Evidence-based practice
Management of combined toxoplasma meningo-encephalitis and Pneumocystis pneumonia in HIV

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Introduction
Although both Pneumocystis jiroveci pneumonia (PCP) and Toxoplasma gondii encephalitis are common opportunistic infections (OI) in USA & UK, combined infection has been only very rarely reported.1 After National Library of Medicine and Medline searches, only one case report by Tsai et al. has been found.1 Two additional cases will be presented and the management challenges associated with treating these two infections simultaneously discussed.

Case Report 1
22 year old African male, recently diagnosed HIV-1 positive, CD4 10 cells/mm³, HIV RNA 107885 copies/ml, presented to another centre, complaining of dry cough associated with night sweats for 2 weeks. He was pyrexial 39°C, sparse basal inspiratory crackles on chest examination, hypoxic with PaO₂ 8.9 kPa on air and chest X-ray was unremarkable. He was treated on clinical grounds for presumed Pneumocystis pneumonia with intravenous co-trimoxazole 120 mg/kg/day. The diagnosis was subsequently confirmed by broncho-alveolar lavage. Microscopy and culture for mycobacterium were negative. He was Hepatitis-B e-antigen positive with Hepatitis B DNA ≥110 million miu/l, alanine transaminase (ALT) 102 u/l. Toxoplasma dye test was 16 iu/ml and IgM negative.

Two days later he was apyrexial with improved respiratory symptoms, but developed diplopia with left-sided sixth nerve palsy. The patient was transferred to regional centre for further investigation. CT scan of head demonstrated multiple ring enhancing lesions measuring up to 14 mm associated with areas of oedema in pons and surrounding areas.

Toxoplasmosis was considered the most likely diagnosis and was treated with sulphadiazine 1.5 g four times daily and pyrimethamine 75 mg once daily, folic acid 15 mg once daily within 24 hours. Co-trimoxazole was changed to oral atovaquone 750 mg twice daily, because of possible summative toxicity. By day 6 clinical and radiological improvement was seen on CT scan. However, by day 10 ALT risen to 238 u/l. No hepatomegaly was demonstrated. In view of evidence of liver drug toxicity, regimen changed to clindamycin 600 mg four times daily, Pyrimethamine 75 mg od, Folinic Acid 15 mg od & Primaquine 15 mg od. By day 15, ALT had improved to 186 u/l. Patient discharged himself against medical advice, but later readmitted to another centre, where treatment course for both infections was completed.

Case Report 2
44 year old Caucasian male, recently diagnosed HIV-1 positive, CD4 40 cells/mm³ was admitted following a 2 week history of cough, fever and breathlessness. His chest x-ray showed bilateral reticulo-nodular shadowing. He was commenced on intravenous Clindamycin 600 mg four times daily, oral pyrimethamine 50 mg once daily, folic acid 15 mg once daily and primaquine 15 mg once daily were commenced. Repeat CT scan on day 17 showed resolution of the oedema and the focal lesion.

Discussion
It is interesting that more toxoplasmosis and PCP co-infections have not been reported even in late presenters, evidence is therefore lacking for the management of cases of proven PCP in association, with clinical and radiographic features very suggestive of cerebral toxoplasmosis. In these cases, the neurological features presented when respiratory condition had improved, thus allowing priority to be given to toxoplasmosis management.

Treatment of PCP in isolation has been well established by several studies.

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In moderate to severe PCP, a randomised controlled comparison between intravenous co-trimoxazole 90 to 120 mg/kg/day and pentamidine 4 mg/kg/day for 17 to 21 days demonstrated better survival rate in the co-trimoxazole arm according to Sattler et al. A multi-centre three-arm randomized trial in mild to moderately severe PCP reported similar two-month survival rates for trimethoprim (15 mg/kg/day) according to Safrin et al. There was no difference in proportions of patients with each therapy that had dose-limiting toxicity or failure of therapy. A multi-centre, randomized comparison of atovaquone 750 mg three times daily with co-trimoxazole 1,920 mg three times daily in mild to moderately severe PCP showed lower response rates, higher death rates attributed to PCP in the atovaquone arm, but more adverse effects requiring change of therapy in the co-trimoxazole arm, reported by Hughes et al.

