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Review

Paradoxical reactions and immune reconstitution inflammatory syndrome in tuberculosis

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SUMMARY

The coalescence of the HIV-1 and tuberculosis (TB) epidemics in Sub-Saharan Africa has had a significant and negative impact on global health. The availability of effective antimicrobial treatment for both HIV-1 (in the form of highly active antiretroviral therapy (HAART)) and TB (with antimycobacterial agents) has the potential to mitigate the associated morbidity and mortality. However, the use of both HAART and antimycobacterial therapy is associated with the development of inflammatory paradoxical syndromes after commencement of therapy. These include paradoxical reactions (PR) and immune reconstitution inflammatory syndromes (IRIS), conditions that complicate mycobacterial disease in HIV seronegative and seropositive individuals. Here, we discuss case definitions for PR and IRIS, and explore how advances in identifying the risk factors and immunopathogenesis of these conditions informs our understanding of their shared underlying pathogenesis. We propose that both PR and IRIS are characterized by the triggering of exaggerated inflammation in a setting of immunocompromise and antigen loading, via the reversal of immunosuppression by HAART and/or antimycobacterials. Further understanding of the molecular basis of this pathogenesis may pave the way for effective immunotherapies for the treatment of PR and IRIS.

1. Introduction

The natural history of tuberculosis (TB) is characterized by immunological processes and the associated inflammation, which are necessary for the host defence against *Mycobacterium tuberculosis* (MTB), yet can also result in disease via immunopathology and associated tissue damage. The contribution of inflammation to the morbidity associated with TB is not limited to its primary presentation, but also has an impact once effective antimicrobial treatment is commenced, in the form of the phenomenon termed 'paradoxical reaction' (PR). This is defined as the worsening of existing lesions or presentation of new lesions during anti-TB therapy,[1] and is typically associated with exaggerated inflammatory symptoms including fever,[2] lymphadenitis,[3] and pulmonary manifestations[1] (illustrated in Figure 1). Post-therapeutic clinical deterioration in TB has been noted for many years,[4] and subsequent epidemiological investigations have

estimated the frequency of PR to lie between 2% and 23%.[2,3,5–8] Similar paradoxical consequences of antimycobacterial therapy have been described in infections with non-tuberculous mycobacteria (NTM) such as *Mycobacterium ulcerans*,[9] suggesting that this phenomenon is not specific to MTB infection.

The single strongest risk factor for the development of active TB is HIV co-infection.[10] This includes patients with preserved blood CD4+ T cell counts[11] and those treated effectively with highly active antiretroviral therapy (HAART).[12] HIV infection is also associated with a syndrome in which paradoxical inflammatory consequences occur during therapy: the immune reconstitution inflammatory syndrome (IRIS). Here, the commencement of HAART leads to an exacerbation of an existing opportunistic disease, or unmasking of a previously subclinical infection.[13] IRIS is most frequently observed in mycobacterial infections,[13,14] and several forms have been described in HIV/TB co-infected individuals. The commonest of these is paradoxical TB-IRIS, in which inflammatory exacerbations of TB symptoms occur after commencement of HAART in HIV-seropositive patients being treated for active TB,[15] the frequency of which was estimated to be 15.7% in a meta-analysis of 3459 individuals.[13] A second form, unmasking

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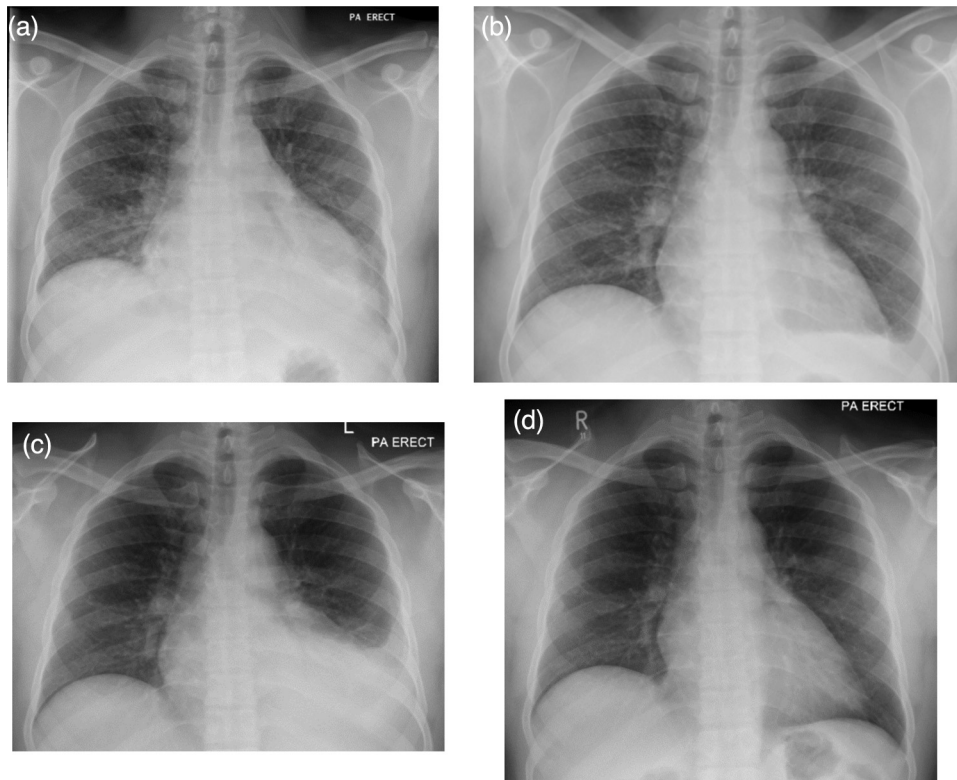 E-mail address: lucy.bell.09@ucl.ac.uk (Lucy C.K. Bell).

