Original Article

Analysis of Tuberculosis-Associated Immune Reconstitution Inflammatory Syndrome in HIV/TB Co-infected Patients During HAART

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Objectives To investigate the clinical features of tuberculosis (TB)-associated immune reconstitution inflammatory syndrome (TB-IRIS) in patients co-infected with HIV/TB or latent infection during highly active antiretroviral therapy (HAART).

Methods HIV-infected patients treated in the Third People's Hospital of Shenzhen, China between March 2012 and March 2013 were recruited, and divided into 3 groups: 1) HIV/TB co-infection group (n = 50), 2) HIV/MTB latent infection group (n = 50), and 3) HIV infection group (n = 50), with 12-month follow-up. Patients in the HIV/TB co-infection group were treated with HAART 2 weeks after TB therapy. Patients were assessed at different time-points.

Results The incidence and mortality rates of TB-IRIS were 40% and 10% in the HIV/TB co-infected patients, and 2% (and no mortality) in the HIV/MTB group. The HIV infected group did not display TB-IRIS or death. About 95% HIV/TB co-infected patients were 20-39 years old when TB-IRIS occurred, and 65% of the patients developed TB-IRIS 2 weeks after HAART. For the co-infection group, those with TB-IRIS (20/20, 100%) had fever, with a significantly higher incidence than those who did not develop TB-IRIS (6.7%, 2/30, $P < 0.05$). The patients with TB-IRIS in co-infection group displayed markedly higher clinical biochemical markers, acute phase reactants, increased CD4⁺ cell counts, and 2 log₁₀-decreases of HIV RNA loads, compared with the patients not presenting with TB-IRIS ($P < 0.05$).

Conclusion HIV/TB co-infected patients presented with a high-risk of developing TB-IRIS during HAART treatment. Early diagnosis and treatment could decrease mortality rates in TB-IRIS.

Key words: HIV; Tuberculosis; Co-infection; HAART; IRIS; Clinical features

A paradoxical clinical worsening of a known condition or the appearance of 1 new condition after initiating antiretroviral therapy (ART) in HIV-infected patients resulting from restored immunity to specific infectious or non-infectious antigens is defined as immune reconstitution inflammatory syndrome (IRIS). As clinical deterioration occurs during immune recovery, which has been described as immune reconstitution syndrome (IRS) and paradoxical reactions. Given the role of host inflammatory response in this syndrome, Shenzhen Third People's Hospital, 518112. Yang Zhou and Hui Wang equally contributed to this work.
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the term (IRIS) has been proposed and has become the most widely used and accepted term to describe the clinical entity.

Infection with mycobacterium tuberculosis (MTB) is the most common opportunistic infection and primary cause of death in patients with acquired immunodeficiency syndrome (AIDS).¹ Tuberculosis (TB)-associated immune reconstitution inflammatory syndrome (TB-IRIS) is regarded as a major challenge in treatment of HIV/AIDS, and is the most important and common complication in HIV/MTB co-infected patients that have been treated with highly active antiretroviral therapy (HAART). The incidence and

clinical features of TB-IRIS in HIV/MTB co-infected patients and latently infected patients remain unclear. How to confirm early diagnosis with TB-IRIS is still a challenging issue.

In present study, HIV newly infected patients were recruited from March 2012, and the patients were divided into three groups, namely HIV/TB co-infection, HIV/MTB latent infection, and HIV infection groups, according to the inclusion criteria. Treatments were applied according to the protocol, and patients were followed up to investigate the incidence and clinical features of TB-IRIS in the three groups.

Herein, we have reported our observations to help clinicians in the early diagnosis and treatment of TB-IRIS in HIV/TB co-infected patients.

PATIENTS AND METHODS

Clinical characteristics

Newly infected patients with HIV were treated at the Third People's Hospital of Shenzhen, China between March 2012 and March 2013, and were recruited to the study. The inclusion criteria were developed according to the Guideline for HIV/AIDS Diagnosis and Treatment (2011 edition)² and issued by the Group of AIDS, Society of Infectious Diseases, Chinese Medical Association, were as follows: 1) Age ≥ 18 years; 2) CD4⁺ T cell count lower than 350 cells/ μ l as determined within 30 days prior to recruitment; 3) Absence of chronic diseases of the heart, brain, lung, liver and kidney; 4) Absence of other AIDS-related opportunistic infections (confirmed by laboratory examinations; 5) No previous treatment with antiretroviral therapy, and 6) Provision of informed consent. Finally 159 eligible patients were included in present study.

