Published in final edited form as:

Clin Infect Dis. 2009 March 1; 48(5): 667–676. doi:10.1086/596764.

Novel Relationship between Tuberculosis Immune Reconstitution Inflammatory Syndrome and Antitubercular Drug Resistance

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Abstract

Background—Tuberculosis (TB) immune reconstitution inflammatory syndrome (IRIS) is emerging as an important early complication of combination antiretroviral therapy in patients with TB in developing countries. The differential diagnosis of TB IRIS includes deterioration caused by other human immunodeficiency virus-related morbidities and drug-resistant TB.

Methods—We prospectively evaluated consecutive patients with suspected TB IRIS from February 2005 through July 2006 at a community-based secondary hospital in Cape Town, South Africa, by means of clinical case definitions for TB IRIS. Specimens were sent for TB culture and susceptibility testing, and a rapid test (FASTplaque-Response) was performed to expedite determination of rifampin susceptibility.

Results—One hundred patients with suspected TB IRIS were evaluated, 26 of whom were being retreated for TB. IRIS symptoms developed a median of 14 days (interquartile range, 7–25 days) after the initiation of combination antiretroviral therapy. In 7 patients, an alternative opportunistic disease was diagnosed. Rifampin-resistant TB was present in 13 patients, 9 of whom received a diagnosis after study entry (7 of 9 had multidrug-resistant TB). Undiagnosed rifampin-resistant TB was thus present in 10.1% of patients (95% confidence interval, 3.9%–16.4%) who presented with TB IRIS, once those with alternative diagnoses and TB with known rifampin resistance were excluded. In the remaining 80 patients, TB IRIS without rifampin resistance was the final diagnosis.

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Potential conflicts of interest. All authors: no conflicts.

Presented in part: 15th Conference on Retroviruses and Opportunistic Infections, Boston, 2008 (abstract 1009).

Conclusions—TB IRIS that is clinically indistinguishable from TB IRIS that occurs in the context of drug-susceptible disease may occur in patients with undiagnosed multidrug-resistant TB. Antitubercular drug resistance should be excluded in all cases of suspected TB IRIS, and corticosteroids should be used with caution for patients with presumed TB IRIS until the result of drug-susceptibility testing is known.

The scale-up of combination antiretroviral therapy (cART) in the developing world is progressing rapidly, improving survival among HIV-infected persons [1, 2]. An emerging complication of cART in countries with high rates of tuberculosis (TB) is TB immune reconstitution inflammatory syndrome (IRIS). “Paradoxical” TB IRIS manifests with new, worsening, or recurrent symptoms, signs, and/or radiological manifestations of TB after cART is initiated in patients receiving treatment for TB [3]. It occurs in 8%–43% of patients who initiate cART while receiving TB treatment [4–11] and is associated with exuberant antimycobacterial immune responses [12]. There is no diagnostic test for TB IRIS, and the differential diagnosis is wide, including failure of TB treatment attributable to antimicrobial resistance, or suboptimal antitubercular drug concentrations [13], drug reactions, or an alternative opportunistic condition. Published case definitions require that these be excluded before a diagnosis of TB IRIS is made [14, 15]. TB IRIS can be severe and life-threatening, and there are anecdotal reports that suggest the use of adjunctive corticosteroid therapy [16, 17].

Concurrent with the increase in the prevalence of TB IRIS, the emergence of multidrug-resistant (MDR) and extensively drug resistant TB in settings in Southern Africa where HIV infection is prevalent has recently been highlighted [18, 19]. Determining the cause of deterioration in patients with TB during cART in resource-limited settings is important, because adjunctive corticosteroid therapy may worsen an already immunosuppressed patient's condition if used in the presence of incompletely efficacious TB treatment or other opportunistic infections. This study prospectively evaluated clinical case definitions of TB IRIS among 100 patients who were considered to have likely cases of TB IRIS. We found a high prevalence of unsuspected drug-resistant TB in this cohort, which has important implications for the diagnosis and management of this condition, as well as wider policy implications.

PATIENTS AND METHODS

Study site and participants

A prospective observational study was conducted under program conditions that involved 100 consecutive patients who were referred to GF Jooste Hospital (Cape Town, South Africa) with likely cases of TB IRIS. The TB incidence rate in the Western Cape province in 2006 was 1031 cases per 100,000 population [20], and the prevalence of antenatal HIV infection was as high as 33% [21]. More than 10,000 people have initiated cART within the catchment area of GF Jooste Hospital (M. Osler, Provincial Government of the Western Cape, personal communication). The national TB program treats new TB cases with 6 months of therapy (rifampin, isoniazid, pyrazinamide, and ethambutol for 2 months, followed by rifampin and isoniazid for 4 months). The retreatment regimen includes the addition of streptomycin, as follows: 2 months of rifampin, isoniazid, pyrazinamide, ethambutol, and streptomycin; 1 month of rifampin, isoniazid, pyrazinamide, and ethambutol; and 5 months of rifampin, isoniazid, and ethambutol. Routine TB drug susceptibility testing (DST) is not performed for new TB cases. Patients receiving retreatment and patients not responding to TB treatment may have DST performed. DST was only performed for rifampin, isoniazid, and ethambutol during the study, in accordance with national guidelines.

