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Frequency, severity and duration of immune reconstitution events in HIV-related tuberculosis

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SUMMARY

SETTING: Patients were enrolled in a prospective trial of rifabutin-based tuberculosis (TB) treatment for human immunodeficiency virus related TB. Antiretroviral therapy (ART) was encouraged, but not required.

OBJECTIVE: To evaluate the frequency, risk factors and duration of immune reconstitution events.

DESIGN: Patients were prospectively evaluated for immune reconstitution events, and all adverse event reports were reviewed to identify possible unrecognized events.

RESULTS: Of 169 patients, 25 (15%) developed immune reconstitution events related to TB. All 25 were among the 137 patients who received ART during TB treatment, so the frequency in this subgroup was 18% (25/137). Risk factors for an immune reconstitution event in multivariate analysis were Black race, the presence of extra-pulmonary TB and a shorter interval from initiation of TB treatment to initiation of ART. The most common clinical manifestations were fever (64%), new or worsening adenopathy (52%) and worsening pulmonary infiltrates (40%). Twelve patients (48%) were hospitalized for a median of 7 days, six underwent surgery and 11 had needle aspiration. The median duration of events was 60 days (range 11–442).

CONCLUSION: Immune reconstitution events were common among patients receiving ART during TB treatment, produced substantial morbidity and had a median duration of 2 months.

KEY WORDS: tuberculosis; HIV; antiretroviral therapy; immune reconstitution

MOST PATIENTS with human immunodeficiency virus (HIV) related tuberculosis (TB) have advanced HIV disease,[1–4] and there is substantial risk of death or new opportunistic illnesses during and soon after TB treatment.[5–7] Use of antiretroviral therapy (ART) during TB treatment has been associated with marked decreases in HIV-related morbidity and mortality.[7,8] While the immune restoration following effective ART reduces the risk of HIV disease progression, it can also result in exacerbation in the clinical manifestations of TB, termed immune reconstitution inflammatory syndrome (IRIS).[9,10] These exacerbations appear to be due to an exaggerated immune response to antigens of *Mycobacterium tuberculosis*.[10,11] Because TB is the most common opportunistic infection worldwide, IRIS events are particularly important in the roll-out of ART to high-burden countries.

Previous studies of IRIS events among patients with HIV-related TB have been limited by relatively small sample sizes and their retrospective design. We prospectively evaluated IRIS events among patients enrolled in a trial of rifabutin (RBT) based TB treatment for HIV-related TB.

STUDY POPULATION AND METHODS

Participants

Patients with HIV-related TB were enrolled in Tuberculosis Trials Consortium Study 23. The primary results of the trial have been reported elsewhere.[8] Patients aged ⩾18 years with HIV infection and culture-confirmed TB were treated with supervised short-course TB treatment, with RBT substituted for rifampicin (RMP). After completion of the first 2 months of TB treatment, therapy was given twice weekly to complete a total of 6 months (9 months for patients

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with a delayed microbiological or clinical response or resistance to isoniazid or pyrazinamide).[12] Study visits were monthly during TB treatment and at 1.5, 3, 6, 12, 18 and 24 months after completing TB treatment.

Use of ART during TB treatment was strongly encouraged but not required; the regimen and the timing of its initiation were at the discretion of the treating clinician. RBT doses were adjusted per United States national guidelines: 600 mg for patients on efavirenz (EFV), 300 mg for patients on nelfinavir and 150 mg for patients on ritonavir-boosted protease inhibitors.[13]

The study protocol was approved by the Institutional Review Boards of the Centers for Disease Control and Prevention and local study sites. All patients provided written informed consent.

Laboratory testing

CD4 lymphocyte counts were determined at certified local laboratories on enrollment, and then at 2, 6 and 12 months after starting TB treatment and at the time of a suspected IRIS event; HIV RNA levels were obtained at the same time as CD4 lymphocyte counts and were measured at a central laboratory (VERSANT® HIV-1 RNA 3.0 Assay [bDNA], Bayer HealthCare LLC, Berlin, Germany).