TB-IRIS diagnostic criteria: French et al have laid down criteria so as to aid the diagnosis.³ Major criteria: Atypical presentation of "opportunistic infections (OI) or tumors" in patients responding to antiretroviral therapy. Decrease in plasma HIV RNA level by at least 1 log₁₀ copies/ml. Minor criteria: (1) Increased blood CD4⁺ T-cell count after HAART; (2) Increase in immune response specific to the relevant

pathogen, e.g. DTH response to mycobacterial antigens; (3) Spontaneous resolution of disease without specific antimicrobial therapy or tumor chemotherapy with continuation of antiretroviral therapy.

According to the Guideline for Pulmonary Tuberculosis Diagnosis and Treatment,⁴ issued by the Tuberculosis Society, Chinese Medical Association, 55 patients presented with HIV/TB co-infection (which were referred to as the co-infection group), and none were treated with anti-TB therapy. Three patients with non-TB mycobacterial infection were excluded, 2 patients were lost to follow-up, and thus we finally had 50 patients in the co-infection group who were available for complete follow-up.

According to ELISpot assays, 52 patients displayed HIV/MTB latent infections (latent infection group). However, 2 patients were lost to follow-up, and thus finally 50 patients in latent infection group were available for following-up. Additionally, 52 patients were infected with HIV (HIV infection group), and 2 of them were lost to follow-up. Thus, we finally got 50 patients available for following-up. The anti-TB therapy applied in present study was the HRZE strategy, which is essentially a combination of Isoniazid, Rifampicin, Ethambutol and Pyrazinamide. HAART therapy was performed for patients after a 2-week course of HRZE treatment.⁵ The preferred treatment strategy of HAART was a combination of Zidovudine (AZT), Efavirenz (EFV) and Zalcitabine (ZDV). The secondary treatment strategy of HAART was a combination of TEF, 3TC and EFV.

Ethics approval

This study was conducted according to the Declaration of Helsinki. All the related documents (including approval documents, study protocol, informed consent forms and guidelines for investigators) were presented to the ethics committee in each research center for approval.

Detection of indexes

HIV RNA was amplified by LightCycler PCR device (Roche, German). Cell counting of CD4⁺ T cells was performed with a flow cytometer (Coulter

Epics XL) and a trichromatic fluorescent-labeled monoclonal antibody isotyping kit. A biochemical analyzer (SYNCHRON LX20) was purchased from Beckman Coulter (USA). ELISpot kits specific for *mycobacterium tuberculosis* (TSPOT-TB) were provided by Oxford Lmmunotec Ltd (UK). Following-up studies were carried out for patients in all 3 groups, and blood samples were collected before and at 6 time points after HAART treatment (namely before the treatment and at 0.5-, 1-, 2-, 3-, 6-, and 12-month after treatment). Other parameters including leukocyte counts (WBC), hemoglobin (Hb), platelets (PLT), lymphocytes (Lym), alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin (ALB), globulin (GLO), total bilirubin (TB), serum creatinine (Cr), total CD4⁺ cell counts, and HIV-RNA load were also detected. Levels of HIV-RNA were described as an logarithm.

Statistical analysis

SPSS 13.0 software was applied for the statistical analysis. Chi-square test was used for the comparison of demographic characteristics, clinical symptoms, experimental results, and incidence of TB-IRIS among the 3 groups. An alpha value of $P \leq 0.05$ was considered statistically significant.

RESULTS

Clinical characteristics of patients before HAART treatment

The duration of TB disease in all 50 patients in the co-infection group ranged from 2 weeks to 2 months, and the mean time was 5.82 ± 3.35 weeks. In addition, 90% patients in co-infection group were male, 40% with a history of smoking, but none of them co-presented with a history of diabetes. Additionally, 18% patients were with other basic diseases, although the differences among the 3 groups were not statistically significant. In addition, no statistically significant differences in WBC counts, liver function, renal function, LDH, ESR, CRP, CD4⁺ cell counts, and HIV RNA was found among the 3 groups (Table 1).

TB-IRIS in co-infection and latent infection groups
TB-IRIS was found in 20 (40%) patients in co-

infection group, and induced deaths were found in 2 (10%) patients. The period between HAART treatment and TB-IRIS diagnosis ranged from 1 week to 3 months. In terms of specificity, 65% patients were diagnosed 2 weeks after HAART treatment, while 2 cases were diagnosed at 10 and 12 weeks after HAART treatment, respectively.