First-line cART in South Africa is stavudine, lamivudine, and either nevirapine or efavirenz. Efavirenz is preferred for patients receiving rifampin-based TB treatment. Patients with a CD4 cell count <200 cells/ μ L and/or World Health Organization stage 4 disease are eligible to commence cART.

Clinical case definitions of TB IRIS (table 1) were prepared, circulated, and discussed with participating primary care physicians. The definitions were in accordance with other published case definitions for IRIS [14, 15], in that they excluded patients with drug-resistant TB. Our case definitions, however, specifically used known resistance to rifampin as an exclusion criterion. We obtained information regarding initial TB diagnosis from the referral letter and by search of records from the regional laboratory, which processes all TB microbiologic specimens in our referral area. All patients aged ≥ 13 years who were referred to the hospital with suspected TB IRIS were included. TB treatment adherence was assessed by self-report and on the basis of the patient's TB clinic card, on which each daily dose taken was documented with a tick. Patients who had <80% adherence to TB treatment reported were not included as patients with suspected TB IRIS. The Research Ethics Committee of the University of Cape Town approved this study (REC 337/ 2004).

Clinical assessment sought to exclude differential diagnoses based on clinical presentation. For example, for patients with respiratory symptoms, bacterial and pneumocystis pneumonia were investigated. Clinical specimens were sent for TB microscopic examination, culture, and DST at the time of presentation with suspected TB IRIS. DST for rifampin and isoniazid was performed at 2 nationally accredited laboratories. Both laboratories used the indirect proportion method: one laboratory used liquid media with the MGIT system, and the other used solid culture medium (Middlebrook 7H11 agar). For 36 patients, a rapid rifampin resistance assay was performed (FASTplaque-Response; Biotec Laboratories) [22]. The result of this assay was confirmed by culture-based DST, and the latter result is reported unless stated otherwise. A purified protein derivative enzyme-linked immunospot assay was performed, as described elsewhere [23]. Patients were classified as having TB IRIS if 2 clinicians agreed that, at initial assessment and during the follow-up period, the patient fulfilled at least 1 of the case definitions.

Statistical methods

Fisher's exact test was used to compare proportions, and the Mann Whitney *U* test was used to analyze differences between medians. The unpaired Student's *t* test with Welch's correction was used to compare enzyme-linked immunospot assay results.

RESULTS

One hundred patients (66 female and 34 male patients) with suspected TB IRIS were evaluated from February 2005 through July 2006. The median age was 31 years (interquartile range [IQR], 26–35 years), and the median baseline CD4 cell count was 50 cells/ μ L (IQR, 26–94 cells/ μ L). Twenty-six patients had received ≥ 1 course of prior TB treatment. Patients developed symptoms prompting referral with suspected TB IRIS a median of 14 days (IQR, 7–25 days) after starting cART. These patients were assessed during screening for a randomized placebo-controlled trial of prednisone for mild and moderate TB IRIS (ISRCTN 21322548). Thirty-eight patients were enrolled in that study, and 25 received corticosteroid treatment for TB IRIS outside that study, usually for severe TB IRIS. Final diagnoses are shown in figure 1.

Follow-up CD4 cell counts during the first year of cART were available for 77 patients. In 73 patients (95%), the follow-up CD4 cell count increased (median increase, 139 cells/ μ L; IQR, 64–241 cells/ μ L) from the pre-cART value. In 4 patients, the CD4 cell count

decreased by 1–50 cells/ μ L during the first year of cART. Follow-up viral loads, usually measured after 6 months of cART, were available for 74 patients. The viral load was <400 copies/mL in 65 patients, 400–1000 copies/mL in 5, and >1000 copies/mL in 4. In all 4 of these patients, the CD4 cell count increased by 77–365 cells/ μ L during cART.

Among the whole cohort, the initial TB diagnosis was made on the basis of culture of *Mycobacterium tuberculosis* in a clinical specimen for 41 patients and positive smear microscopy results for 31 patients. For 25 patients, a diagnosis of smear-negative or extrapulmonary TB was made on the basis of clinico-radiological data [24–26]. Although the other 3 patients were receiving TB treatment at presentation, the initial diagnosis of TB was incorrect, and they had nontuberculous mycobacterial infection.