Definition, identification and grading of severity of immune reconstitution events

IRIS events were defined as exacerbations in symptoms, signs, or laboratory or radiographic manifestations of TB not due to TB treatment failure or another process (infection, malignancy or drug reaction). Before the study, investigators were informed of common manifestations of IRIS and suspected events were reported prospectively. At the time of a suspected IRIS event, mycobacterial cultures (if the site was accessible), a CD4 lymphocyte count and an HIV RNA level were obtained. A committee reviewed all adverse event reports occurring during TB treatment to detect IRIS events that may not have been identified as such by site investigators. Events were graded using the toxicity scale of the National Cancer Institute.[14]

Data analysis

Because all IRIS events occurred among patients who received ART during TB treatment, we restricted the analysis of risk factors to patients who received ART during TB treatment. Categorical variables were compared using the χ^2 test and continuous variables using Wilcoxon signed rank tests. In analyses of risk factors for IRIS events, factors associated with $P < 0.20$ in univariate analysis were included in a multivariate logistic regression model using backwards selection. Analyses were performed using the Epi Info (version 6.04, CDC, Atlanta, GA, USA) and SAS (version 8.2, SAS Institute Inc, Cary, NC, USA) software packages.

RESULTS

Study population

Between March 1999 and February 2002, 169 patients were enrolled. Study participants were mostly men (133, 79%) and had a median age of 40 years (interquartile range [IQR] 34–46 years). Most had advanced HIV disease; at the time of enrollment, the median CD4 lymphocyte count was 90 cells/mm^3 and the median HIV RNA level was 5.3 $\log_{10}$ copies/ml.

Twenty-five patients developed 27 IRIS events. Two of these events were thought to be related to infections other than TB (one disseminated coccidioidomycosis and one exacerbation of oral human papilloma virus infection). This analysis focuses on the 25 IRIS events thought to be related to TB. All IRIS events occurred among patients on ART during TB treatment (25/137, 18%, 95% confidence interval [CI] 12–26, compared with 0/32 patients not on ART during TB treatment, $P < 0.01$). Of the 137 patients who received ART during TB treatment, 21 were on ART at the time that TB treatment was started, and an additional 109 patients started ART during TB treatment; seven patients had an uncertain date of ART initiation. All 25 IRIS events related to TB occurred after ART had been started.

Antiretroviral therapy

The median time from starting TB treatment to the onset of an IRIS event was 69 days (IQR 55–87). Six of the 25 IRIS events (24%) occurred among patients who had started ART before starting TB treatment. Among the 21 patients who began ART before the start of TB treatment, there were two (22%) IRIS events among the nine starting ART >60 days before TB treatment (median 661 days, range 174–1242) and four (33%) IRIS events among the 12 starting ART within 60 days of TB treatment (median 31 days, range 6–57).

Among 109 patients who started ART during TB treatment, the median time from starting ART to the onset of IRIS was 34 days (IQR 8–97); the shortest time from antiretroviral initiation to IRIS was 3 days. The median change in CD4 cell count between the start of TB treatment and the onset of an IRIS event was 0 cells/mm^3 (IQR −8–78); the median change in HIV RNA level was a decrease of 1.8 $\log_{10}$ copies/ml (IQR −2.9–−0.2).

Risk factors for an IRIS event

In an analysis limited to the 109 patients who started ART during TB treatment, factors associated with IRIS in univariate analysis were Black race, extra-pulmonary TB and starting ART sooner in the course of TB treatment ($P < 0.20$) (Table 1). There was no statistically significant association between CD4 cell count and viral load at the time of the diagnosis of TB with development of IRIS events.

