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Immunological Profile of HIV-Infected Patients with Tuberculosis Associated-Immune Reconstitution Inflammatory Syndrome: A Systematic Review

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Abstract

Objective: This study systematically reviews the literature that describes the immunological profile associated with the development of tuberculosis-associated immune reconstitution inflammatory syndrome (TB-IRIS) in HIV-infected individuals.

Methods: Between the primary and secondary searches, a total of 20 articles were selected for the final analysis.

Results: The results obtained herein indicated that TB-IRIS was associated with the recovery of Mtb-specific immune response, demonstrated by an increased frequency of specific IFN-g-producing cells and specific multifunctional T-lymphocytes (TNF and IFN-γ-producing). In addition, an increased production of inflammatory cytokines and chemokines was found in TB-IRIS patients compared to non-IRIS individuals.

Conclusion: These data suggest that expansion of Mtb-specific cells may not be the main factor for the occurrence of IRIS. Further studies are needed to better evaluate the dynamic of restoration of Mtb-specific memory cells and to clarify the role of innate immune responses in immunopathogenesis of TB-IRIS patients.

Keywords: HIV; AIDS; Tuberculosis; Immune reconstitution inflammatory syndrome; Antiretroviral therapy; HAART; *Mycobacterium tuberculosis* antigens; Cytokines; Specific immune

Introduction

Highly active antiretroviral therapy (HAART) had a major impact in reducing mortality and morbidity associated with AIDS and a significant improvement in patients' quality of life [1,2]. Although HAART is effective at controlling viral replication and inducing partial restoration of $CD4^+$ T-lymphocyte repertoires, around 16% of treated patients experience a clinical deterioration [3,4]. They present an overwhelming inflammatory response against pre-existing antigens that is named inflammatory immune reconstitution syndrome (IRIS) [5,6]. This syndrome results from the immune system's restored ability to mount a potent inflammatory response after HAART. IRIS can manifest as a paradoxical response, in which clinical worsening occurs when patients start on pathogen-specific therapy and HAART simultaneously. Alternatively, it can occur as an unmasking IRIS, in which a latent opportunistic infection is identified following HAART initiation [7,8].

Mycobacterium tuberculosis (Mtb) infection is one of the pathogens most commonly associated with IRIS, especially in endemic areas for tuberculosis [6-10]. Patients with tuberculosis-associated IRIS (TB-IRIS) frequently present fever, tachycardia, exacerbation of tuberculosis symptoms, peripheral and mediastinal lymphadenopathy, neurological symptoms, and abdominal manifestations that include hepatosplenomegaly and cavitary masses [11-13].

The immune reconstitution following HAART is characterized by an increase in the number of $CD4^+$ T-lymphocytes, restoration of lymph oproliferative response to memory antigens, and a shift from a T helper (Th) type 2 to a type 1 cytokine profile, with an increase in IL-2 and IFN-g levels [14-17]. Although the immunological mechanism involved in TB-IRIS remains partially unclear, it has been suggested that the intense inflammatory response results from an exaggerated antigen-specific response [18,19]. Moreover, the production of spontaneous pro-inflammatory cytokines and chemokines [19] and/or an imbalance in the immune regulatory response [20] are found in the course of TB-IRIS. Studies assessing the immune pathogenesis of TB-IRIS are scarce, include small samples of patients and describe different aspects of the immune response. The present study aims to systematically review the pertinent literature to describe the immunological profile associated with the development of TB-IRIS in HIV-infected individuals.

Methods

The systematic review was performed in the Medline, Scielo, Lilacs and Web of Science virtual databases by two independent researchers. Languages were restricted to Portuguese, English, Spanish and French,

and there was no limit for the year of publication. The following keywords were used: "immune reconstitution inflammatory syndrome", "immune reconstitution disease", "immune restoration syndrome", "immune restoration disease", "*Mycobacterium tuberculosis*", "*M. tuberculosis*", "*Mycobacterium tuberculosis* antigens", "tuberculin", "PPD", "Tuberculosis", "Treg cell", "T-lymphocytes", "CD4-positive T-lymphocytes", "CD8 T-lymphocytes", "FOXP3", "Th1 cell", "type 1 helper T cells", "Th1 response", "IL-6", "tumor necrosis factor alpha", "TNF-alpha", "IFN-gamma", "Interferon-gamma release tests", "cytokines", "Chemokines", "C-reactive protein", "antibodies", "specific immune", "HIV", "AIDS", "antiretroviral therapy" and "HAART". All keywords, except "type 1 helper T cells", were found in the Mesh database.