Figure 1. Chest X-rays (CXR) demonstrating radiographic features of a paradoxical reaction in an HIV-negative male with pericardial and miliary drug-sensitive tuberculosis (TB). (a) CXR at presentation showing an enlarged heart and lung nodules; the patient commenced antimycobacterial therapy and corticosteroids. (b) CXR at 2 weeks after the commencement of treatment (when the patient was feeling better) revealing radiographic improvement. (c) CXR at week 5 (patient reported a slight increase in breathlessness) showing deterioration with cardiac enlargement and worsening left pleural effusion; anti-TB therapy was continued and the corticosteroid dose was increased. (d) CXR at week 10; the patient was feeling better and the chest radiograph shows considerable improvement.

TB-IRIS, is when a new presentation of active TB arises after commencing HAART. It has been so named as it is ostensibly due to HAART-mediated reconstitution of the immune response causing inflammation and thus revealing/'unmasking' disease.[16] The occurrence of unmasking TB-IRIS is thought to be lower than paradoxical TB-IRIS,[15] with estimates varying between 1.4% and 23%.[14,17–19] It is also suggested that HIV-seropositive individuals with active TB may have an increased incidence of PR when commencing antimycobacterial therapy, compared to HIV-sero-negative individuals.[6,17]

The clinical features of TB-IRIS are similar to those of PR, commonly including fever, while other manifestations reflect the baseline form of TB disease, such as lymph node swelling and deterioration of respiratory symptoms.[15] Like PR, a cardinal feature is exacerbated inflammation – which is also implicated more widely in IRIS caused by a range of pathogens in HIV-seropositive individuals.[13] These include NTM such as *Mycobacterium avium* complex (MAC) organisms.[15,20] Inflammatory symptoms including lymphadenopathy and fever are also common in NTM-related IRIS.[21]

Both PR and mycobacterial IRIS are associated with morbidity and mortality, though this is dependent on factors such as the primary disease site. For example, patients with neurological lesions may have higher rates of mortality and suffer residual neurological deficits,[22] while lymph node disease generally causes much less significant sequelae and episodes often self-limit.[3] The mortality of paradoxical TB-IRIS has been estimated as 3.2% within a recent meta-analysis,[13] and considerable rates of hospitalization and intervention in TB-IRIS patients have been observed.[23,24] Similar results were reported in a large randomized controlled trial (RCT) with the aim of optimizing the timing of HAART initiation.[25,26] Understanding the pathogenesis of PR and IRIS

may improve clinical outcomes for these patients through promoting avoidance of PR/IRIS and identifying potential for immunotherapies, and may also contribute to a wider under-standing of inflammatory pathologies in TB and mycobacterial diseases. In this review, we discuss the definitions of PR and TB-IRIS, and explore risk factors and immunopathogenesis in these inflammatory mycobacterial syndromes. We propose a core, underlying hypothesis for their occurrence, and discuss the potential for immunotherapeutic treatment.

2. Defining paradoxical reactions and immune reconstitution inflammatory syndrome

Although a formal consensus case definition for PR has not been established, the worsening of clinical or radiological findings following the initiation of appropriate antimycobacterial therapy is broadly accepted as the cardinal description of this condition.[27] Case definitions for paradoxical and unmasking TB-IRIS are still debated,[15,28] but consensus definitions for use in clinical and research settings have now been validated in prospective studies.[18,28,29]

The consensus definition for paradoxical TB-IRIS is summarized by a confirmed diagnosis of TB with a positive initial response to antimycobacterial therapy, onset of defined inflammatory clinical manifestations within 3 months of subsequently commencing HAART, with exclusion of plausible alternative explanations for this clinical deterioration.[28] Wider pan-pathogen IRIS case definitions have similarly used temporal criteria in relation to HAART initiation and identification of inflammatory manifesta-tions.[30] Developing a consensus case definition for unmasking TB-IRIS has posed more of a challenge, largely due to the range of

alternative explanations for a new diagnosis of TB after HAART initiation, such as residual immunodeficiency predisposing to new primary infection, a previously missed diagnosis of prevalent TB, reactivation of latent TB infection, or progression of existing subclinical disease.[16] The latter two scenarios fulfil a definition of 'unmasking' disease, but also represent the natural history of TB (in that that they may have occurred without HAART being given); both may contribute to the high incidence rates of active TB observed during the first 3 months of HAART.[31] The consensus case definition currently in use emphasizes that the diagnosis of unmasking TB-IRIS is predicated on heightened clinical inflammatory manifestations in a primary presentation of TB occurring within 3 months of commencing HAART.[16,28] This recognizes that there may be a wider incidence of 'ART-associated TB', and a prospective study using this definition has suggested that the incidence rate of true unmasking TB-IRIS as part of this group may be lower than previously reported, at 1.6 per 100 person-years.[29]