Table 1 Factors associated with immune reconstitution events related to tuberculosis among patients who received ART during tuberculosis treatment (univariate analysis)

Characteristics	Patients with an immune reconstitution event (n = 25) n (%)	Patients without an immune reconstitution event (n = 112) n (%)	P value
Demographic factors			
Median age (IQR)	39 (35–49)	40 (33–46)	0.84
Male	19 (76)	91 (81)	0.55
Race/ethnicity			
Hispanic	6 (24)	48 (43)	0.08
White, non-Hispanic	1 (4)	15 (13)	0.30
Black	16 (64)	44 (39)	0.02
Native American	0	2 (2)	1.00
Asian/Pacific Islander	2 (8)	3 (3)	0.23
Born outside the US and Canada	13 (52)	61 (54)	0.82
Body mass index at TB diagnosis, median (IQR)	21.1 (17.8–23.3)	21.6 (18.4–24.1)	0.58
Aspects of TB			
Site of TB involvement			
Pulmonary only	9 (36)	63 (56)	0.07
Any extra-pulmonary	16 (64)	49 (44)	
Cavitation on chest radiograph, n (% of those with pulmonary involvement)	3 (14)	15 (16)	1.00
Bilateral lung involvement on chest radiograph, n (% of those with pulmonary involvement)	3 (14)	14 (15)	1.00
Tuberculosis treatment			
Use of twice-weekly therapy during intensive phase	11 (46)	48 (43)	0.79
Sputum culture positive at 2 months, n (% of those with pulmonary involvement)	0	3 (3)	1.00
Aspects of HIV/ART			
Median CD4 cell count at TB diagnosis (IQR)	61 (35–128), (n = 20)	88 (30–175), (n = 98)	0.46
Median HIV RNA level at TB diagnosis (IQR)	5.6 (5.1–5.8), (n = 18)	5.3 (4.8–5.7), (n = 74)	0.27
Time from start of TB therapy to start of ART, days (IQR), among those started on ART*	56 (23–70), (n = 19)	68 (21–113), (n = 90)	0.19
Type of antiretroviral therapy (among those started on ART)			
Two nucleosides + protease inhibitor	11 (44)	59 (53)	0.43
Two nucleosides + EFV or nevirapine	12 (48)	44 (39)	0.42
Triple class regimen	2 (8)	9 (8)	1.00
Response to ART during the first 12 months after TB diagnosis			
Change in CD4 cell count, median (IQR)	147 (80–236), (n = 16)	106 (21–170), (n = 73)	0.10
Change in viral load decrease ($\log_{10}$), median (IQR)	−2.19 (−3.89–−0.65), (n = 10)	−2.74 (−3.50–−0.92), (n = 36)	0.85

* This analysis does not include the 6 patients with immune reconstitution events and the 15 without immune reconstitution events who were on ART at the time TB treatment was started and the 7 patients without immune reconstitution events for whom an accurate date for the initiation of ART could not be determined.

ART = antiretroviral treatment; IQR = interquartile range; TB = tuberculosis; HIV = human immunodeficiency virus; EFV = efavirenz.

In multivariate analysis, Black race (odds ratio [OR] 3.80, 95%CI 1.40–10.28, P = 0.009), extra-pulmonary involvement (OR 2.51, 95%CI 0.91–6.90, P = 0.07) and a shorter time from TB treatment to the initiation of ART were associated with IRIS (OR for each 10 days earlier 1.11, 95%CI 1.00–1.22, P = 0.04, Figure 1).

Patients who had IRIS events had similar changes in CD4 lymphocyte count and HIV RNA levels in the year after TB diagnosis compared to those who did not have IRIS (Table 1). The risk of TB treatment failure or relapse was similar among those patients who did and did not have IRIS (4% and 6%, P = 1.00).