Studies were selected according to the following criteria: original articles and articles whose results presented the assessment of markers of the Mtb-specific immune response in HIV-infected patients with TB-IRIS. The exclusion criteria were: letters to the journals and animal model studies. These criteria were first applied to titles and abstracts and then to full text articles. The final article selection was defined by consensus between the two researchers. Secondary search was additionally performed from references included in the original articles.

The following information was systematically extracted from each article: (1) basic information (title, year, authors, objectives, and keywords), (2) study design, (3) methods used for evaluation of the immune system (innate and antigen-specific response), (4) subjects (setting, sample, data collection, procedures and tools), and (5) results obtained. The systematic literature review was structured according to the PRISMA checklist.

$CD4^+$ T-cell count, HIV viral load and the number of Mtb-specific IFN-g-producing cells evaluated by enzyme-linked immunospot assay (ELISPOT) of TB-IRIS patients and non-IRIS were extracted from all articles where information was available. The data of TB-IRIS patients and non-IRIS were compared using U Mann-Whitney test ($p<0.05$).

Results

From the primary search 97 articles were selected of which 80 were excluded. Among the articles excluded, 30 were duplicates and 49 were ineligibles and one was unable to obtain full text (Figure 1). The secondary search added three articles, totaling 20 studies. When considering study designs, prospective studies were the most frequent (15), followed by case reports (3), case-control (1) and cross-sectional study (1). The majority of patients were from Sub-Saharan Africa [18,20-29] and Asia (Malaysia, Cambodia, and Thailand) [19,30-36]. Only one study included European patients [37]. Three studies evaluated patients from the same African cohort [18,21,22], two from the same Malaysian cohort [30,35] and four from the same Cambodian cohort [19,31,33,36]. Patients classified as HAART-associated tuberculosis (TB-ART) [19,31,33,36] were considered herein as unmasking TB-IRIS since TB occurred after reconstitution of the immune system and the control of viral replication. A total of 237 patients with TB-IRIS were reported, and those evaluated by more than one study were only counted once (Table 1).

Study design	Origin of patients	TB-IRIS group N	Control group (non-IRIS) N	Time between HAART onset and IRIS (days)	$CD4^+$ T-lymphocyte (at pre-HAART) (cell/mm^3)	$CD4^+$ T-lymphocyte (at IRIS) (cell/ mm^3)	References
Case report	England	1	2	35	150	294	[37]
Prospective	Sub-Saharan Africa*	7 (pIRIS)	12	23	32	107	[18]
Prospective	Malaysia†	3 (pIRIS)	8	Patient 1: 21 Patient 2: 84 Patient 3: 98	NI	NI	[30]
Prospective	Sub-Saharan Africa*	11 (pIRIS)	13	23	26	86	[21]
Cross-sectional	South Africa	35 (pIRIS)	19	14	51	181	[20]
Prospective		10 (pIRIS)	41	15	195	NI	
Prospective	Sub-Saharan Africa*	11 (pIRIS)	13	26	37	108	[22]
Prospective	Cambodia§	15 (pIRIS)	55	10	45	NR	[31]
		11 (uIRIS)	206	10			
Prospective	Thailand	22 (pIRIS)	104	14	35	144	[32]
Prospective	Cambodia§	15 (pIRIS)	30	10	45	NI	[33]
Prospective	Cambodia§	15 (pIRIS)	30	10	45	NI	[19]
Case report	Thailand	1 (uIRIS)	4	60	46	155	[34]
Case report	South Africa	22 (pIRIS)	22	14	NI	NI	[23]