Treatment of Toxoplasma encephalitis in isolation is also been well-studied. Both pyrimethamine + clindamycin 1,200 mg four times daily (PC) and pyrimethamine + sulfadiazine (PS) 100 mg/kg showed showed no significant difference in relative survival rates in a randomized, multi-centre with crossover for failure or intolerance of the initial regimen, according to Dannemann et al. In a multi-centre randomised comparison of PC and PS in an intent-to-treat analysis also showed no difference in effectiveness in the acute phase, using of pyrimethamine 50 mg once daily with either clindamycin 600 mg or sulfadiazine 1 g four times daily for 6 weeks, followed by maintenance therapy of pyrimethamine 25 mg daily with either clindamycin 1.2 g or sulfadiazine 2 g daily. Toxic effects of PC led to fewer stopping therapy than those of PS, but higher relapse rates reported with PC was noted by Katlama et al. Atovaquone 1,500 mg twice daily in combination with either pyrimethamine or sulfadiazine 1.5 g three times daily was shown to be effective for treatment of toxoplasma encephalitis by Chingwin et al. Pyrimethamine 200 mg loading dose, then 75 mg once daily was used in all three investigations. One small case series reported by Canessa et al. demonstrated effectiveness of co-trimoxazole alone. The evidence for effectiveness of this regime in severe disease is limited. These regimens have been recommended when standard therapy not tolerated.

Taking account of the above in treating both infections, the main issue is that combination of both drugs of choice is expected to result in unacceptable drug toxicity. There are drugs which can be used in treating both conditions but their effect on both conditions may not be equal. Thus in most of clinical situations, one condition gets precedence or priority over the other and the first line drug is used for one, not for both as happened in both these cases. Where a decision could not be made or prioritisation could not be made, the lack of a drug controlling or treating both conditions could become serious; otherwise the summated toxicity could become a problem. Combination of drugs in treating combined infection can result in summative more serious toxicity.

Decisions on the best combination of medication were based on the criteria listed in Figure 1, using commonly accepted standards for hierarchy of quality of evidence for the treatment of individual infections. In both these cases, toxoplasmosis was clinically the more significant at the time that signs of this infection were apparent. In case 1, raised ALT improved when sulfadiazine was changed. Liver toxicity was considered to be due to sulfadiazine alone, summative drug toxicity or a combination of drug toxicity and hepatitis B infection. Pyrimethamine-clindamycin + primaquine was the preferred regime for both cases because available evidence indicates effectiveness of PC in treating acute Toxoplasma compared to PS. Both sulphonamides co-trimoxazole and sulfadiazine demonstrate synergy with the dihydrofolate reductase release inhibitors, pyrimethamine and trimethoprim; such combinations were avoided.

Another important issue demonstrated in case 2 is the lack of any available parental preparations for toxoplasmosis.

In conclusion, decisions for each specific case will be guided by the relative severity of individual infections. Table 1 summarises the choice of drugs. In a case where PCP was the priority, the two conditions were present with equal severity options 1 or 3 may be considered, although it is not clear what the optimum drug combinations would be. Option 4 is preferred when Toxoplasma is the priority. Option 3 is not recommended in view of lower effectiveness for treating PCP and rates of elevated transaminases in clinical trials, as reported by Haile and Flaherty. Benefits of subsequent early commencement of antiretroviral drugs needs to balanced against the risks associated with drug-drug interactions. The majority of patients presenting with the opportunistic infections (OIs) discussed, should be started early (median of 12 days after starting treatment for OI), according to Zolopa et al.

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Table 1. Summary of drug choice combinations

| Drug regime (No. of active agents) | Anticipated cross-over in adverse events | Possible drug-drug interactions | Responses relevant to case 1 & 2 | Comments |
|-----------------------------------|----------------------------------------|---------------------------------|---------------------------------|----------|
| **Option 1** co-trimoxazole + pyrimethamine-sulfadiazine (4) | rash, abnormal transaminases, renal impairment, nausea and vomiting | interaction between folate antagonists pyrimethamine and trimethoprim. | Case 1 changed to option 2 following clinical diagnosis of toxoplasmosis, to avoid summative toxicity of option 1 | One case report. Treatment continued for 4.5 months. Stopped because of skin rash. Complete clinical and CT scan resolution at 12 months. |
| **Option 2** atovaquone + pyrimethamine-sulfadiazine (3) | rash, abnormal transaminases, nausea and vomiting | None. | Suspected liver toxicity in Case 1 led to change to Option 4. | Higher rates of PCP treatment failure and adverse reactions requiring discontinuation reported with Atovaquone. |
| **Option 3** co-trimoxazole + pyrimethamine-clindamycin (4) | None | Interaction between folate antagonists pyrimethamine and trimethoprim | | Reduced dose Pyrimethamine-Sulphadiazine would be considered after 6 weeks, as prophylactic therapy, with view to reduction of toxoplasmosis relapse rate |
| **Option 4** pyrimethamine-clindamycin + primaquine (3) | None | None | Regime chosen in Case 2 as toxoplasmosis was then the priority and intravenous preparation of clindamycin available | Reduced dose Pyrimethamine-Sulphadiazine would be considered after 6 weeks, as prophylactic therapy, with view to reduction of toxoplasmosis relapse rate as secondary prophylaxis |

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