The shared features of the case definitions for PR and the forms of TB-IRIS are the initiation of effective therapy, with subsequent development of heightened inflammatory clinical manifestations. The importance of inflammation in these syndromes is further emphasized by the observation that patients already experiencing unmasking IRIS have increased rates of PR after antimycobacterial therapy,[17] inferring a critical underlying proinflammatory phenotype in these syndromes. The triggering of inflammatory reactions by a therapeutic intervention can be postulated, therefore, as the shared underlying disease definition for PR and TB-IRIS. Consequently, investigating risk factors and the inflammatory processes involved in these conditions may inform understanding of a common pathogenesis.

3. Responses to treatment, risk factors, and pathogenesis

Antimycobacterial therapy and HAART have an impact on two major factors that may subsequently be implicated in the pathogenesis of PR/IRIS: mycobacterial bacillary/antigen loads and immune system function. Previous consideration of the underlying pathogenesis of both PR and TB-IRIS has highlighted their interaction as the potential critical determinant of disease.[15,22]

The role of mycobacterial bacillary/antigen loads in determining pathogenesis is suggested by several observations. An increased risk of both PR and IRIS has been identified in patients with disseminated or extrapulmonary disease, who are considered to have higher bacillary/antigen loads, although this may not necessarily be the case in patients with apparently isolated peripheral lymph node disease.[1,8,17,18,32] The risk of paradoxical IRIS has been demonstrated to be highest when HAART is initiated early during antimycobacterial therapy, at a point when mycobacterial loads are still near-maximal. This risk has been confirmed in large RCTs seeking to optimize the timing of HAART initiation.[25,26,33] Additionally, higher bacillary/antigen loads have been measured directly in patients who go on to develop PR/IRIS compared to those who do not. In the lung, baseline sputum smear positivity was independently associated with paradoxical TB-IRIS in one study,[34] and a trend towards a similar association has been observed in patients with PR.[3] MTB culture-positive cerebrospinal fluid at the time of diagnosis of TB meningitis (TBM) is a more common finding in patients with subsequent paradoxical TBM-IRIS.[35] Also, patients with paradoxical TB-IRIS have higher pre-treatment levels of the MTB antigen lipoarabinomannan in their urine.[36]

These findings suggest that higher bacillary/antigen levels are a risk factor for, or at least strongly associated with, PR and IRIS, and thus may have utility in predicting patients at greatest risk of the syndromes. However, its contribution to pathogenesis is less clear. It has been suggested that rapid killing of bacilli with antibiotics may lead to the release of large amounts of microbial components,

which stimulate an exuberant inflammatory response,[4] and that higher baseline numbers of bacilli may potentiate this process and so contribute to PR/IRIS. It has also been postulated that this is essentially a hypersensitivity reaction to persistent mycobacterial antigen.[3] However, high baseline bacillary/antigen levels may also be a marker of severe immunodeficiency, which as discussed later is a separate risk factor for PR and IRIS; thus, whether these high antigenic loads directly contribute to pathogenesis is difficult to conclude. It is also possible that variability in antigen persistence between anatomical locations may contribute to the differential risk of PR/IRIS in different primary disease sites, e.g. the strong association with lymph node disease[3,15] may arise because this is a site where persistent mycobacterial antigen might be anticipated, as has been shown for other pathogens.[37]

A recent prospective study observed a correlation between positive sputum culture (as a marker of high antigenic load) and inflammatory monocyte activation markers, which were strongly predictive for the development of paradoxical TB-IRIS, suggesting that in pathogenesis, high antigen loads and inflammation may work in concert.[38] Although investigations into the relationship between PR/IRIS and MTB strain types have not identified specific links,[39,40] host genetic associations between single nucleotide polymorphisms in proinflammatory cytokines and the development of IRIS have been demonstrated,[41] suggesting that host inflammatory responses may be stronger determinants of IRIS pathogenesis than mycobacterial factors.

Other data also indicate the contribution of the host immune system to the pathogenesis of PR and IRIS. Pre-existing immunodeficiency has been shown to predispose to both PR and IRIS. In HIV-seronegative individuals, low baseline lymphocyte counts at the time of TB diagnosis are associated with an increased risk of developing PR,[2,8] whilst in HIV-seropositive individuals, low CD4+ T cell counts have been related to subsequent IRIS in a range of studies.[13,18,23,24,34] Advanced HIV disease has also been identified as a risk factor for IRIS, consequent on high pre-HAART HIV-1 viral loads.[34] Given that a relationship between active TB and lymphopenia has been reported,[42] and it is suggested that active TB is associated with a degree of immunodeficiency,[43] one could hypothesize that a baseline immunodeficient phenotype in both HIV seronegative and seropositive individuals is implicated in the development of both PR and IRIS. A mouse model of MAC-IRIS has been utilized to explore mechanisms underlying this, and has suggested that it is immune reconstitution occurring in a lymphopenic setting that is the causative factor, rather than specific cellular functions or phenotypes generated during immunodeficiency.[44]