Prospective	Malaysia†	3 (pIRIS)	9	49	15	147	[35]
Case-control	South Africa	18 (uIRIS)	58 (HIV) / 51 (HIV-TB)	55	115	154	[24]
Prospective	South Africa	1 (uIRIS) / 5(pIRIS)	NI	28	4 / 42	41	[25]
Prospective	South Africa	8 (TB-MDR) / 3 (TB-RM)	25 (TB-FS)	14	50 / 55	NI	[26]
Prospective	Cambodia§	15 (pIRIS)	30	10	45	NI	[36]
Prospective	South Africa	16	18	14	93	158	[27]
Prospective	Gambia	20 (pIRIS)	16	21	60	180	[28]
Prospective	Uganda	18 (pIRIS)	18	14	19	NI	[29]

pIRIS: tuberculosis associated with paradoxical IRIS; uIRIS: tuberculosis associated with unmasking IRIS; NI: Not Informed; TB-MDR: Tuberculosis Multi-Drug Resistant; TB-RM: Tuberculosis Mono-Resistant to Rifampicin; TB-FS: Tuberculosis Full Sensitive;*, †, §patients evaluated in the same studies.

Table 1: Characteristics of included studies.

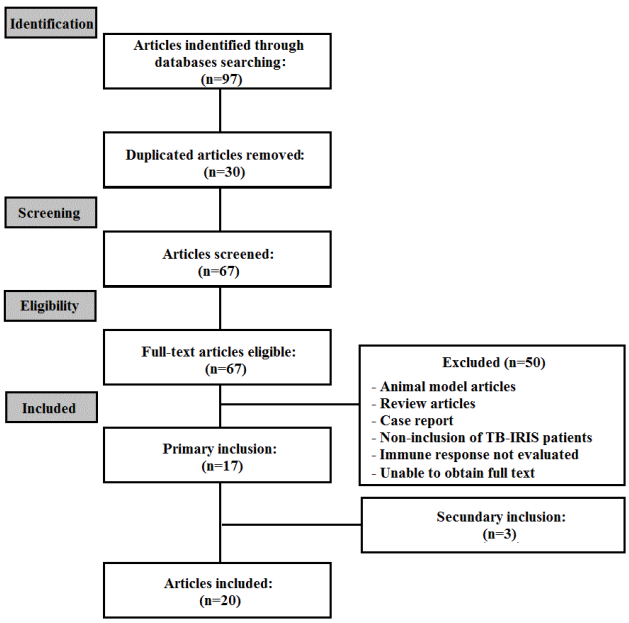

Figure 1: Flow diagram for selecting studies for systematic review.

Ninety percent of the studies (18/20) compared the immune response of patients with TB-IRIS to the HIV-infected individuals without IRIS (non-IRIS, n=417). IRIS occurred on average 28 days (SD 24 days) after HAART initiation. The increase in $CD4^+$ T-lymphocyte counts after HAART was significant in both groups with and without IRIS, while a significant reduction in viral load was observed only in patients with IRIS (Figure 2).

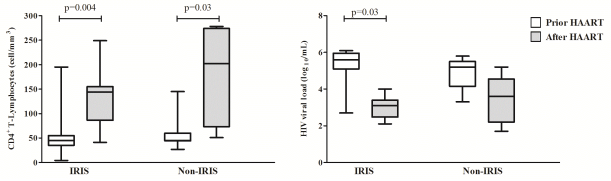

Figure 2: $CD4^+$ T-cell counts and HIV viral load (VL) of TB-IRIS patients and non-IRIS individuals evaluated. Data were extracted from all studies where information was available [18-28,31-37]. The data are presented as median (interquartile range), U Mann-Whitney test ($p<0.05$).

The specific response to Mtb antigens was analyzed in 15 studies (Table 2). An increase in the number of Mtb-specific IFN-g-producing cells was observed in TB-IRIS patients following HAART [18,22,30,35] or when compared to non-IRIS individuals [18,20,22,35]. The number of Mtb-specific IFN-g-producing cells evaluated using ELISPOT was seven times higher in TB-IRIS patients compared to non-IRIS individuals ($p=0.03$) (Figure 3) [18,20,22,30,35]. In two studies, no increase was observed during TB-IRIS [25,29]. Moreover, a higher frequency of monofunctional ($CD4^+IFN\text{-}g^+$, $CD8^+IFN\text{-}g^+$ and $CD8^+TNF^+$) [28] and multifunctional ($CD4^+IFN\text{-}g^+TNF^+IL\text{-}2$-) T-lymphocytes [22,28] was found in TB-IRIS patients compared to non-IRIS individuals. Increased production of chemokines and Th1 cytokines (CXCL-9, CXCL10, IL-1b, IL-6, IL-8, TNF, IL-2, IL-12, and IFN-g) was found in TB-IRIS patients compared to non-IRIS individuals in four studies [18,23,35,36]. The IFN-g level evaluated by IFN-g release assay (IGRA) was found to be similar in both groups [31-33]. Only one study observed no difference in IL-2 and IL-12 production in TB-IRIS and non-IRIS individuals [32]. Regarding humoral immune responses, two out of three patients with TB-IRIS evaluated by Tan et al. had an increase of anti-PPD IgG compared to

