there was a significantly higher incidence of hematologic toxicity in the dapsone-containing combination. As a result of this, in February 2008 the manufacturers withdrew the product (Dacart), and LapDap as well, from further development and commercial use. This means that dapsone-containing combination antimalarial therapies are effectively no longer available and are not recommended in any form for malaria treatment or prophylaxis (WHO, 2008; Global Malaria Programme, 2015). A recent Cochrane review assessed the role of various regimens, including dapsone-containing protocols, in the prevention of malaria in pregnant women in endemic areas (Radeva-Petrova *et al,* 2014).

7d. *Pneumocystis jiroveci (carinii)* infection

Dapsone is a well-established alternative to TMP–SMX for treatment and prophylaxis of PCP. *P. jiroveci* has now been accepted taxonomically as a fungus; however, it was originally thought to be a protozoan. *P. jiroveci* is now the name of the species that infects humans, and *P. carinii* is the species that infects rats. Infection is common: seroprevalence studies have indicated that about two-thirds of children have evidence of exposure by 4 years of age. Progressive, symptomatic pneumonitis is, however, rare in the non-immunocompromised. Although the infection was known and described as a rare clinical entity before he global epidemic of HIV infection, it was this epidemic with its associated severe immunodeficiency state (AIDS) that led the expansion of research into the biology of the organism and the progress in the discovery of ways to manage the infection. Clinical disease is likely to be a result of primary acquisition of the organism or, less commonly, reactivation of a latent carrier state. In patients with a severe T-cell immunodeficiency state such as AIDS, or as a result of immunosuppression as a consequence of organ transplantation or chemotherapy for hematologic malignancy, the risk of infection is substantial. Both primary and secondary chemoprophylaxis has proven to be effective in preventing infection in these high-risk groups. There is no form of immunization available.

Initially, animal studies demonstrated that dapsone had efficacy against *P. carinii* and that combination with trimethoprim showed significant synergy, but that TMP–SMX was more effective for treatment (Hughes and Smith, 1984). Further studies in corticosteroid-treated rats demonstrated that dapsone was highly effective in chemoprophylaxis, even when given at monthly intervals (Hughes, 1988). After the encouraging reports in animal studies, the first human trials of dapsone for *Pneumocystis* infection were carried out. The first study carried out in 15 patients with AIDS and PCP in San Francisco was an open-label study of dapsone at 100 mg/day and trimethoprim at 20 mg/kg/day. All patients improved both clinically and radiologically (Leoung *et al.,* 1986). Another study evaluated dapsone alone. Eighteen patients with AIDS and PCP were given dapsone 100 mg daily for 21 days. Eleven of the 18 (61%) responded satisfactorily (Mills *et al.,* 1988). A further small study was published of seven patients with mild PCP treated with dapsone alone at 200 mg once daily. All seven patients had a poor outcome, leading the authors to conclude that dapsone alone was an inferior therapy and should not be part of further comparative trials (Safrin *et al.,* 1991).

A randomized, double-blind trial of 60 patients with mild PCP and AIDS who were randomized to either oral TMP–SMX or oral trimethoprim–dapsone found that there was a low failure rate of about 10% in each group and that severe drug-related toxicity was less common in the dapsone-treated group (Medina *et al.,* 1990).

In 1996, a randomized double-blind trial of dapsone plus trimethoprim versus TMP–SMX versus clindamycin plus primaquine was carried out in 181 patients with AIDS and moderate to severe PCP. No difference was seen among the three groups in response rates, or dose-limiting toxicity, although there were differences in the milder adverse effects seen in the groups. Although this is the largest study of the efficacy of the dapsone combination for treatment of PCP, the sample size was insufficient to demonstrate equivalence (Safrin *et al.,* 1996). Since that time, there have been no further large treatment trials of dapsone in PCP reported. Dapsone combined with trimethoprim is recommended as an alternative to TMP–SMX for the treatment of mild to moderate PCP in AIDS (NIH, 2015).

For patients with PCP who have problems with treatment-related toxicity, the appropriate response is to switch to one of the alternative proven regimens. Treatment failure for microbiologic reasons is rare, although possible resistance to DHFR inhibitors has been observed, particularly in those who have been previously exposed to the drugs (Crothers *et al.,* 2005; see Chapter 92, Trimethoprim and Trimethoprim–Sulfamethoxazole [Co-trimoxazole]). One meta-analysis (Smego *et al.,* 2001) concluded that the best alternative therapy for TMP–SMX treatment failure is a switch to the combination of clindamycin plus primaquine. This recommendation has not been subjected to validation in a clinical trial.

Primary prophylaxis in the setting of severe immunodeficiency has proven to be effective in patients with HIV infection, as well as those who are immunosuppressed for reasons other than HIV infection. Attack rates for patients with non-HIV immunodeficiency states have been reported as follows: acute lymphoblastic leukemia, 6.5–42.9%; severe combined immunodeficiency syndrome, 27–42%; rhabdomyosarcoma, 4–25%; Wegener's granulomatosis, 3.5–12%; Hodgkin's disease, 1.3%; collagen-vascular diseases, < 2%; and central nervous system tumors, 1.3–1.7% (Rodriguez and Fishman, 2004).

Before PCP prophylaxis became standard practice, the rate of PCP in patients with AIDS was about 80%. Since the introduction of primary prophylaxis and highly active antiretroviral therapy, the incidence of the disease in populations that can access treatment has markedly declined. It does, however, remain prevalent; a significant proportion of individuals with HIV still have PCP as their first sign of the disease. By the late 1990s, there had been more than 40 studies of PCP prophylaxis that involved the use of dapsone, and these