Seven of the 25 patients with a clinico-radiological diagnosis had microbiological confirmation when they presented with suspected TB IRIS (4 were smear positive, and 3 were culture positive). For the other 18 patients, the diagnosis of TB was not microbiologically proven. These patients had TB symptoms and lymphadenopathy on abdominal ultrasound (5 patients), on chest radiograph (2), or peripherally (1); miliary infiltrates on chest radiograph (4); other radiographic pulmonary infiltrates (2); pericardial effusion (2); or pleural effusion (2). One of the patients who received a diagnosis on the basis of symptoms and abdominal nodes on ultrasound was subsequently found to have lymphoma and probably did not have TB.

Seven patients with suspected TB IRIS had clear evidence of an alternative opportunistic condition (figure 1). In 3 patients, this was a nontuberculous mycobacterial infection. These patients had experienced some symptomatic improvement while receiving TB treatment before initiation of cART and were then referred with suspected TB IRIS after commencing cART. Review of the initial sputum culture results revealed nontuberculous mycobacterial infection. In 2 of the 3 patients, nontuberculous mycobacteria were also cultured from blood samples at the time of assessment for suspected TB IRIS.

Twenty-five patients had DST performed at initial TB diagnosis. For 19 of these patients, the isolate was susceptible to rifampin and isoniazid; 2 had isolates monoresistant to isoniazid, 1 had an isolate monoresistant to rifampin, and 3 had MDR TB. In an additional patient (patient 3), DST of the isolate at TB diagnosis was performed retrospectively after presentation with suspected TB IRIS, and the isolate demonstrated monoresistance to rifampin (table 2). For this patient, the culture result at the time of presentation with TB IRIS was negative. All 4 patients who presented with suspected TB IRIS with known rifampin resistance were receiving appropriate therapy for MDR TB and reported at least partial clinical improvement before initiation of cART. These patients then presented with clinical deterioration 7–45 days after starting cART. Their clinical manifestations included fever or night sweats (2 patients), marked weight loss (2), new peripheral nodes (1), new pulmonary infiltrates on chest radiograph (2), and other recurrent TB symptoms. Although these features are typical of TB IRIS, the case definitions that we used excluded this diagnosis.

Eighty-five patients had at least 1 culture for *M. tuberculosis* performed during assessment for TB IRIS. Cultures for *M. tuberculosis* were performed on sputum (for 55% of patients), lymph node or abscess aspirate (18%), pleural fluid (8%), CSF (8%), or other clinical specimens (11%). Culture yielded *M. tuberculosis* for 17 patients (20%; 8 had MDR TB, 1 had isoniazid-monoresistant TB, and 7 had TB that was susceptible to rifampin and isoniazid). Drug susceptibility was undetermined for 1 patient (patient 6) (table 2), because the culture of the patient's sample yielded both nontuberculous mycobacteria and *M. tuberculosis*. This patient had a FASTplaque assay indicative of rifampin resistance.

Including the patient whose initial isolate was rifampin resistant (patient 3) (table 2) and the patient with a FASTplaque result indicating rifampin resistance (patient 6) (table 2), 10 patients were found to have rifampin-resistant TB at the time of TB IRIS presentation. One of these patients was previously known to have MDR TB; thus, 9 (10.1%; 95% CI, 3.9%–16.4%) of 89 patients with suspected TB IRIS had rifampin-resistant TB that was previously unsuspected (table 2). All 9 of these patients reported symptomatic improvement after commencing standard TB treatment. For 1 of these patients (patient 8) (table 2), culture and DST at initial TB diagnosis revealed susceptibility to rifampin and isoniazid, but repeat DST performed for suspected TB IRIS revealed MDR TB.

Table 3 compares the baseline characteristics of the 4 diagnostic groups. No statistically significant differences existed in univariate analysis, with the exception of shorter duration from initiation of TB treatment to initiation of cART in the group of patients who received diagnoses of TB IRIS with no rifampin resistance, compared with those who were known to have rifampin-resistant disease when they presented with suspected TB IRIS (median, 68 days vs. 199 days; $P = .02$).

Table 4 shows clinical, radiological, and laboratory features of the TB IRIS episode for the 80 patients who received a final diagnosis of TB IRIS without rifampin resistance. The TB IRIS case definitions that were fulfilled are also shown. Many patients fulfilled >1 case definition, and frequently, TB IRIS involved >1 organ system. The most frequent TB IRIS symptoms among these 80 patients were constitutional (68 patients; 85%), including night sweats, malaise, anorexia, and weight loss; respiratory (48; 60%); and abdominal (47; 59%), including abdominal pain, nausea, vomiting, and diarrhea. The symptoms, signs, and radiological findings for the 9 patients with rifampin-resistant TB diagnosed after presentation with suspected TB IRIS did not differ significantly from those of the patients who had TB IRIS without rifampin-resistant TB, with the exception of more frequent presence of lymphadenopathy on chest radiograph (7 of 9 patients vs. 30 of 80 patients; $P = .03$). Blood investigations were also similar between the 2 groups, although for the 9 patients with rifampin-resistant TB, the median C-reactive protein level was higher (179 mg/L [IQR, 100–212 mg/L] vs. 96 mg/L [IQR, 70–152 mg/L]; $P = .05$). Purified protein derivative enzyme-linked immunospot assay demonstrated evidence of immune activation in both groups, although the degree was less in the patients with rifampin-resistant TB (figure 2).