TB patients not infected with HIV [30]. Anti-PGL-Tb1 was found only in non-IRIS individuals [21].

Evaluated antigen	Immunological assay	Main results	Rseferences
PPD, ESAT-6, 85B	IFN-γ-producing cells (ELISPOT); cytokines (chemiluminescence)	Increased number of PPD-specific IFN-γ-producing cells and higher IL-2, IL-12, IFN-γ, CXCL9 and CXCL10 levels in TB-IRIS patients compared to baseline and to non-IRIS individuals	[18]
PPD, ESAT-6	IFN-γ-producing cells (ELISPOT)	Increased number of PPD-specific IFN-γ-producing cells during IRIS (two out of three patients), compared to baseline. No IFN-γ response to ESAT-6 antigen	[30]
PGL-Tb1, ESAT-6, CFP10	Antibodies (ELISA)	Similar anti-ESAT-6/CFP10 and anti-ManLAM antibody levels in TB-IRIS and non-IRIS individuals	[21]
PPD, ESAT-6, 38kD, Acr 1 e 2	IFN-γ-producing cells (ELISPOT)	Increased number of ESAT-6 and PPD-specific IFN-γ-producing cells in TB-IRIS patients compared to non-IRIS individuals	[20]
PPD	IFN-γproducing cells (ELISPOT); (ICC, flow cytometry)	Increased number of PPD-specific IFN-γ-producing cells in TB-IRIS patients compared to non-IRIS. Multifunctional (IFN-γ $^{+}$TNF-a^{+}IL-2-) CD4^{+} T-cells	[22]
RD1, PPD	IFN-γ level (IGRA)	Similar IFN-γ levels between pTB-IRIS and non-IRIS patients. Increased IFN-γ levels in uTB-IRIS patients compared to controls	[31]
RD1 e PPD	IFN-γ level (IGRA); IL-2 and IL-12 (ELISA)	Increased IFN-γ levels to PPD during IRIS compared to baseline. Similar IFN-γ, IL-2 and IL-12 levels in TB-IRIS patients compared to non-IRIS individuals	[32]
PPD	IFN-γ level (IGRA); IL-5 (ELISA)	Similar IFN-γ and IL-5 levels in TB-IRIS patients and non-IRIS individuals	[33]
Mtb H37Rv, PPD	Cytokines (RT-PCR and ELISA)	Increase quantity of cytokines transcripts (IL1-β, IL-5, IL-6, IL-10, IL-13, IL-17a, IFN-γ, GM-CSF and TNF) and of IL-12p40, IL-1β, GM-CSF, TNF, IL-10, IL-6, IL-2 and IL-8 levels in TB-IRIS patients compared to non-IRIS individuals	[23]
PPD e Lipomannan	IFN-γ-producing cells (ELISPOT); cytokines (ELISA)	Increase number of PPD-specific IFN-γ-producing cells and of TFN levels in response to lipomannan Mtb antigen in TB-IRIS patients compared to non-IRIS individuals	[35]
PPD	IFN-γ-producing cells (ICC, flow cytometry)	Increased frequency of PPD-specific IL-2, IL-10 and TNF-producing CD4^{+} T-cells following resolution of IRIS	[25]
ESAT-6, 38 kD, Acr 1 e 2, PPD e MtbH37Rv	IFN-γ-producing cells (ELISPOT); cytokines (flow cytometry)	Similar frequency of specific IFN-γ-producing cells among TB-IRIS groups (TB-MDR, TB-RM and TB-FS). Higher IFN-γ/ IL-10 and L-2/IL-10 ratios in TB-IRIS FS compared to TB-IRIS MDR and TB-IRIS RM	[26]
PPD e RD1	Cytokines (flow cytometry)	Increased of CXCL10 levels in TB-IRIS patients compared to no-IRIS individuals	[36]
PPD, ESAT-6, CFP10	IFN-γ-producing cells (ICC, flow cytometry)	Higher frequency of PPD-specific IFN-γ^{+}CD4^{+}, IFN-γ+TNF $^{+}$CD4^{+}, IFN-γ^{+}CD8^{+} and TNF^{+}CD8^{+} T-cells in TB-IRIS patients compared to non-IRIS individuals	[28]
PPD, ESAT-6. CFP10	IFN-γ-producing cells (ELISPOT); cytokines (flow cytometry)	Similar number of specific IFN-γ-producing cells among TB-IRIS patients and non-IRIS individuals	[29]