Manifestations and severity of immune reconstitution events

The most common clinical manifestations of IRIS were fever (64%), new or worsening adenopathy

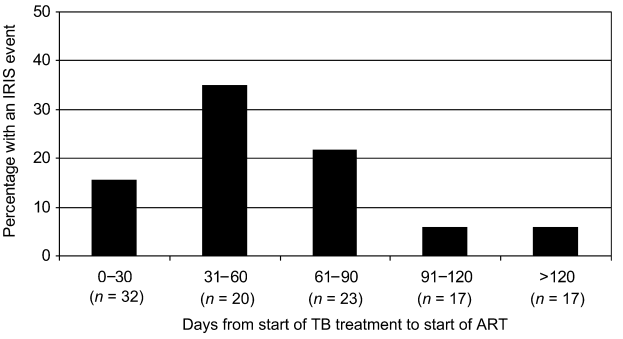

Figure Association between timing of ART (days from starting TB treatment to the initiation of ART) and risk of an immune reconstitution event. Twenty-one patients who started ART before TB treatment and 7 patients whose start date for ART was not known with certainty are not included in this figure. IRIS = immune reconstitution inflammatory syndrome; ART = antiretroviral treatment; TB = tuberculosis.

Table 2 Details of patients developing immune reconstitution events thought to be related to tuberculosis

Patient number	Clinical/radiographic manifestations	Maximum toxicity grade*	Hospitalized for management	Surgery or needle aspiration	Corticosteroid treatment used (initial dose)	Duration of immune reconstitution event, days
1	Fever, cervical and axillary adenopathy, pulmonary infiltrates	4	Yes, twice	Yes, multiple times	No	229
2	Axillary adenopathy	3	Yes	Yes	Yes	442
3	Cervical adenopathy	1	No	Yes	No	96
4	Cervical adenopathy, pulmonary infiltrates	1	No	Yes	No	98
5	Fever, cervical and axillary adenopathy	3	No	Yes	No	91
6	Subcutaneous abscess	3	No	No	No	21
7	Cervical adenopathy	1	Yes	No	No	99
8	Fever, adenopathy (multiple sites), subcutaneous abscesses, pulmonary infiltrates	4	No	Yes, multiple times	Yes (dosage not available)	511
9	Supraclavicular adenopathy	1	No	Yes, multiple times	No	100
10	Fever, pulmonary infiltrates	3	No	No	No	60
11	Fever, pulmonary infiltrates	1	No	No	No	58
12	Fever, cervical adenopathy	3	No	Yes, multiple times	Yes (10 mg)	142
13	Fever, pulmonary infiltrates	4	Yes	No	No	82
14	Fever, pulmonary infiltrates	3	Yes	No	No	42
15	Fever, pulmonary infiltrates	4	No	Yes	No	45
16	Fever, axillary adenopathy	2	No	Yes	No	67
17	Fever, pulmonary infiltrates	3	Yes	No	No	39
18	Expanding brain lesion	5 (death)	Yes	Yes	No	37
19	Fever, cervical adenopathy	3	Yes	Yes	Yes (dosage not available)	11
20	Fever, pulmonary infiltrates	4	Yes	No	Yes (20 mg)	49
21	Fever, supraclavicular and cervical adenopathy	4	No	Yes	No	313
22	Fever, pulmonary infiltrates	4	Yes	No	No	23
23	Cervical adenopathy	1	No	No	No	67
24	Fever, pulmonary infiltrates	4	Yes	No	No	48
25	Axillary and cervical adenopathy	1	No	No	No	55

* Per toxicity grading scale of the National Cancer Institute.[14]

(52%) and worsening pulmonary infiltrates (40%) (Tables 2 and 3). Of the nodal IRIS events, eight patients had more than one enlarging lymph node. Nodal IRIS events involved peripheral (cervical, axillary, ilioinguinal) as well as central lymph nodes (intra-thoracic or intra-abdominal); nodal IRIS events also occurred at sites not clinically involved at the time of the initial presentation of active TB.

IRIS events had a range of severity, as measured by the National Cancer Institute (NCI) toxicity scale (Table 4).[14] We defined 'severe IRIS' as grade 4 severity or which resulted in hospitalization or death. Using this definition, 16 IRIS events (64%) were severe. Twelve patients (48%) were hospitalized for a median duration of 7 days as a result of IRIS. Patients with severe events were more often Black. There were no differences in baseline CD4 cell count or the timing of ART (Table 5).