DISCUSSION

In Cape Town, the triple coincidence of very high TB case notification rates, an expanding epidemic of HIV infection, and the large-scale roll-out of cART has led to a large increase in the number of cases of TB IRIS (to date, there are hundreds of cases) presenting at our health care service. We prospectively evaluated clinical case definitions for TB IRIS for 100 cases; this was, to our knowledge, the largest TB IRIS case series reported to date. Once patients with alternative conditions (7 patients) and known rifampin-resistant TB (4 patients) were excluded, 9 (10%) of the remaining 89 patients were found to have rifampin-resistant TB only after presenting with suspected TB IRIS. This has important implications for the diagnosis and treatment of HIV-infected patients with TB whose conditions deteriorate after the introduction of cART.

In the 9 patients with rifampin-resistant TB, presentation was suggestive of TB IRIS, with improvement while receiving TB treatment before initiation of cART and then deterioration during the weeks after the initiation of cART. The obvious question is whether the condition of the patients with drug-resistant TB deteriorated because of suboptimally treated TB, TB IRIS, or both? Our case definitions, which are similar to those used by other researchers [14, 15], classified known rifampin resistance as excluding TB IRIS. However, in light of our

observations, we propose that antitubercular drug resistance and TB IRIS are not mutually exclusive and may overlap in the same person. First, given that TB IRIS immunopathology is attributable to restored antigen-specific immunity to *M. tuberculosis* antigens [12], it is reasonable to conclude that TB IRIS may occur in response to drug-susceptible or drug-resistant strains, whether the latter are treated or untreated. The antigen stimulus for TB IRIS is unlikely to differ in these scenarios.

Second, in the 4 patients with known rifampin-resistant TB, all improved while receiving treatment for MDR TB, and then their conditions deteriorated after cART initiation. The deterioration of their conditions was most likely attributable to TB IRIS, given the timing. These patients may be at higher risk of TB IRIS than patients with rifampin-susceptible TB. *M. tuberculosis* bacillary load has been suggested as a risk factor for the condition [7], and even those patients who are effectively treated for MDR TB are likely to have slow bacillary clearance. This may partially account for our observation that these 4 patients developed TB IRIS despite a long interval between initiation of TB therapy and initiation of cART (table 3).

Third, 9 patients had undiagnosed rifampin-resistant TB when they presented with suspected TB IRIS. These patients all reported at least partial symptomatic response to standard TB treatment before the initiation of cART. It is possible for patients with MDR TB to initially respond to first-line TB treatment [27-29], either because the organism is sensitive to ethambutol and pyrazinamide or because the patient is dually infected with MDR TB and a susceptible strain [30]. In addition, patients may improve while receiving treatment for drug-susceptible TB and then be reinfected with drug-resistant TB, or the infecting organism may develop rifampin resistance during treatment. Either of these scenarios could have occurred for patient 8 (table 2). For these 9 patients who received a diagnosis of rifampin-resistant TB after presenting with suspected TB IRIS, symptomatic deterioration occurred 3–48 days after the initiation of cART—the characteristic timing of TB IRIS. The clinical and radiological features of these patients when they presented with suspected TB IRIS, with the exception of more frequent presence of lymphadenopathy on chest radiograph, were not significantly different from those of patients with TB IRIS with no drug resistance. We propose that TB IRIS exacerbated undiagnosed drug-resistant TB. Support for the idea that TB IRIS was present in this group comes from the enzyme-linked immunospot assay data, which showed expansions of purified protein derivative-specific IFN- γ -producing T cells (which are a reported characteristic of TB IRIS [12]), irrespective of drug susceptibility. The overlap of IRIS and drug resistance with respect to cryptococcal infection has been highlighted elsewhere [31].

Seven patients with suspected TB IRIS had alternative opportunistic diseases that explained their clinical deterioration. Patients with advanced immunosuppression may have multiple opportunistic conditions. A thorough examination for alternative infections and malignancies before diagnosis of TB IRIS is essential. Three patients receiving TB treatment at their local clinic actually had nontuberculous mycobacterial infection when the result of the original culture was followed up; this underscored the importance of reviewing the original TB diagnosis during the assessment of these patients. The performance of these case definitions may not be the same in settings with lower TB incidence rates, where patients might more frequently present with other reasons for deterioration.