pIRIS: tuberculosis associated with paradoxical IRIS; uIRIS: tuberculosis associated with unmasking IRIS; non-IRIS: patients without IRIS; ELISPOT: Enzyme Linked Immunospot Assay; PPD: Purified Protein Derivative; ESAT-6: Early Secretory Antigenic Target-6; RD1: Region of Difference 1; PGL-Tb1: Glycolipid Antigen of Mtb; ELISA: Enzyme Linked Immunosorbent Assay; IGRA: Interferon Gamma Release Assay; ICC: Intracellular Cytokines; RT-PCR: Reverse Transcription Polymerase Chain Reaction. TB-MDR: Tuberculosis Multi-Drug Resistant; TB-RM: Tuberculosis Rifampicin Mono-Resistant; TB-FS: Tuberculosis Fully Sensitive.

Table 2: Evaluation of the immune response to *Mycobacterium tuberculosis* antigens in patients with TB-IRIS.

The Table 3 summarizes the phenotypic profile of different cell subsets and the ex vivo cytokine levels in patients with TB-IRIS. The spontaneous production of Th1-type (IFN-γ, IL-2, IL-12) and innate (TNF, IL-6, IL-1β, IL-18, CXCL10, EGF and HGF) cytokines were higher in patients with TB-IRIS compared to non-IRIS individuals [18,19,23,24,27,34,37]. Moreover, a three-fold increase in C-reactive

protein (CRP) plasmatic levels was found in TB-IRIS patients [20,24]. Six studies performed phenotypic analyses of T-lymphocyte subsets, natural killer (NK) cells, monocytes and dendritic cells [18,20,22,25,30,35]. Activation of $CD4^+$ T-lymphocytes, macrophages and NK cells were observed by several authors [18,24,30,35]. The expansions of KIR-$TCR\gamma\delta^+V\delta2^+$ T-cells as well as the reduction of Myeloid Dendritic Cells (MDC) were unchanged during TB-IRIS, when these alterations were preexistent before HAART [22]. Tan et al found an increased expression of TLR2 in monocytes and MDCs of TB-IRIS patients. Increased expression of TLR2 was associated with high levels of TNF and IL-12p40 and low levels of IL-10 [35].

Discussion

The results of this systematic review show that the presence of TB-IRIS was concomitant with the restoration of the Mtb-specific immune response. In the majority of the evaluated studies (11/15), a higher number of Mtb specific-IFN-γ producing cells [18,20,22,35] and of specific multifunctional T-lymphocytes (IFN-γ and TNF-producing) [22,28] as well as higher production of Th1 cytokines [18,23,35,36] were found in TB-IRIS patients compared to non-IRIS individuals. However, the peak in the number of antigen-specific IFN-γ-producing cells did not always coincide with the onset of IRIS, occasionally occurring after IRIS resolution [22,25]. In only four out of 15 studies, three using IGRA and one using ELISPOT, differences in IFN-γ production in response to Mtb antigens were not reported between groups [29,31,33]. Interestingly, the aforementioned study using ELISPOT also found a low production of IFN-γ in response to cytomegalovirus and influenza antigens in TB-IRIS patients, suggesting that those patients were immunosuppressed [29]. None of studies using IGRA found any difference in the production of IFN-g between TB-IRIS and non-IRIS groups. This could indicate that ELISPOT sensitivity to Mtb antigens may be higher than IGRA in patients with advanced HIV infection [38,39].