One death was attributed to IRIS (4% of patients who had IRIS, 0.7% of patients who received ART

Table 3 Summary of clinical manifestations of immune reconstitution events and their frequency among the 25 patients with event related to tuberculosis

Clinical manifestations	*n* (%)
Systemic symptoms (fever, malaise)	16 (64)
New or worsening lymphadenopathy	13 (52)
Single anatomic site	9 (36)
Multiple sites	4 (16)
Increasing pulmonary infiltrates	10 (40)
Enlarging brain lesion	1 (4)
Multiple manifestations	18 (72)

Table 4 Severity and duration of immune reconstitution events

	Immune reconstitution events *n* (%)
NCI toxicity scale	
Grade 1	7 (28)
Grade 2	1 (4)
Grade 3	7 (28)
Grade 4 or 5	10 (40)
Hospitalization	12 (48)
Median duration, days (IQR)	7 (3–12, range 3–66)
Severe immune reconstitution event (grade 4, death and/or hospitalization	16 (64)
Median duration of initial immune reconstitution event, days (IQR)	60 (45–98, range 11–442)

NCI = National Cancer Institute; IQR = interquartile range.

Table 5 Comparison of demographic and clinical characteristics of patients with severe immune reconstitution events (Grade 4,* death or hospitalization) vs. those of patients with less severe immune reconstitution events (Grades 1–3)*

Characteristic	Severe immune reconstitution event (n = 16)	Non-severe immune reconstitution event (n = 9)	P value
Age, years (IQR)	35 (35–49)	41 (34–48)	0.71
Male/female, n	12/4	7/2	1.00
Race/ethnicity, n (%)			
Hispanic	3 (19)	3 (33)	0.63
White, non-Hispanic	0	1 (11)	0.36
Black	13 (81)	3 (33)	0.03
Other	0	2 (22)	0.12
Site of TB involvement, n (%)			
Pulmonary only	4 (25)	5 (56)	
Any extra-pulmonary	12 (75)	4 (44)	0.20
Median CD4 cell count at TB diagnosis (IQR)	66 (29–130), (n = 12)	57 (37–123), (n = 8)	0.82
Median HIV RNA level at TB diagnosis (IQR)	5.6 (4.8–5.9)	5.5 (5.2–5.8)	0.89
Time from start of TB therapy to start of ART, days (IQR)†	56 (23–61)	63 (53–83)	0.36

* Grades per the toxicity grading scale of the National Cancer Institute.[14]
† Does not include the 6 patients with immune reconstitution events who were on ART at the time TB treatment was started.
IQR = interquartile range; HIV = human immunodeficiency virus; ART = antiretroviral treatment; TB = tuberculosis.

during TB treatment). This patient presented with disseminated, drug-susceptible TB and advanced acquired immune-deficiency syndrome (CD4 cell count 36 cells/mm^3, HIV RNA level 5.62 $\log_{10}$ copies/ml). He was started on ART between 49 and 56 days after starting TB treatment, and 1–8 days later he developed an expanding intracerebral mass lesion. Despite empiric treatment for toxoplasmic encephalitis, the lesion did not resolve and the patient died 37 days after the onset of this event. The mass was not biopsied and an autopsy was not performed.

Management of IRIS events

Six patients underwent surgical drainage for nodal or soft-tissue abscesses. Needle aspiration was used to drain abscesses in 11 patients, four of whom had multiple needle aspirations (up to 108 aspirations). Four patients were treated with corticosteroids; three patients had fever and worsening adenopathy and one had fever and chest pain (Table 2). The median overall duration of IRIS events was 60 days (IQR 45–98 days, range 11–442). Five IRIS events (20%) continued after the completion of TB treatment.

