dosage of lopinavir/ritonavir from 400 mg/100 mg twice daily to 800 mg/200 mg twice daily over 2 weeks. This so-called "double dosing" of boosted lopinavir may result in hepatotoxicity and careful clinical monitoring is necessary [215]. Alternatively, "super boosting" of lopinavir, though poorly tolerated in adults, is sometimes effective, especially in children. In this instance, the dosage of lopinavir is maintained at 400 mg twice daily, but ritonavir dosage is increased from 100 mg twice daily to 400 mg twice daily. Super boosting of ritonavir is poorly tolerated in adults, however, and the double-dosing strategy is preferred. These complicated interactions underscore the importance of expert consultation in treating individuals with concurrent HIV and tuberculosis infections. For situations involving complex drug–drug interactions, some clinicians prefer to measure the concentrations of the interacting drugs, and to dose these drugs based upon individualized data [242].

Immune Reconstitution Inflammatory Syndrome

Transient worsening of tuberculosis symptoms and lesions in response to antituberculous therapy has previously been reported in HIV-uninfected patients [277]. Patients with HIV infection and tuberculosis are at an increased risk of developing paradoxical worsening of symptoms, signs, or clinical manifestations of tuberculosis after beginning antituberculosis and antiretroviral treatments. These reactions develop as a consequence of reconstitution of immune responsiveness brought about by ART, and are designated as the IRIS. Tuberculosis IRIS has been noted to be more common in participants with earlier ART initiation and $CD4^+$ lymphocyte counts <50 cells/μL. In the STRIDE study, IRIS occurrence was infrequent at 7.6%. When tuberculosis IRIS occurred, the majority (69%) of cases were mild to moderate in severity; however, 31% were hospitalized with tuberculosis IRIS and more than half received corticosteroids [68]. Signs of IRIS may include high fevers, worsening respiratory symptoms, increase in size and inflammation of involved lymph nodes, new lymphadenopathy, expanding central nervous system (CNS) lesions, worsening of pulmonary parenchymal infiltrations, new or increasing pleural effusions, and development of intra-abdominal or retroperitoneal abscesses [69]. Such findings are attributed to IRIS only after excluding other possible causes, especially tuberculosis treatment failure from drug-resistant tuberculosis or another opportunistic disease, such as non-Hodgkin lymphoma or infection. Antiretroviral treatment of patients with incubating, subclinical tuberculosis may also result in what is called "unmasking IRIS," where tuberculosis symptoms and clinical manifestations become more pronounced, though whether this represents normal progression of untreated tuberculosis is not known [187].

The relative risk of developing IRIS for patients who receive ART during therapy for tuberculosis is 1.88 (95% CI, 1.31–2.69), and those who start ART within 2 weeks after starting tuberculosis therapy have higher rates than those who start between 8–12 weeks [261–263]. In general, development of IRIS does not worsen treatment outcomes for either tuberculosis or HIV infection, and most episodes can be managed symptomatically. An exception to this is the development of IRIS in patients with CNS tuberculosis, where IRIS may cause severe or fatal neurological complications. In a study of patients with tuberculosis meningitis and HIV infection, early initiation of ART (within 2 weeks) was associated with increased rates of adverse events and higher mortality [278]. Thus, ART is not initiated in the first 8 weeks of antituberculosis therapy for patients with HIV infection and tuberculous meningitis (or other CNS tuberculosis), even for patients with CD4 cell counts <50 cells/μL.

Management of IRIS is symptomatic. Based on expert opinion, for most patients with mild IRIS, tuberculosis and antiretroviral therapies can be continued with the addition of anti-inflammatory agents such as ibuprofen. For patients with worsening pleural effusions or abscesses, drainage may be necessary. For more severe cases of IRIS, treatment with corticosteroids is effective. In a placebo-controlled trial of prednisone for patients with moderate IRIS, prednisone 1.25 mg/kg/day significantly reduced the need for hospitalization or surgical procedures [70]. For patients who develop IRIS, prednisone may be given at a dose of 1.25 mg/kg/day (50–80 mg/day) for 2–4 weeks, with tapering over a period of 6–12 weeks or longer. Controlled trials investigating whether treatment with nonsteroidal anti-inflammatory agents or corticosteroids can prevent the development of IRIS are under way or in development.

Children

Children commonly develop tuberculosis as a complication of the initial infection with *M. tuberculosis* (primary tuberculosis). The radiographic presentation of primary tuberculosis in children is characterized by intrathoracic lymphadenopathy with or without lung opacities, occasionally presenting with lymph node enlargement to a degree that there is compression of airways with or without hyperinflation or collapse of lobe or lung; breakthrough of node(s) in the airways can manifest with lobar or segmental infiltration, and a miliary pattern [279, 280]. The diagnosis of tuberculosis in children is challenging, especially in young children (<5 years) due to the paucibacillary nature of the disease. Depending on the setting and resources, diagnosis is microbiologically confirmed in only 15%–50% of pediatric cases, and clinical case definitions for tuberculosis in children have recently been updated [281]. Children, rarely, and adolescents, more frequently, can also develop adult-type tuberculosis (upper lobe opacities and cavitation associated with sputum production). The lesions of primary tuberculosis have fewer *M. tuberculosis* organisms than those of adult-type pulmonary tuberculosis; thus, treatment failure, relapse, and development of secondary resistance are less common events among children when standard treatment regimens are initiated in a timely