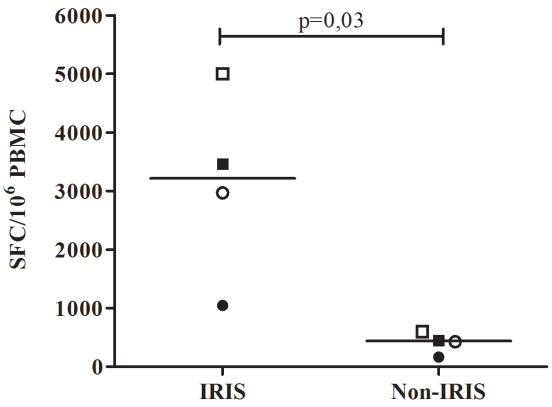

Figure 3: Quantification of *Mycobacterium tuberculosis* (Mtb)-specific IFN-g-producing cells of TB-IRIS patients and non-IRIS individuals using ELISPOT. Data were extracted as median from all articles that used ELISPOT to quantify IFN-g-producing cells in response to Mtb antigens (PPD, ESAT-6, 85B, 38KD, Acr 1 and 2 and lipomannan) [18,20,22,30,35]. TB-IRIS group: median: 3,216 SFC/106 PBMC, IQR 1,528-4,616 SFC/106 PBMC; non-IRIS group: (441.5 SFC/106 PBMC, IQR 233.5-563.3 SFC/106 PBMC). Mann-Whitney test ($p<0.05$).

Immunological assay	Main results	Reference
Plasma cytokines (ELISA)	Higher IL-6 level in TB-IRIS patients compared to non-IRIS individuals	[37]
Cell phenotyping (WB, flow cytometry)	Increased TNF, IL-6, IL-1β, IL-10, RANTES, and MCP-1 levels and high frequency of activated $CD4^+$ T-cells in TB-IRIS patients	[18]
Cell phenotyping (WB, flow cytometry)	Similar frequencies of activated $CD4^+$ and $CD8^+$ T-cells and $CD4^+$ Treg cells among TB-IRIS and non-IRIS individuals	[20]
Cell phenotyping (PBMC, flow cytometry)	Higher frequency of activated $CD4^+$ T-cells and $CD4^+$ Treg cells ($CD25^+CD127^{low}$ and CTLA-4^+) in TB-IRIS patients compared to healthy individuals.	[30]
Cell phenotyping (WB, flow cytometry)	Lower frequency of TCRγδ and $V\delta2^+$ T cells expressing CD94/NKG2 and CD158ah, b in TB-IRIS patients compared to non-IRIS individuals.	[22]
Plasma cytokines (flow cytometry and ELISA)	Increased IL-18 and CXCL10 levels and decreased CCL2 in TB-IRIS patients compared to non-IRIS individuals.	[19]
Plasma cytokines (ELISA)	At baseline, higher TNF and IL-10 levels in TB-IRIS patient compared to non-IRIS individuals. Higher IFN-γ levels in TB-IRIS patients after HAART compared to baseline.	[34]
Plasma cytokines (Luminex technology)	Higher frequency of activated NK cell and C-reactive protein, IL-8, EGF, and HGF levels in TB-IRIS patients compared to non-IRIS patients.	[24]
Cell phenotyping (whole blood, flow cytometry)	Higher expression of TLR2 on mDC and monocytes of TB-IRIS patients compared to non-IRIS individuals	[35]

Cytokines (RT-PCR)	Increase quantity of IL-2, IL-5, IL10, IL-12p40, IL-13, IL-15, IL-17A, TGF-β, and TNF transcripts in TB-IRIS patients compared to non-IRIS individuals	[23]
Cell phenotyping (WB, flow cytometry)	Expansion of central memory $CD4^+$ T-cells following HAART.	[25]
Cytokines levels (CSF, flow cytometry)	Higher TNF, IFN-γ and IL-6 levels in TB-IRIS patients compared to non-IRIS individuals	[27]

Table 3: Cytokine and phenotypic profile of patients with TB-IRIS evaluated ex vivo.