The ages of patients at TB-IRIS diagnosis ranged from 10 to 39 years old. By contrast, only 1 patient in latent group developed TB-IRIS, and no patient in HIV infection group developed TB-IRIS. The characteristics of patients who developed TB-IRIS are displayed in Table 2.

Clinical features of patients in co-infection group that developed TB-IRIS

For patients in co-infection group, all 20 (100%) patients developing TB-IRIS presented with the clinical symptom of repeated fever, while only 2 of the other 30 patients (6.7%) who did not develop TB-IRIS presented with repeated fever. Chi-square test showed that the differences were statistically significant ($\chi^2 = 42.424$, $P < 0.001$). In addition, 18 patients were with a temperature higher than 39°C when TB-IRIS were confirmed, with the incidence rate as 90.0% (18/20). By contrast, the incidence of fever with a temperature higher than 39 °C was only 3.3% (1/30) in patients developing TB-IRIS in co-infection group. The difference was statistically significant ($\chi^2 = 38.257$, $P < 0.001$). No significant difference was found in other symptoms, including chills, weakness, mental state, appetite, shortness of breath, diarrhea, cough, and expectoration between patients who developed and those who did not develop TB-IRIS in co-infection group ($P > 0.05$, Table 3).

Laboratory features of patients in co-infection group who developed TB-IRIS

For patients in co-infection group, CD4⁺ cell counts increased 4-fold higher in all (20/20, 100%) patients that developed TB-IRIS, and HIV RNA levels decreased by 2 logarithms in 95% (19/20) patients, with statistically significant difference compared with the patients who did not develop TB-IRIS in co-infection group ($P < 0.001$). The inflammatory

Table 1. Characteristics of patients in three groups before HAART treatment

	Co-infection group (n = 50)	Latent TB infection group (n = 50)	HIV infection group (n = 50)	P values
Male (n, %)	45 (90.0)	42 (84.0)	42 (84.0)	0.644
Age (years)				
< 20	1 (2.0)	1 (2.0)	1 (2.0)	0.950
20 - 39	40 (80.0)	39 (78.0)	43 (86.0)	
40 - 59	7 (14.0)	9 (18.0)	5 (10.0)	
> 60	2 (4.0)	1 (2.0)	1 (2.0)	
History of smoking (n, %)	20 (40.0)	17 (34.0)	22 (44.0)	0.620
Basic diseases (n, %)	9 (18.0)	6 (12.0)	8 (16.0)	0.780
Diabetes (n, %)	0 (0.0)	0 (0.0)	0 (0.0)	-
Hypertension (n, %)	2 (4.0)	0 (0.0)	1 (2.0)	0.773
HBV infection (n, %)	2 (4.0)	1 (2.0)	3 (6.0)	0.871
HCV infection (n, %)	5 (10.0)	4 (8.0)	8 (16.0)	0.524
WBC median (IQR), /ml	4.11 ± 1.96	5.45 ± 1.38	5.54 ± 1.49	0.107
Lymphocyte median (IQR), 10 ⁹ /L	1.63 ± 0.42	1.73 ± 0.36	1.59 ± 0.51	0.748
Hemoglobin median (IQR), g/dl	141.00 ± 28.64	149.90 ± 10.77	151.60 ± 10.99	0.411
PLT median (IQR), /L	194.30 ± 90.45	195.80 ± 91.51	207.60 ± 36.15	0.915
ALT median (IQR), U/L	23.90 ± 15.07	23.50 ± 9.85	25.10 ± 10.10	0.952
AST median (IQR), U/L	30.60 ± 12.00	24.00 ± 9.49	20.90 ± 8.03	0.104
ALB median (IQR), g/dl	43.36 ± 5.76	45.56 ± 3.16	44.25 ± 2.92	0.500
GLO median (IQR), g/dl	41.95 ± 6.12	41.74 ± 3.81	38.45 ± 4.92	0.237
TB median (IQR), µmol/L	10.66 ± 5.41	9.85 ± 4.68	9.81 ± 5.37	0.918
Cr median (IQR), mmol/L	79.20 ± 18.37	89.00 ± 15.57	86.50 ± 10.66	0.340
CRP median (IQR), mg/dl	12.07 ± 9.26	9.58 ± 6.98	9.60 ± 9.13	0.756
LDH median (IQR), mmol/L	206.50 ± 44.52	172.80 ± 49.81	181.00 ± 38.40	0.228
ESR median (IQR), mm/H	28.20 ± 20.63	14.80 ± 6.05	15.90 ± 9.05	0.064
CD4 median (IQR), /µl	200.61 ± 64.04	221.89 ± 77.46	240.78 ± 88.70	0.306
HIV RNA median (IQR), copies/ml	5.67 ± 0.69	5.50 ± 0.52	5.38 ± 0.38	0.424

