treatment for toxoplasma gondii encephalitis. *Emerg Infect Dis*. 2019;25(4):841-843.
33. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*. 1981;30(2):239-245.

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