Studies in humans also indicate that immune reconstitution is implicated in the pathogenesis of PR/IRIS, supporting the use of this latter term in the clinical nomenclature. The risk of PR has been associated with the rate of peripheral blood lymphocyte recovery after commencing antimycobacterial therapy,[1,2,8] a finding that also suggests that the active TB treatment response involves an immune reconstitution process. In HIV-seropositive patients, the rate of CD4+ T cell count recovery post-HAART has been associated with both paradoxical[32] and unmasking IRIS.[19] Although this has not been corroborated in some studies,[5,17] it has been speculated that HAART may also trigger local immune reconstitution via increased numbers of infiltrating MTB-specific CD4+ T cells at the site of infection, which may not be reflected in peripheral blood.[17]

The processes of immune reconstitution that occur after HAART are well-described and their relevance to the development of IRIS has previously been considered.[15,45] During the 3 months following HAART initiation, at which time IRIS risk is highest,[25,26,33] the principal population of CD4+ T cells contributing to rising peripheral counts are activated CD45RO+ memory cells.[46] These redistribute from sites of sequestration,[47] lending support to the

hypothesis that MTB-specific T cells may infiltrate infection sites, with the potential to exacerbate inflammatory processes.[15] Whether CD4+ T cells themselves are the main agent of pathogenic immune reconstitution has been questioned, as some patients experience IRIS before any evident rise in circulating CD4+ count,[15,19,29] although local reconstitution might still be occurring in such a context.[17] Other immune-reconstituting processes have been described in the 3 months post-HAART, such as increases in blood B and natural killer (NK) cell counts and recovery of CD4+ T cell functional deficits.[45] It is interesting to speculate on the role of these processes in IRIS. However, other observations support the hypothesis that reconstitution of T helper 1 (Th1) CD4+ T cell-driven cell-mediated immune (CMI) responses is central to PR/IRIS. Both are associated with the conversion of tuberculin skin tests (TSTs) from anergic (negative) to positive after treatment initiation;[1,6,20] this demonstrates in vivo that patients experiencing these syndromes have reconstituted CMI, as the TST is a classic model of a CMI delayed-type hypersensitivity response. HAART initiation is also associated with a shift from T helper 2 (Th2) to Th1 cytokine patterns,[48] and the restoration of T cell lymphoproliferative responses.[46] MAC-IRIS has been found to involve vigorous granulomatous inflammation at the tissue level, another characteristic marker of CMI.[49]

4. Immunopathogenesis and immune phenotypes

Observations in both HIV seronegative and seropositive patients implicate Th1-driven CMI responses in a setting of multibacillary disease and immunodeficiency in the pathogenesis of PR/IRIS. This is supported by data from the MAC-IRIS mouse model, where it was demonstrated that CD4+ T cells and interferon gamma production can drive disease.[44] Expansions of MTB-specific Th1 cells have been identified in patients with paradoxical and unmasking IRIS,[50,51] but the finding that similar expansions can occur in non-IRIS active TB patients calls into question whether these are the central or sole pathogenic events.[52] As such, a wide body of work has been performed assessing immune phenotypes in patients undergoing PR/IRIS, to inform understanding of the immunopathogenesis of these conditions. This is summarized in Table 1, and includes both innate and adaptive immune response phenotypes.

Although a role for the adaptive immune response is supported, for example by studies showing expansions of pathogen-specific polyfunctional CD4+ T cells in pan-pathogen IRIS,[53] the innate immune response has been strikingly implicated in PR/IRIS

pathogenesis through descriptions of raised myeloid-derived proinflammatory cytokine levels and increased numbers of activated monocytes.[38,54] However, the mechanistic basis of these observations is not yet understood, and they may represent phenomena resulting from the underlying disease process, rather than driving PR/IRIS pathogenesis. Several observed responses have been implicated in TB pathogenesis more broadly. These include raised levels of circulating matrix metalloproteinases (MMPs)[55] and tumour necrosis factor alpha (TNFα) levels,[35,56] lending support to the view that they may at least be implicated in PR/IRIS disease manifestations, if not in pathogenesis.

A recent hypothesis regarding the underlying mechanism of IRIS describes an 'uncoupling' of the adaptive and innate responses, wherein an immunodeficient antigen-loaded phenotype leads to a build-up of primed innate immune cells (such as monocytes and macrophages), which are then triggered to cause exuberant inflammation once the adaptive immune response reconstitutes post-HAART.[57] Whether these populations of primed innate immune cells exist in vivo is yet to be established, though a hypothesis that reconciles roles for both innate and adaptive immunity in the pathogenesis of IRIS is compelling. This concept of a baseline phenotype that predisposes to PR/IRIS raises the question of whether an underlying host predisposition is necessary for PR/IRIS to occur. Work suggesting that not only do those who develop IRIS appear to have an increased frequency of some inflammatory cytokine polymorphisms,[41] but also that differences in cytokine pathways may be detectable prior to starting IRIS-triggering treatment in some settings,[58] does implicate host genetics as a potential contributor, and may ultimately offer opportunities for genotypic risk stratification in clinical practice.