Table 2. Characteristics of patients in co-infection and latent infection groups with TB-IRIS diagnosis

	Co-infection group n/N (%)	Latent TB infection group n/N (%)	χ^2	P values
TB-IRIS	20/50 (40.0)	1/50 (2.0)	96.19	< 0.001
TB-IRIS death	2/20 (10.0)	0/1 (0.0)	-	0.495
Time to TB-IRIS diagnosis (weeks)				
< 1	0/20 (0.0)	0/1 (0.0)	1.43	1
1 - 2	13/20 (65.0)	1/1 (100.0)		
2 - 4	5/20 (25.0)	0/1 (0.0)		
> 4	2/20 (10.0)	0/1 (0.0)		
TB-IRIS duration (weeks)				
< 1	2/20 (10.0)	1/1 (100.0)	5.51	0.190
1 - 2	12/20 (60.0)	0/1 (0.0)		
2 - 4	5/20 (25.0)	0/1 (0.0)		
> 4	1/20 (5.0)	0/1 (0.0)		
Age at TB-IRIS diagnosis (years old)				
< 20	0/20 (0.0)	0/1 (0.0)	-	1
20 - 39	19/20 (95.0)	1/1 (100.0)		
40 - 59	1/20 (5.0)	0/1 (0.0)		
> 60	0/20 (0.0)	0/1 (0.0)		

Table 3. Parameters of patients developed and those who did not develop TB-IRIS in co-infection group

	TB-IRIS [(n, %), N = 20]	No TB-IRIS [(n, %), N = 30]	χ^2	P values
Fever	20 (100.0)	2 (6.7)	42.424	< 0.001
Highest temperature > 39 °C	18 (90.0)	1 (3.3)	38.257	< 0.001
Chills	4 (8.0)	1 (3.3)	-	0.143
Weakness	4(20.0)	4 (13.0)	-	0.697
Mental state	15 (75.0)	24 (8.0)	0.005	0.944
Appetite	17 (85.0)	23 (76.7)	0.130	0.718
Cough	5 (25.0)	3 (10.0)	-	0.240
Expectoration	3 (15.0)	3 (10.0)	-	0.672
Shortness of breath	1 (5.0)	0 (0.0)	-	0.400
Diarrhea	4 (20.0)	3 (10.0)	-	0.416
WBC > 10×10 ⁹ /L	3 (15.0)	0 (0.0)	-	0.058
CRP > 10 mg/L	15 (75.0)	3 (10.0)	22.005	< 0.001
ESR > 20 mm/h	12 (60.0)	2 (6.7)	16.931	< 0.001
ALT > 40 U/L	4 (20)	3 (10.0)	-	0.416
AST > 40 U/L	5 (25)	3 (10.0)	-	0.240
LDH > 250 U/L	11 (55)	2 (6.7)	14.570	< 0.001
Cr > 133 μmol/L	1 (5.0)	0 (0.0)	-	0.400
GLO > 30 g/L	15 (75)	19 (63.3)	0.751	0.386
CD4 > 4 folds	20 (100)	7 (23.3)	28.395	< 0.001
CD8 > 4 folds	2 (10)	1 (3.3)	-	0.556
HIV RNA decreased by 2 log ₁₀	19 (95)	5 (16.7)	19.759	< 0.001

parameters including CRP ($\chi^2 = 22.0$, $P < 0.001$), ESR ($\chi^2 = 16.9$, $P < 0.001$, and LDH ($\chi^2 = 14.5$, $P < 0.001$) were significantly different between patients who developed and those who did not develop TB-IRIS in co-infection group. By contrast, no statistically significant differences in WBC, ALT, AST, Cr and GLO were found between patients who developed and those who did not develop TB-IRIS in co-infection group (Table 3).

DISCUSSION

Approximately one quarter to one third of patients with AIDS may develop IRIS after HAART, and *mycobacterium* TB is the most common IRIS-related pathogen. The incidence rate of TB-IRIS in patients co-infected with HIV, and TB ranges from 11% to 68.8%.^{6,7} The co-infection rate of HIV and TB is increasing steadily in China, which makes TB-IRIS the most important and commonly early complication for patients who received HAART treatment, and co-infected with HIV and TB. However, only several studies have reported the incidence of TB-IRIS and the clinical features.

