In the pre-ART era, relapses were frequent and secondary prophylaxis with fluconazole had been recommended for life-long. The studies of ART initiation among patients with cryptococcosis in resource-limited settings have shown that the incidence of new cases and rate of relapsed disease are dramatically reduced, and the survival has markedly increased. Prospective studies from resource-limited settings had also demonstrated that discontinuation of secondary prophylaxis is safe when patients achieve successful immune restoration from ART.

Cryptococcal immune reconstitution inflammatory syndrome (C-IRIS) is characterized a clinical deterioration of cryptococcosis following initiation of ART. Some studies report that C-IRIS is observed more frequently in severely immunocompromised patients with disseminated infection or early ART initiation after cryptococcosis. This may partly explain the high incidence of C-IRIS in resource-limited settings. However, a standard case definition of C-IRIS has not been available. The International Network for the Study of HIV-associated IRIS has been working for the practical case definition of C-IRIS to provide a tool for clinical use, particularly in resource-limited settings, and future epidemiologic studies.

The effectiveness of existing drugs is increasingly compromised by the emergence of drug-resistant pathogens. Upregulating multidrug-resistance (MDR) pumps, which confers enhanced resistance to chemically unrelated alien substances, is a major source of microbial drug resistance. A major challenge in developing efficacious antibiotics against drug-resistant pathogens is to identify compounds that could counteract MDR functions. In the human pathogen Candida albicans, Mdr1p plays a key role in azole-resistant clinical isolates. Here we report an unexpected consequence of MDR1 upregulation: it confers enhanced sensitivity to a natural product, berberine. This effect of MDR1 overexpression is at least in part due to enhanced accumulation of berberine inside cells. In support of this notion, a number of berberine structural analogues exhibited a similar MDR1-dependent antifungal activity. We also show that berberine is indeed highly efficacious in inhibiting the growth of azole-resistant clinical C. albicans isolates with upregulated MDR1 from HIV infected patients. Our study reveals a novel function of MDR1 in raising sensitivity of drug-resistant fungal pathogens to selected natural products. Thus, the drug resistance phenotype conferred by MDR1 overexpression could be harnessed through the use of MDR1-dependent cytotoxic agents, such as berberine, for effective antifungal strategies.

Invasive fungal infections have always been a difficult to treat infectious diseases with high mortality. This is due to the immunocompromised state of the patients as well as toxicities of antifungal treatments. Traditionally, only the azoles and the polyenes are available for treatment of these patients. Recently, a novel class of antifungal agents, the echinocandins, have emerged with promising safety profiles. These agents act by inhibiting the synthesis of 1,3-β-D-glucan of fungal cell wall.