The low IGRA sensitivity observed could also be explained by the antigenic components of this test, ESAT-6, CFP-10 and TB 7.7, which are derived from region of difference 1 (RD1) in the Mtb genome. In fact, two studies that evaluated ESAT-6 response in patients with paradoxal TB-IRIS using ELISPOT detected low number of spot forming cells (SFC), whereas the number of SFC in response to protein purified derivate to Mtb (PPD) was high [18,30]. Conversely, higher IFN-γ-production in response to both PPD and RD1 antigens, including ESAT-6, was observed in patients with unmasking TB-IRIS compared to non-IRIS individuals [31]. As RD1 antigens are solely derived from Mtb, as opposed to PPD, it has been proposed that the inflammatory response in unmasking TB-IRIS would be triggered by antigens from live bacteria, while in paradoxal TB-IRIS that response is mainly triggered by antigens from dead bacteria [30]. Thus, IGRA could be useful distinguishing unmasking and paradoxal TB-IRIS.

This systemic review also found a low frequency of polyfunctional ($IFN\text{-}g^+IL\text{-}2^+TNF^+$) $CD4^+$ and $CD8^+$ T-lymphocytes in response to PPD in TB-IRIS patients. The majority of patients had a specific multifunctional T-lymphocytes secreting IFN-γ and TNF, but not IL-2 in response to Mtb antigens stimulation [22,28]. These findings suggest that the quality of the specific immune response to Mtb antigens recovery is limited [28]. Mono-functional T-lymphocytes ($CD4^+IFN\text{-}g^+$) response is mainly found during persistent infection with high antigen load, as occurs during an infection associated with IRIS. Maintaining a high level of antigens impairs the establishment of a polyfunctional response capable of sustaining its own expansion and effector activity [40].

In addition to a high secretion of Th1 cytokines (IFN-γ, IL-2, IL-12) in response to Mtb antigens, several studies found higher production of cytokines and chemokines released from innate immune cells (TNF, IL-6, IL-1β, IL-10, IL-18, CCL-5, CCL-2, CXCL10) [18,19,23,24,34,35,37] in patients with TB-IRIS compared to non-IRIS individuals. Non-specific release of proinflammatory cytokines and chemokines may induce the systemic inflammatory reaction present in IRIS. It has been proposed that once HAART controls the viral load and promotes the reconstitution of T-lymphocyte repertoires, specific lymphocytes could produce cytokines that stimulate macrophages which were previously infected by intracellular pathogens during the period of immunosuppression (AIDS). In turn, these macrophages and other cells of the innate immune system would secrete high levels of proinflammatory cytokines and chemokines, which would result in the inflammatory manifestations of IRIS [41].

Moreover, inflammatory response during TB-IRIS could also be caused by a dysfunction of regulatory T-lymphocytes. Two studies found similar frequencies of $Foxp3^+CD4^+$ T-cells in patients with TB-IRIS and non-IRIS individuals [20,42]. Tan et al studying three patients with TB-IRIS, observed an increase in the proportion of T-cells with regulatory profile ($CD4^+CD25^+CD127^{low}$ and $CD4^+CTLA\text{-}4^+$) in comparison to healthy controls, but these findings have not been compared to patients who did not develop IRIS [30]. This review was unable to find studies evaluating the regulatory T-cell function in TB-IRIS patients. This review has some limitation we did not assess the evidence strength of results presented in the articles included and also the risk of bias in these articles.

In conclusion, the findings presented in this review suggest that during TB-IRIS an increase in the specific response to Mtb antigens occurs, as evidenced by a higher number of IFN-γ producing cells and by higher levels of cytokines. The potential role of innate immune response, with increased production of proinflammatory cytokines and chemokines, as well as activated NK cells and macrophages was also observed during TB-IRIS. Taken together, these data suggest that expansion of Mtb specific cells may not be the determining factor for the occurrence of IRIS. Further studies are needed to better evaluate the dynamic of restoration of Mtb-specific memory cells and to clarify the role of innate immune responses in immunopathogenesis of TB-IRIS. Modulating the proinflammatory cytokine storm observed during IRIS may be beneficial to patients by decreasing morbidity and mortality of TB-IRIS patients.

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