5. Core pathogenesis of PR and IRIS and clinical insights

The known risk factors for PR and IRIS strongly suggest that the key baseline phenotype in both syndromes involves immune compromise and multibacillary disease. It is also clear that immune reconstitution processes occurring during therapy, primarily involving CMI, are central to pathogenesis. Exploring immune phenotypes has suggested roles for both the adaptive and innate immune responses in triggering exaggerated inflammation, a cardinal feature of these syndromes. These observations have resulted in a hypothesis to explain IRIS in HIV-seropositive individuals, where TB-IRIS results from accelerated outgrowth of MTB in poorly inflamed or anergic environments in an immuno-suppressed patient, followed by a pathological inflammatory

Table 1
Immune phenotypes in paradoxical reactions and TB-IRIS

Immune phenotype[a]	Paradoxical reaction	Paradoxical TB-IRIS	Unmasking TB-IRIS
Adaptive responses			
Expansion of mycobacteria-specific Th1 CD4+ T cells		Bourgarit et al.[50]	Wilkinson et al.[51]
Increased activation of circulating CD4+ T cells		Antonelli et al.[71,b]	
Expansion of polyfunctional CD4+ T cells		Mahnke et al.[53,b]	
Increased numbers of γδ T cells		Bourgarit et al.[72]	
Low expression of MTB-specific anti-phenolic glycolipid antibody		Simonney et al.[40]	
Innate responses			
Hypercytokinaemia/increased circulating proinflammatory cytokines/spontaneous cytokine production	Bekker et al.[73]	Andrade et al.[38], Tadokera et al.[54]	
Increased MMP expression		Tadokera et al.[55]	
Increased numbers/activation of peripheral blood monocytes	Hawkey et al.[3]	Andrade et al.[38]	
Dysregulated complement component expression in monocytes		Tran et al.[74]	
High TLR-2 expression on monocytes		Tan et al.[75]	
High rates of NK cell activation		Pean et al.[76]	Conradie et al.[77]
High neutrophil counts and TNFα at site of disease	Jung et al.[7]	Marais et al.[35]	

TB, tuberculosis; IRIS, immune reconstitution inflammatory syndrome; MTB, Mycobacterium tuberculosis; MMP, matrix metalloproteinase; TLR, toll-like receptor; NK, natural killer; TNFα, tumour necrosis factor alpha.

[a] All observations were made in samples obtained from the peripheral blood (serum, plasma, peripheral blood mononuclear cells, whole blood), unless otherwise stated.

[b] Study including IRIS events caused by TB and other pathogens.

overshoot when immunosuppression is reversed, resulting in the clinical manifestations[16,57] (illustrated in Figure 2). This is supported by widely described clinical phenotypes in HIV-seropositive patients, with high rates of TB smear positivity found in the absence of symptoms,[59] commonly observed mycobacteraemia,[60] and high rates of undiagnosed disseminated TB identified at post-mortem.[61] The tissue pathology of TB in HIV co-infection is also supportive, where a paucity of inflammation with many extracellular bacilli is described.[62]

We suggest that this hypothesis for HIV TB-IRIS, where a baseline immunosuppressed phenotype is the precursor to inflammatory pathogenesis, is broadly applicable to mycobacterial PR/IRIS, including in HIV-seronegative individuals (summarized in Figure 3). The similarity of PR and TB-IRIS risk factors, such as pre-treatment immunosuppression, disseminated disease, and the rate of reconstitution, supports this hypothesis. There are some instances in which presentations, of PR in particular, may not be explained easily by this schema, such as lymph node swelling after or late in antimycobacterial treatment.[3] However, even these could be accounted for by persistent mycobacterial antigen being detected by the host immune response, resulting in a PR episode.

It has been reported that HIV-seronegative patients who are treated with anti-TNFα therapy for autoinflammatory conditions not only have an increased risk of active TB due to immunosuppression, but may also experience a form of TB-IRIS when therapy is withdrawn.[63] This also fits the proposed model (Figure 3), where immunosuppression may lead to the establishment of poorly inflamed, multibacillary TB lesions and hyper-inflammatory disease when immunosuppression is removed.[57] The pathology in another significant mycobacterial disease, leprosy, may also be
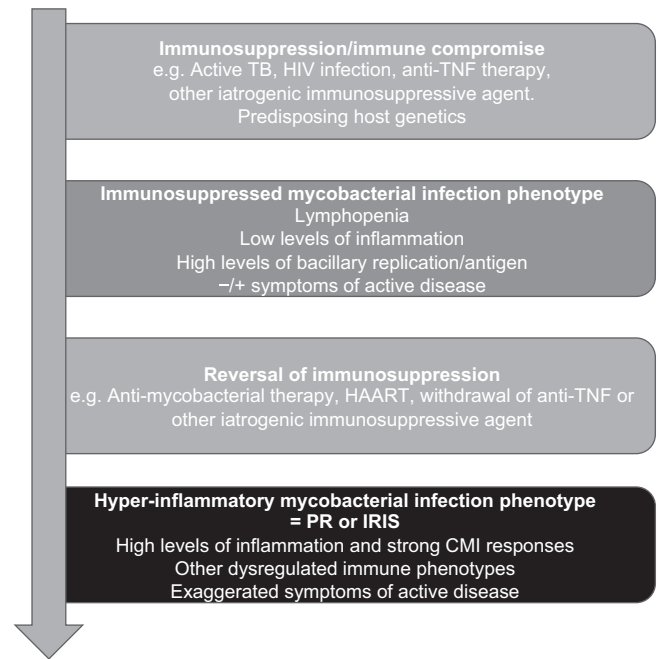