DISCUSSION

In this prospective study, IRIS events were common, relatively severe and prolonged, lasting a median of 2 months. Because of the localized suppuration caused by these events, surgical procedures and needle aspiration were commonly required and some patients had multiple drainage procedures. The risk factors for the occurrence of IRIS were Black race, presence of extra-pulmonary manifestations of TB and earlier initiation of ART.

The association between the use of ART and the risk of IRIS has been consistently noted.[10,15] The frequency of IRIS among patients starting ART during TB in our study (18%) is within the broad range reported from previous studies (11–42%).[10,16–22] Our study is distinguished by its prospective nature, by a comprehensive review of suspected events and other adverse events to detect IRIS events and by the use of established criteria for grading the severity of events.

Extra-pulmonary manifestations of TB have been a risk factor for IRIS in several previous studies,[15,16,21] and a similar trend was present in our study. Although the association was not statistically significant in all studies, baseline CD4 lymphocyte counts were somewhat lower among patients with IRIS in this and previous studies.[10,15,16,18,22] Black race was associated with IRIS in our study and, among patients with immune reconstitution events, Black race was also associated with more severe events. Previous studies have not identified an association between race and the risk of an IRIS event,[15,17] and we are uncertain of the explanation for this association in our study. Starting ART earlier in the course of TB treatment was a risk factor for IRIS in this and several previous studies,[15,17,19,22] although this association was not found in studies from India and Thailand.[20,21]

For simplicity, our multivariate analysis was restricted to patients who began ART after starting TB treatment. However, we did assess the small number of patients who reported beginning ART before TB treat-

ment and found a high rate of IRIS among them (6/21, 29%). As described by others,[23,24] we found two subgroups of such patients: nine who began ART at least 6 months earlier and 12 who began ART within 2 months of the start of TB treatment. This latter subgroup may represent persons with subclinical TB, whose disease was rendered clinically identifiable by ART.

Fever, suppurative adenopathy and increased pulmonary infiltrates were the most common clinical manifestations of IRIS in this and previous studies. Because of their retrospective nature, previous reports have not quantified the severity of IRIS events in a uniform manner, although there are numerous reports of severe events[16,25–28] and several reported fatal events.[21,22] In a previous study, patients with IRIS events related to TB, *M. avium* complex disease or cryptococcosis were more often hospitalized and underwent surgical procedures than did controls who had these infections but did not have IRIS.[17] The duration of IRIS events was 7–64 days in the initial report of this syndrome;[10] subsequent studies have not reported duration in a uniform manner. In our study, IRIS events were often prolonged, lasting a median of 2 months. The prolonged inflammatory response in some patients is probably related to the persistence of mycobacterial antigens in tissues.[29]

As in previous studies,[16,17,30] suppurative adenitis and other soft-tissue abscesses often resulted in surgical or needle drainage procedures; these procedures provided symptomatic relief and appeared to be safe. Adjunctive corticosteroids were used in the management of IRIS at the discretion of site investigators, but the limited observational data from our study do not provide answers to the many questions that remain regarding the effectiveness and safety of corticosteroids in the management of immune reconstitution events.

The decision of when to initiate ART in patients being treated for active TB is complex.[31,32] With the expansion of ART in areas of the world with very high TB rates, this question is now of central importance. Our study adds to the evidence that early initiation of ART may increase the frequency of IRIS.[15,17,19,22] However, delaying the initiation of ART may increase the risk of opportunistic diseases and death.[5,7]

Our study has several limitations. First, because the clinical and radiographic manifestations of IRIS overlap with those of other HIV-associated conditions, it is possible that we misclassified some events. We minimized these risks by training investigators in common clinical presentations of IRIS and by having a clinical events committee review all reported adverse events. Second, decisions about the timing of ART initiation and the management of IRIS were not standardized. Third, we lacked clinical and laboratory data from some patients. Finally, although this is one of the larger studies of IRIS, our sample size had limited statistical power, particularly for subgroup analyses.