Frequently, patients had signs, symptoms, and radiological manifestations suggestive of multiple organ system involvement with TB IRIS. This may be explained by profound immunosuppression (median nadir CD4 cell count, 50 cells/ μ L), predisposing to disseminated TB. The most frequent organ systems involved were the respiratory system (respiratory symptoms and chest radiograph infiltrates) and, hitherto little appreciated, the

abdominal organs. Of the 80 patients with TB IRIS with no rifampin resistance, 59% had abdominal symptoms; 56% had hepatomegaly, 9% had splenomegaly, and 5% had peritonism. Abdominal nodes were present in 77% of those who underwent ultrasonography. Liver function derangement, particularly a cholestatic pattern, was common. These findings suggest that, if patients develop abdominal symptoms or liver function derangement after commencing cART, TB IRIS should be considered in the differential diagnosis in addition to drug-related adverse effects, such as pancreatitis, lactic acidosis, and drug-induced hepatitis.

There were several limitations to our study. For most patients, the initial TB diagnosis had been made in primary care according to program guidelines, and only 41% of the cases were confirmed by culture. Most patients also initiated cART at the same facilities; thus, examination and radiographic data were incomplete. All patients had a chest radiograph performed to investigate TB IRIS, but few were performed at the time of cART initiation. In addition, patients who are smear positive do not routinely undergo chest radiography at TB diagnosis. Therefore, for many patients with symptoms of TB IRIS who had radiographic pulmonary infiltrates (65% had infiltrates), it was impossible to determine whether these were new or expanding, which potentially underestimated the number of cases fulfilling the pulmonary infiltrate case definition and, similarly, the serous effusion case definition. Many patients had hepatomegaly (56% of patients) with cholestatic liver derangement, which suggested granulomatous hepatitis [32], but this was only confirmed in 2 patients, because severity otherwise was insufficient to warrant a biopsy. The number of cases fulfilling the granulomatous hepatitis case definition might, for this reason, also be underestimated. It is for these reasons that the diagnosis of TB IRIS was made exclusively on the basis of a clear history of symptom improvement before the initiation of cART, followed by new, worsening, or recurrent TB symptoms after the initiation of cART in many patients (26% of patients). Follow-up CD4 cell count and HIV viral load measurements during cART were unavailable for one-quarter of the patients. These tests are performed every 6 months during cART under program conditions; however, many patients were transferred to other facilities, and some were lost to follow-up or died by 6 months. Determination of viral load or CD4 cell count at the time of TB IRIS diagnosis did not, however, form part of our case definitions. For patient 6 (table 2), the FASTplaque assay demonstrated rifampin resistance. This could not be confirmed by culture-based DST. The presence of nontuberculous mycobacterial coinfection in the patient's specimen may have affected the FASTplaque result, but it is worth noting that the specimen was culture positive for *M. tuberculosis* after 7 months of TB treatment; this supported a diagnosis of rifampin-resistant TB.

Corticosteroids have been proposed as a treatment for TB IRIS, although the only evidence currently available is anecdotal [17]. There are potential risks of corticosteroid treatment for HIV-infected patients with TB, including herpes virus reactivation and Kaposi sarcoma [33, 34]. There is no present clinical trials evidence supporting the use of corticosteroids for the treatment of TB IRIS, other than for TB meningitis and, perhaps, pericardial disease (neither with evidence in the context of cART [35, 36]). Assessment of suspected TB IRIS should trigger re-evaluation of the TB diagnosis and the adequacy of antimicrobial therapy. Such assessment should occur before the instigation of corticosteroid therapy; otherwise, there is a risk that patients who remain deeply immunosuppressed (despite IRIS) may receive steroid therapy without adequate antimicrobial coverage. Our study highlights the pressing need to develop and implement rapid techniques to diagnose drug resistance that are appropriate to resource-limited conditions. The use of the FASTplaque assay in the present study was an attempt to overcome this problem, and there are encouraging data emerging from other studies of rapid tests [37]. Overall, our data also support the use of routine DST for HIV-infected patients with TB.

Acknowledgments

We thank Priscilla Mouton, for her contribution to clinical characterization and care of patients; Keira Skolimowska and Ronnett Seldon, for technical assistance with enzyme-linked immunospot assays; the primary care doctors who referred patients; and Shireen Grimwood, Vanessa January, and Andrew Whitelaw, who conducted the FASTplaque-Response assays.

Financial support. Medical Research Council of South Africa, Wellcome Trust (081667 and 072070), European and Developing Countries Clinical Trials Partnership award (060613 to M.X.R.), and Perinatal HIV Research Unit from the United States Agency for International Development and President's Emergency Plan for AIDS Relief (to D.J.P.).

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Figure 1.

Final diagnosis for 100 patients with suspected cases of tuberculosis (TB) immune reconstitution inflammatory syndrome (IRIS). MDR, multidrug resistant; NTM, nontuberculous mycobacteria.