Figure 3. Proposed common mechanism for pathogenesis in mycobacterial PR/IRIS. Flowchart depicting the proposed hypothesis for the development of PR and IRIS in mycobacterial infections in HIV seronegative and seropositive individuals.

analogous to this. In leprosy, a cutaneous and neural infection caused by *Mycobacterium leprae*, commencing therapy is associated with type 1 reversal reactions, in which poorly inflamed multibacillary lepromatous-type lesions shift towards highly inflamed tuberculoid-type lesions.[64] Recent advances in our understanding of the molecular basis of lepromatous leprosy, which have implicated type I interferon-driven immunosuppression,[65] may therefore inform our understanding of baseline states in the pathogenesis of PR/IRIS.

Other recent advances in identifying the basis of mycobacterial pathogenesis, and which may enhance an appreciation of PR/IRIS, have been made in the *Mycobacterium marinum* zebrafish infection model. This has shown that either too little or too much production of TNFα can drive disease, whilst 'just the right amount' is protective[56,66] – a so-called 'Goldilocks effect'. The downstream impact of either low or high TNFα is macrophage necrosis and uncontrolled extracellular replication of bacteria. The potential relevance of this phenotype to human TB is confirmed by genetic studies of homologues of implicated factors.[56,66] The model of a spectrum of inflammation being bimodally associated with disease may be very relevant to PR/IRIS, as it mechanistically demonstrates how an overly exuberant inflammatory response driven by TNFα, such as might be found in PR/IRIS patients at the time of reaction, can cause mycobacterial disease. In addition, this model has been used to explore immunotherapeutic options for TB, by demonstrating that genetic polymorphisms in components of the implicated pathways can predict responses to corticosteroid treatment in TBM,[56] thus potentially paving the way for host-directed immunotherapy in TB.

As corticosteroids are a mainstay of therapeutic intervention in the treatment of IRIS,[67] this may provide opportunities for patient stratification and therapeutic optimization in PR and IRIS. It has been shown that the effective use of corticosteroids in IRIS correlates with the suppression of innate-produced proinflammatory cytokines, suggesting a potential mechanism for their efficacy and demonstrating that modulation of the immune system in these syndromes has therapeutic potential.[68] Further understanding of the molecular basis of pathogenesis may also yield novel
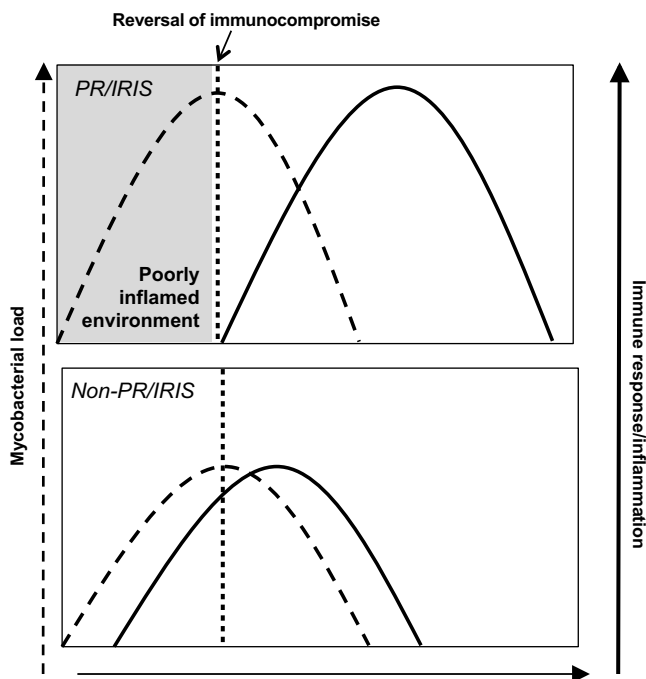

Figure 2. Schematic diagram demonstrating the proposed pathogenesis of PR/IRIS in relation to time, mycobacterial load, and the immune response. The lower panel shows pathogenesis in the non-PR/IRIS context, wherein mycobacterial burden and the immune response/inflammation are closely coupled temporally, and where inflammation (and clinical features) resolves in tandem with mycobacterial burden when treatment is initiated. The upper panel shows pathogenesis in the context of PR/IRIS, wherein the baseline immunocompromised phenotype means there is excessive mycobacterial outgrowth in a poorly inflamed environment. When treatment is initiated that reverses immunocompromise, an excessively exuberant inflammatory response develops (PR/IRIS) with symptoms temporally distinct from those arising as part of the original untreated infection.

therapeutic targets, as the potential for host-directed immuno-therapy for TB based on specific inflammatory pathways is increasingly investigated.[69] Immunotherapy for PR/IRIS has also been explored in the mouse MAC-IRIS model, in which the blockade of interleukin 6 (IL-6) signalling with neutralizing antibodies extended survival and alleviated pathology.[70] However, as both PR and IRIS are self-limiting in many cases, the specific utility of corticosteroids and other immune-modulating treatments should be considered in the context of the impact of inflammation in specific clinical scenarios.