In this prospective study, we found that 20 of 50 patients with HIV/TB co-infection developed TB-IRIS, with an incidence rate of 40%. Two of these 20 patients died, with a mortality rate of 10%. By contrast, only 1 of the 50 patients with HIV/MTB latent infection developed TB-IRIS, with an incidence rate of 2%, no death was identified in this group. In a previous study performed by Huruy et al,⁷ the incidence rate of TB-IRIS was as high as 68.8% in AIDS patients who were treated with HAART in Ethiopia. Another retrospective study conducted in Guangxi Province, China also demonstrated that the incidence rate of IRIS in HIV/TB co-infected patients was about 48.8%.⁸ These results suggested that TB-IRIS is a critical challenge for patients with HIV/TB co-infection.

Studies have shown that TB-IRIS occurs in African patients at the 5th day of HAART, while for most patients, the symptoms appeared at about 2-6 weeks after HAART. For some cases, the symptoms were evident even 1-4 years after HAART.⁷ In present study, the earliest time to TB-IRIS was 7 days after HAART treatment in HIV/TB co-infected group, while the last patient displaying symptoms occurred

longer than 90 days after HAART. Additionally, 65% (13/60) patients occurred TB-IRIS at 7- to 14- day after HAART. It is also found that TB-IRIS occurred longer than 2 months after HAART in the 2 observed deaths. This observation was consistent with the results of van Oosterhout et al.⁹ The ages of patients with TB-IRIS diagnosis were 20-39 years old, and the 2 patients who died with TB-IRIS diagnosis were 28 years and 38 years, respectively. It is suggested that young patients are at a high risk of developing TB-IRIS, which suggested that TB-IRIS is associated with the patient's age and the duration of HAART treatment. However, further studies are in urgent need to investigate the mechanisms.

Excessive inflammatory responses induced by the destruction of cellular immune balance have been universally confirmed as the basis of IRIS. Disruption of immunoregulation of Th1/Th2 CD4⁺ T helper responses might induce excessive inflammation in response to latent MTB infection and thus would induce TB-IRIS.¹⁰ However, other studies also found that Th1 cells were increased in patients who did not develop TB-IRIS, while MTB antibody specific for IFN- γ was found in both TB-IRIS and non-TB-IRIS groups, although the difference was not statistically significant.¹¹ CD4⁺ IL-17⁺ T cells were significantly decreased in patients co-infected with HIV and MTB. By contrast, HAART treatment rescued CD4⁺ IL-17⁺ T cells, and decreased Treg cells, which suggested that the disequilibrium of Treg/Th17 cells might represent an important mechanism in the development of TB-IRIS.¹²⁻¹⁴ However, further studies are warranted to explore the exact mechanism.

The main symptoms of patients presenting with TB-IRIS was repeated fever (20/20, 100%) in present study, and the incidence was significantly different as compared with co-infected patients who did not develop TB-IRIS ($\chi^2 = 42.4$, $P < 0.01$). However, no significant difference was found between the patients who develop and those who did not develop TB-IRIS in co-infection group when considering other symptoms like chills, weakness, mental state, appetite, shortness of breath, diarrhea, cough and expectoration ($P > 0.05$).

These findings suggested that the symptoms of

TB-IRIS could be different from those induced simply by TB infection, and the systemic toxic symptoms were relatively mild when fever appeared in patients with TB-IRIS. This might assist clinicians in early identification of the causes of fever in HIV/TB co-infected patients by reviewing their medical history.

In present study, clinical laboratorial examinations revealed that the levels of CRP (75%, 15/20), ESR (60%, 12/20), and LDH (55%, 11/20) increased significantly in patients with TB-IRIS as compared to those who without TB-IRIS ($P < 0.01$). This suggested that TB-IRIS is associated with increased levels of CRP, ESR and LDH. Previous studies have demonstrated that CD4⁺ cells increased after HAART. Additionally, the decrease in number of HIV RNA is associated with short time duration between the disease onset and the initiation of ART treatment. Moreover, high level of CRP was a risk factor of IRIS.¹⁵ These results were inconsistent with our findings. Therefore, if increased levels of CRP, ESR and LDH are found in HIV/TB co-infected patients, some features including the duration of HAART treatment, clinical symptoms, CD4⁺ cell counts and HIV RNA loads should be considered along with the infection to comprehensively evaluate the possibility of developing IRIS and to help make the most appropriate early treatment strategy.

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