Figure 2.

Comparison of purified protein derivative enzyme-linked immunospot assay results for 33 patients with tuberculosis (TB) immune reconstitution inflammatory syndrome (IRIS) with no rifampin (RIF) resistance (median, 1047 spot-forming cells [SFC] $\times 10^6$ PBMCs; interquartile range, 417–1700 SFC $\times 10^6$ PBMCs) with those for 5 patients who received a diagnosis of RIF-resistant TB after presenting with TB IRIS (median, 529 SFC $\times 10^6$ PBMCs; interquartile range, 89–680 SFC $\times 10^6$ PBMCs; $P = .04$).

Table 1
Case definitions for tuberculosis (TB) immune reconstitution inflammatory syndrome (IRIS).

Criteria that must be met for the diagnosis of TB IRIS before the initiation of cART
Microbiologic, histologic, or very strong clinical evidence of TB
Initial improvement of 1 of the following during multidrug TB treatment: symptoms, Karnofsky score, weight, fever, clinical signs, or radiographic findings
The infecting strain of <i>Mycobacterium tuberculosis</i> is susceptible to rifampin (if this result is available)
The patient was receiving antitubercular therapy when cART was initiated
Criteria that must be met for the diagnosis of TB IRIS within 3 months after the initiation of cART
New or recurrent TB-related symptoms and/or
New or worsening TB manifestations, such as 1 of the following:
New or expanding lymph nodes
New or expanding tuberculous cold abscesses
New or expanding intracranial tuberculomas
New or expanding pulmonary infiltrates (radiographically confirmed)
New or recurrent tuberculous meningitis (after exclusion of bacteria and fungi)
New or enlarging serous effusions (pericardial, pleural, or ascitic; radiographically confirmed)
New or worsening granulomatous hepatitis
New or worsening granulomatous infiltration of bone marrow
Other new or worsening tuberculous lesions
No other opportunistic disease to explain the new or recurrent symptoms and/or new or worsening TB manifestations

Table 2
Cases of rifampin-resistant tuberculosis (TB) diagnosed after presentation with suspected TB immune reconstitution inflammatory syndrome (IRIS).

Patient	Age, years	Sex	Nadir CD4 cell count, cells/ μ L	Previous TB	Initial TB diagnosis	Course of events	TB IRIS manifestations
1	24	F	94	No	Pleural and pulmonary; not confirmed microbiologically	Symptoms improved and pleural effusion decreased while receiving Rif, INH, Pza, and Eth; started cART 8 weeks later; suspected TB IRIS onset 14 days later; sputum culture negative for TB twice at IRIS onset; sputum and pleural aspirate samples from 8–10 weeks after IRIS onset grew MDR <i>M. tuberculosis</i>	Recurrent constitutional, respiratory, and abdominal symptoms; fever and weight loss; cervical node enlargement, hepatomegaly; CXR showed progressively worsening nodular infiltrates and enlarging pleural effusion
2	29	F	16	No	Disseminated (pulmonary infiltrates on CXR and ascites on ultrasound); not confirmed microbiologically	Started on Rif, INH, Pza, and Eth; symptoms improved; started cART 13 weeks later; suspected TB IRIS onset 39 days later; bronchoscopy performed 8 weeks later (bronchial brushings grew MDR TB); thereafter, ongoing IRIS manifestations despite MDR TB treatment	High fevers, weight loss, and abdominal and constitutional symptoms; right hilar node enlargement on CXR with bronchial compression (on bronchoscopy); new right middle lobe infiltrate on CXR; enlarging cervical nodes
3	26	F	44	Yes	Disseminated; lymphadenopathy and hepatosplenomegaly on abdominal ultrasound; urine sample culture positive for <i>Mycobacterium tuberculosis</i> ; DST not requested at the time	Started Rif, INH, Pza, Eth, and Sm; reported 2-kg weight gain, and CRP level decreased (202 to 69 mg/L); started cART 1 month later; 5 days later, developed suspected TB IRIS; DST requested on initial urine isolate revealed Rif monoresistance	Abdominal pain, constitutional symptoms, and weight loss; progressively enlarging hepatomegaly; cervical node enlargement, para-umbilical cold abscess, peritonism, and marked tachycardia
4	51	F	35	No	Pulmonary; sputum sample cultured for <i>M. tuberculosis</i> ; DST not performed at the time	Symptomatic improvement while receiving Rif, INH, Pza, and Eth (cough and night sweats resolved, and patient felt stronger); started cART 2 months later; 7 days later, developed suspected TB IRIS; lymph node aspirate culture positive for MDR <i>M. tuberculosis</i>	Constitutional symptoms, marked weight loss, and respiratory symptoms; cervical node enlargement; CXR showed pulmonary infiltrates and enlarging thoracic nodes
5	31	F	3	No	Disseminated (CXR revealed pulmonary infiltrates and cervical adenitis); lymph node aspirate smear positive and sputum culture positive for <i>M. tuberculosis</i> ; no DST performed at the time	Initially improved while receiving Rif, INH, Pza, and Eth (night sweats resolved and general condition improved); then had chronic diarrhea followed by recurrent TB symptoms prior to cART; started cART 4 months after TB treatment; 3 days later, began deteriorating more rapidly, requiring admission; sputum culture positive for MDR <i>M. tuberculosis</i>	Recurrent cough; constitutional and abdominal symptoms; new pulmonary infiltrates with cavitation on CXR
6	24	M	47	No	Disseminated; CXR revealed pulmonary infiltrates; abdominal ultrasound showed lymphadenopathy and splenic microabscesses; urine sample culture positive for <i>M. tuberculosis</i> ; no DST was performed at the time	Reported symptomatic improvement while receiving Rif, INH, Pza, and Eth; started cART 6 months after TB treatment; 29 days later, developed suspected TB IRIS; node aspirate grew <i>M. tuberculosis</i> and NTM; thus, formal DST could not be done; FASTplaque demonstrated Rif resistance	Constitutional symptoms, fever, new axillary lymphadenopathy, and tender hepatomegaly with jaundice
7	28	F	187	Yes ^a	Pulmonary (smear positive)	Started receiving Rif, INH, Pza, Eth, and Sm with some adherence lapses, but symptomatically better when started cART 5 months later; 7 days after	Fever and constitutional symptoms; pulmonary infiltrates on CXR