6. Conclusions

PR and IRIS constitute a spectrum of clinical presentations occurring during infections with mycobacteria including MTB and NTM. They are associated with morbidity and some mortality in HIV seronegative and seropositive patients. We propose that the unifying feature of these conditions is the triggering of inflammation in an immunodeficient, antigen-loaded setting, via the reversal of immunosuppression, an event that may itself result from the initiation of immune-reconstituting treatments or the withdrawal of immunosuppressive therapies. Defining the fundamental processes that are shared between the syndromes and the molecular mechanisms underlying this pathogenesis will inform the development of appropriate immunotherapy for PR/IRIS and may also enhance our understanding of the role of immunodeficiency and inflammation in mycobacterial and related infections.

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References

1. Cheng VC, Ho PL, Lee RA, Chan KS, Chan KK, Woo PC, et al. Clinical spectrum of paradoxical deterioration during antituberculosis therapy in non-HIV-infected patients. *Eur J Clin Microbiol Infect Dis* 2002;**21**:803–9.
2. Cheng SL, Wang HC, Yang PC. Paradoxical response during anti-tuberculosis treatment in HIV-negative patients with pulmonary tuberculosis. *Int J Tuberc Lung Dis* 2007;**11**:1290–5.
3. Hawkey CR, Yap T, Pereira J, Moore DA, Davidson RN, Pasvol G, et al. Characterization and management of paradoxical upgrading reactions in HIV-uninfected patients with lymph node tuberculosis. *Clin Infect Dis* 2005;**40**:1368–71.
4. Campbell IA, Dyson AJ. Lymph node tuberculosis: a comparison of various methods of treatment. *Tubercle* 1977;**58**:171–9.
5. Breen R, Smith C, Bettinson H, Dart S, Bannister B, Johnson M, et al. Paradoxical reactions during tuberculosis treatment in patients with and without HIV co-infection. *Thorax* 2004;**59**:704–7.
6. Narita M, Ashkin D, Hollender ES, Pitchenik AE. Paradoxical worsening of tuberculosis following antiretroviral therapy in patients with AIDS. *Am J Respir Crit Care Med* 1998;**158**:157–61.
7. Jung JW, Shin JW, Kim JY, Park IW, Choi BW, Seo JS, et al. Risk factors for development of paradoxical response during anti-tuberculosis treatment in HIV-negative patients with pleural tuberculosis. *Tohoku J Exp Med* 2011;**223**:199–204.
8. Cheng VC, Yam WC, Woo PC, Lau SK, Hung IF, Wong SP, et al. Risk factors for development of paradoxical response during antituberculosis therapy in HIV-negative patients. *Eur J Clin Microbiol Infect Dis* 2003;**22**:597–602.
9. Nienhuis WA, Stienstra Y, Abass KM, Tuah W, Thompson WA, Awuah PC, et al. Paradoxical responses after start of antimicrobial treatment in *Mycobacterium ulcerans* infection. *Clin Infect Dis* 2012;**54**:519–26.
10. Walker NF, Meintjes G, Wilkinson RJ. HIV-1 and the immune response to TB. *Future Virol* 2013;**8**:57–80.
11. Sonnenberg P, Glynn JR, Fielding K, Murray J, Godfrey-Faussett P, Shearer S. How soon after infection with HIV does the risk of tuberculosis start to increase?. A retrospective cohort study in South African gold miners. *J Infect Dis* 2005;**191**:150–8.
12. Gupta A, Wood R, Kaplan R, Bekker LG, Lawn SD. Tuberculosis incidence rates during 8 years of follow-up of an antiretroviral treatment cohort in South Africa: comparison with rates in the community. *PLoS One* 2012;**7**:e34156.
13. Müller M, Wandel S, Colebunders R, Attia S, Furrer H, Egger M. Immune reconstitution inflammatory syndrome in patients starting antiretroviral therapy for HIV infection: a systematic review and meta-analysis. *Lancet Infect Dis* 2010;**10**:251–61.
14. Haddow LJ, Moosa MY, Mosam A, Moodley P, Parboosing R, Easterbrook PJ. Incidence, clinical spectrum, risk factors and impact of HIV-associated immune reconstitution inflammatory syndrome in South Africa. *PLoS One* 2012;**7**:e40623.
15. Lawn SD, Bekker LG, Miller RF. Immune reconstitution disease associated with mycobacterial infections in HIV-infected individuals receiving antiretrovirals. *Lancet Infect Dis* 2005;**5**:361–73.
16. Lawn SD, Wilkinson RJ, Lipman MCI, Wood R. Immune reconstitution and "unmasking" of tuberculosis during antiretroviral therapy. *Am J Respir Crit Care Med* 2008;**177**:680–5.