CONCLUSIONS

In summary, IRIS events are common when ART is used during TB treatment. These events can cause substantial morbidity and, rarely, mortality and lasted an average of 2 months. Clinical trials are underway to evaluate the effects of the timing of ART on the competing risks of HIV disease morbidity and mortality vs. that of severe IRIS events.

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RÉSUMÉ

CONTEXTE : Patients enrôlés dans un essai prospectif de traitement de la tuberculose (TB) basé sur la rifabutine pour des cas de TB liés au virus de l'immunodéficience humaine. Un traitement antirétroviral (ART) a été encouragé mais non exigé.

OBJECTIF : Evaluer la fréquence, les facteurs de risque et la durée des reconstitutions immunitaires.

SCHÉMA : On a évalué les patients de manière prospective pour tous les cas de reconstitution immunitaire et l'on a revu tous les rapports des effets indésirables pour identifier les événements possibles non reconnus.

RÉSULTATS : Parmi 169 patients, chez 25 d'entre eux (15%) un syndrome de reconstitution immunitaire (IRIS) est apparu en rapport avec la TB. Les 25 cas se retrouvaient parmi les 137 patients ayant bénéficié d'un ART pendant le traitement de la TB, en sorte que dans ce sous-groupe la fréquence est de 18% (25/137). Les facteurs de risque pour un IRIS sont, lors d'une analyse multivariée, la race noire, la présence d'une TB extrapulmonaire et un intervalle plus court entre le début du traitement de la TB et celui du ART. Les manifestations cliniques les plus courantes ont été la fièvre (64%), des adénopathies nouvelles ou en extension (52%) ainsi que l'extension d'infiltrats pulmonaires (40%). Chez 12 patients (48%) il y a eu hospitalisation pour une durée médiane de 7 jours, chez six une intervention chirurgicale et chez 11 une ponction-aspiration à l'aiguille. La durée médiane des événements a été de 60 jours (extrêmes 11 à 442 jours).

CONCLUSION : Les IRIS ont été courants chez les patients bénéficiant d'un ART au cours du traitement de la TB. Ils ont entraîné une morbidité substantielle et leur durée médiane a été de 2 mois.

RESUMEN

MARCO DE REFERENCIA : Pacientes inscritos en un estudio prospectivo de tratamiento con rifabutina, en individuos con tuberculosis (TB) asociada con la infección por el virus de la inmunodeficiencia humana. El tratamiento antirretrovírico (ART) se recomendó pero no constituyó un requisito para la inclusión en el estudio.

OBJETIVOS : Evaluar la frecuencia, los factores de riesgo y la duración del síndrome de reconstitución inmune (IRIS).

MÉTODOS : Se evaluaron los pacientes en forma prospectiva en busca de signos del IRIS y se analizaron todos los informes de reacciones adversas con el fin de detectar posibles manifestaciones no reconocidas.
RESULTADOS : De 169 pacientes, 25 (15%) presentaron manifestaciones de reconstitución inmune, relacionadas con la TB. Los 25 pertenecían al grupo de 137 que recibieron ART durante el tratamiento antituberculoso ; la frecuencia en este subgrupo fue 18% (25/137). El análisis multifactorial reconoció como factores de riesgo del IRIS la etnia negra, la presencia de TB extrapulmonar y un intervalo más corto entre el comienzo del tratamiento antituberculoso y del ART. Las manifestaciones clínicas más frecuentes fueron fiebre (64%), aparición o agravación de adenopatías (52%) y agravación de los infiltrados pulmonares (40%). Doce pacientes estuvieron hospitalizados (48%), con una mediana de estancia de 7 días, seis requirieron cirugía y 11 drenaje por punción. La mediana de la duración de las manifestaciones fue 60 días (intervalo 11–442).
CONCLUSIÓN : El IRIS fue más frecuente en los pacientes que recibieron ART durante el tratamiento antituberculoso, produjo una morbilidad considerable y tuvo una duración mediana de 2 meses.