Patient	Age, years	Sex	Nadir CD4 cell count, cells/ μ L	Previous TB	Initial TB diagnosis	Course of events	TB IRIS manifestations
8	28	F	103	No	Disseminated; abdominal ultrasound showed lymphadenopathy and splenic microabscesses; sputum culture positive for <i>M. tuberculosis</i> ; susceptible to Rif and INH	starting cART, developed suspected TB IRIS; sputum culture positive for MDR <i>M. tuberculosis</i> Symptomatically improved while receiving Rif, INH, Pza, and Eth, with reported weight gain; 6 weeks after TB treatment, started cART; developed suspected TB IRIS 13 days later; then sputum culture positive for MDR <i>M. tuberculosis</i>	Respiratory, abdominal, and constitutional symptoms; weight loss, fever, and tachycardia; peritonism on examination; cervical node enlargement; CXR showed progressive pulmonary infiltrates and enlarging thoracic nodes
9	31	M	12	Yes ^a	Disseminated; CXR revealed pulmonary infiltrates and CSF smear positive for acid-fast bacilli; patient also received a diagnosis of cryptococcal meningitis before initiation of cART	Symptomatically improved while receiving treatment for TB and cryptococcal meningitis prior to cART; 48 days after starting cART, developed suspected TB IRIS; sputum culture positive for MDR <i>M. tuberculosis</i>	Respiratory and constitutional symptoms, weight loss, and headaches; hepatomegaly; CXR showed infiltrates with cavitation; CSF showed worsened lymphocytic meningitis that could have been due to TB or cryptococcal IRIS

NOTE. cART, combined antiretroviral therapy; CRP, C-reactive protein; CXR, chest radiograph; DST, drug susceptibility testing; Eth, ethambutol; INH, isoniazid; MDR, multidrug resistant; NTM, nontuberculous mycobacteria; Pza, pyrazinamide; Rif, rifampin; Stm, streptomycin.

^aPreviously defaulted TB treatment.

Table 3
Characteristics of the cohort.

Characteristic	Patients			
	Received a diagnosis of TB IRIS without Rif resistance (n = 80)	Presented with suspected TB IRIS and then received a diagnosis of Rif-resistant TB (n = 9)	Known to have Rif-resistant TB at presentation with suspected TB IRIS (n = 4)	Presented with suspected TB IRIS and then received a diagnosis of an alternative OD (n = 7)
Female sex	52 (65)	7 (78)	1 (25)	6 (86)
Age, years	31 (27–36)	29 (26–31)	31 (28–35)	30 (24–34)
Previous TB	18 (23)	3 (33)	2/3 (67)	3 (43)
Prior cART ^a	4 (5)	1 (11)	1 (25)	0 (0)
WHO clinical stage ^b				
3	28 (35)	2 (22)	0 (0)	2 (29)
4	52 (65)	7 (78)	4 (100)	5 (71)
cART regimen at assessment				
d4T, 3TC, and EFV	64 (80)	8 (89)	4 (100)	6 (86)
Other	16 (20)	1 (11)	0 (0)	1 (14)
TB disease form ^c				
Pulmonary	36 (45)	3 (33)	2 (50)	3 (43)
Extrapulmonary	44 (55)	6 (67)	2 (50)	4 (57)
Time from start of TB treatment to start of cART, days	68 (35–93)	84 (47–115)	199 (121–447)	69 (21–125)
Time from start of cART to TB IRIS onset, days	14 (8–23)	13 (7–29)	35 (17–45)	35 (7–52)
Baseline CD4 cell count, cells/ μ L	50 (26–94) ^d	44 (16–94)	84 (55–184)	72 (13–85)
Baseline viral load measured	61 (76)	5 (56)	0 (0)	5 (71)
Baseline viral load, value $\times 10^5$ copies/mL	2.1 (9.8– 5.0)	1.7 (1.4–5.6)	...	2.5 (1.1–5.0)

