described an HIV-infected adult who developed aseptic meningitis after both the CoT combination and TMP alone. In this case, and the others reviewed by the authors, all patients had a similar abrupt onset of symptoms and prompt resolution with cessation of therapy. Encephalitis due to TMP alone has also been reported (Hedlund *et al*., 1990). The mechanism of the aseptic meningitis is uncertain, although previously most authors had favored a hypersensitivity reaction. A recent discovery by Haruki *et al*. (2013) suggests that sulfonamides inhibit tetrahydrobiopterin biosynthesis, a co-factor of aromatic hydroxylases involved in dopamine and serotonin production pathways. Crystal structures demonstrated SMX binding to the relevant enzyme, with *in vitro* studies demonstrating inhibiting of neurotransmitter biosynthesis (i.e. catecholamines), potentially explaining the nonaseptic meningitis CNS-related side effects (Haruki *et al*., 2013).

6g. Pneumonitis

Pneumonitis has been rarely associated with both CoT (Holdcroft and Ellison, 1991; Kelly *et al*., 1992) and TMP alone (Higgins and Niklasson, 1990) but probably represents a hypersensitivity reaction. In AIDS patients, this may mimic PJP (Holdcroft and Ellison, 1991; Kelly *et al*., 1992). Kelly *et al*. (1992) described three HIV-infected patients who developed pneumonitis and shock after treatment and rechallenge with CoT, and they reviewed the literature regarding this rare side effect. Oshitani *et al*. (1998) have described the same phenomenon in a patient with refractory ulcerative colitis being treated for PCP. Acute fibrinous organizing pneumonia has also been reported after CoT therapy (Jamous *et al*., 2014).

6h. Miscellaneous side effects

Various other rare reactions have occurred during CoT therapy. These include acute rheumatoid arthritis, anaphylaxis, angioneurotic edema, glossitis, parotitis, severe vasculitis, hypoglycemia, leg paresthesiae, hallucinations, myopia, tremor, vertigo, visual disturbances, headache, depression, and psychosis (Hanley, 1969; Frisch, 1973; Borucki *et al*., 1988; Schattner *et al*., 1988; McCue and Zandt, 1991; Johnson *et al*., 1993; Lewis, 1995; Sternbach and State, 1997; Slavik *et al*., 1998; Saidinejad *et al*., 2005; Geber *et al*., 2013; Kamath *et al*., 2012; Nunnari *et al*., 2010; Patel and Scheiner, 2011). Polyneuropathy associated with CoT therapy has been described in one patient (Grossman *et al*., 1977), but this may have been a complication of cardiac surgery performed on the patient (Vincent, 1977). The significance of these anecdotal reports is not clear. One study showed that CoT given in standard doses could lower thyroid hormone levels, but in another there were no clinically significant changes in these hormone levels in patients taking continuous low-dose CoT for more than a year. CoT may cause hyperphenylalaninemia, but the clinical significance of this is not known (Leeming, 1980). There seems to be a sufficient number of reports about rhabdomyolysis related to CoT use in HIV-positive patients to suggest that there is a link with this rare adverse reaction (Singer *et al*., 1998; Jen and Sharma, 2011). TMP has also been reported to elevate plasma levels of homocysteine, theoretically increasing thrombotic risk (Smulders *et al*., 1998), although there have been no clinical reports of thrombosis. When used in low doses as prophylaxis against *Pneumocystis* pneumonia in HIV-infected individuals, homocysteine levels are not elevated (Smulders *et al*., 2001).

6i. Immunosuppressive effect

CoT inhibits DNA synthesis in lymphocytes cultured in the presence of phytohemagglutinin. This effect occurs with both TMP and SMX separately, but it is more pronounced with the drug combination (Gaylarde and Sarkany, 1972). Arvilommi *et al*. (1972) demonstrated that CoT partially suppresses antibody response after tetanus vaccination. TMP and SMX, individually as well as in combination, inhibit chemiluminescence of human polymorphs in response to phagocytosis (Siegel and Remington, 1982). Somewhat contradictory results were reported by Oleske *et al*. (1983). They found that CoT and its separate components caused some enhancement in chemotaxis and chemiluminescence of normal polymorphs and that this effect was more marked with cells from patients with leukocyte chemotaxis and chemiluminescence defects. These observations suggest that CoT may have some immunosuppressive effects, and reports of a possible role for CoT in the treatment of granulomatosis with polyangiitis add interest to this concept. Neutrophil phagocytosis, random migration, and chemotaxis are not affected by TMP and SMX, individually or in combination (Anderson *et al*., 1980). Overall, however, the clinical relevance of these observations is unclear.

6j. Safety in pregnancy

Large doses of TMP are teratogenic in animals. This is to be expected because TMP is a folic acid antagonist. The drug has been used in a small number of patients during the first 16 weeks of pregnancy without encountering any fetal malformations. However, folate levels are often marginal in pregnant women. A recent study by Yang *et al*. (2011) found that CoT, among other FDA class C and D drugs, had the strongest associations with preterm birth and low birth weight. For this reason, it has in the past been recommended that the use of CoT or TMP be avoided when possible during pregnancy, particularly during the first trimester. The advent of HIV infection and AIDS in developing countries, however, has changed this perspective, primarily because of the low cost and efficacy of CoT in prevent *Pneumocystis* pneumonia in that setting, in which the benefits are perceived to outweigh the risks (Ahmad *et al*., 2001). Forna *et al*. (2006) conducted a systematic review of the evidence and concluded that there was no evidence of hyperbilirubinemia in neonates of mothers given CoT prophylaxis, and that the evidence for teratogenicity (oral clefts, neural tube defects, and cardiovascular and urinary abnormalities) was mixed. A systematic