NOTE. Data are no. (%) of patients or median value (interquartile range). cART, combination antiretroviral therapy; d4T, stavudine; EFV, efavirenz; IRIS, immune reconstitution inflammatory syndrome; OD, opportunistic disease; Rif, rifampin; TB, tuberculosis; 3TC, lamivudine; WHO, World Health Organization.

^aExcludes patients who received single-dose nevirapine for prevention of mother-to-child transmission.

^bWHO staging includes current TB diagnosis.

^cThe pulmonary TB category includes patients who had pulmonary TB only, and the extrapulmonary TB category includes patients with extrapulmonary TB only and those with both pulmonary TB and extrapulmonary TB.

^dSeventy-nine of these 80 patients had a baseline CD4 cell count available.

Table 4
Clinical, radiographic, and laboratory features of tuberculosis (TB) immune reconstitution inflammatory syndrome (IRIS) in 80 patients who received a diagnosis of TB IRIS without rifampin resistance.

Variable	Patients
TB IRIS case definitions fulfilled	
New, recurrent, or worsening symptoms	80 (100)
New or worsening TB manifestations	59 (74) ^a
New or expanding lymph nodes	35 (44)
New or expanding cold abscesses	3 (4)
New or expanding intracranial tuberculomas	1 (1)
New or expanding pulmonary infiltrates	22 (28)
New or recurrent TB meningitis ^b	6 (8)
New or enlarging serous effusions	13 (16)
New or worsening granulomatous hepatitis	2 (3)
New or worsening granulomatous bone marrow infiltrate	5 (6)
Other new or worsening TB lesion ^c	3 (4)
Other physical signs	
Fever (temperature, >37.4°C)	31 (39)
Hepatomegaly	45 (56)
Splenomegaly	7 (9)
Peritonism	4 (5)
New neurological signs	7 (9)
Radiographic features	
On chest radiograph	
Pulmonary infiltrates	52/80 (65)
Hilar/mediastinal nodes	30/80 (38)
Pleural effusion	17/80 (21)
On ultrasound	
Abdominal nodes	27/35 (77)
Ascites	10/35 (29)
Pericardial effusion	10/35 (29)
Focal splenic lesions	7/35 (20)
On CT: head lesions	3/8 (38) ^d
Laboratory features	
Total bilirubin level, $\mu\text{mol/L}$ ($n = 13$) ^e	54 (16–103) [0–21]
Alkaline phosphatase level, IU/L ($n = 56$)	181 (103–326) [40–120]
Alanine aminotransferase level, IU/L ($n = 62$)	41.5 (28–59.8) [5–40]
γ -Glutamyl transferase level, IU/L ($n = 15$)	217 (152–482) [0–35]
Hemoglobin level, g/dL ($n = 73$)	9.1 (7.8–10) [M: 13.0–17.0; F: 12.0–15.0]
WBC count, value $\times 10^9$ cells/L ($n = 71$)	5.4 (3.7–8.7) [4.0–10.0]
Platelet count, value $\times 10^9$ cells/L ($n = 65$)	362 (268–462) [178–400]

Variable	Patients
C-reactive protein level, mg/L (<i>n</i> = 72)	96 (70–152) [0–10]
C-reactive protein level >10 mg/L (<i>n</i> = 72)	71 (99)

NOTE. Data are no. (%) of patients or median value (interquartile range) [reference range].

^aThe other 21 patients fulfilled only the case definition relating to new, worsening, or recurrent symptoms.

^bTB IRIS meningitis was defined as ≥ 5 lymphocytes and/or polymorphs in a CSF sample from a patient with new or recurrent meningism or other new neurological symptoms after exclusion of bacterial and fungal meningitis.

^cThe other manifestations were arthritis (in 2 patients) and bursitis (in 1 patient).

^dEight patients had CT performed: tuberculomas were shown for 1 patient and a new infarct (in 1 patient) and hydrocephalus (in 1 patient) were shown for the others.

^eBilirubin level measurement was performed mainly for those patients in whom jaundice was clinically apparent. Nine of the 13 patients who had their bilirubin level measured had a total bilirubin level $>21 \mu\text{mol/L}$.