17. Breen RA, Smith CJ, Cropley I, Johnson MA, Lipman MC. Does immune reconstitution syndrome promote active tuberculosis in patients receiving highly active antiretroviral therapy? *AIDS* 2005;**19**:1201–6.
18. Worodria W, Menten J, Massinga-Loembe M, Mazakpwe D, Bagenda D, Koole O, et al. Clinical spectrum, risk factors and outcome of immune reconstitution inflammatory syndrome in patients with tuberculosis–HIV coinfection. *Antivir Ther* 2012;**17**:841–8.
19. Valin N, Pacanowski J, Denoeud L, Lacombe K, Lalande V, Fonquernie L, et al. Risk factors for "unmasking immune reconstitution inflammatory syndrome" presentation of tuberculosis following combination antiretroviral therapy initiation in HIV-infected patients. *AIDS* 2010;**24**:1519–25.
20. French MA, Mallal SA, Dawkins RL. Zidovudine-induced restoration of cell-mediated immunity to mycobacteria in immunodeficient HIV-infected patients. *AIDS* 1992;**6**:1293–7.
21. Phillips P, Bonner S, Gataric N, Bai T, Wilcox P, Hogg R, et al. Nontuberculous mycobacterial immune reconstitution syndrome in HIV-infected patients: spectrum of disease and long-term follow-up. *Clin Infect Dis* 2005;**41**:1483–97.
22. Afghani B, Lieberman JM. Paradoxical enlargement or development of intracranial tuberculomas during therapy: case report and review. *Clin Infect Dis* 1994;**19**:1092–9.
23. Lawn SD, Myer L, Bekker LG, Wood R. Tuberculosis-associated immune reconstitution disease: incidence, risk factors and impact in an antiretroviral treatment service in South Africa. *AIDS* 2007;**21**:335–41.
24. Luetkemeyer AF, Kendall MA, Nyirenda M, Wu X, Ive P, Benson CA, et al. Tuberculosis immune reconstitution inflammatory syndrome in A5221 STRIDE: timing, severity, and implications for HIV–TB programs. *J Acquir Immune Defic Syndr* 2014;**65**:423–8.
25. Naidoo K, Yende-Zuma N, Padayatchi N, Naidoo K, Jithoo N, Nair G, et al. The immune reconstitution inflammatory syndrome after antiretroviral therapy initiation in patients with tuberculosis: findings from the SAPiT trial. *Ann Intern Med* 2012;**157**:313–24.
26. Abdool Karim SS, Naidoo K, Grobler A, Padayatchi N, Baxter C, Gray A, et al. Timing of initiation of antiretroviral drugs during tuberculosis therapy. *N Engl J Med* 2010;**362**:697–706.
27. Park JA, Park SS, Park SE. A paradoxical reaction during antituberculosis therapy for congenital tuberculosis. *Int J Infect Dis* 2009;**13**:e279–81.
28. Meintjes G, Lawn SD, Scano F, Maartens G, French MA, Worodria W, et al. Tuberculosis-associated immune reconstitution inflammatory syndrome: case definitions for use in resource-limited settings. *Lancet Infect Dis* 2008;**8**:516–23.
29. Worodria W, Massinga-Loembe M, Mayanja-Kizza H, Namaganda J, Kambugu A, Manabe YC, et al. Antiretroviral treatment-associated tuberculosis in a prospective cohort of HIV-infected patients starting ART. *Clin Dev Immunol* 2011;**2011**:758350.
30. Haddow LJ, Easterbrook PJ, Mosam A, Khanyile NG, Parboosing R, Moodley P, et al. Defining immune reconstitution inflammatory syndrome: evaluation of expert opinion versus 2 case definitions in a South African cohort. *Clin Infect Dis* 2009;**49**:1424–32.
31. HIV-CAUSAL Collaboration. Impact of antiretroviral therapy on tuberculosis incidence among HIV-positive patients in high-income countries. *Clin Infect Dis* 2012;**54**:1364–72.
32. Breton G, Duval X, Estellat C, Poaletti X, Bonnet D, Mvondo Mvondo D, et al. Determinants of immune reconstitution inflammatory syndrome in HIV type 1-infected patients with tuberculosis after initiation of antiretroviral therapy. *Clin Infect Dis* 2004;**39**:1709–12.
33. Blanc FX, Sok T, Laureillard D, Borand L, Rekacewicz C, Nerrienet E, et al. Earlier versus later start of antiretroviral therapy in HIV-infected adults with tuberculosis. *N Engl J Med* 2011;**365**:1471–81.
34. Bonnet M, Baudin E, Jani IV, Nunes E, Verhoustraten F, Calmy A, et al. Incidence of paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome and impact on patient outcome. *PLoS One* 2013;**8**:e84585.
35. Marais S, Meintjes G, Pepper DJ, Dodd LE, Schutz C, Ismail Z, et al. Frequency, severity, and prediction of tuberculous meningitis immune reconstitution inflammatory syndrome. *Clin Infect Dis* 2013;**56**:450–60.
36. Conesa-Botella A, Loembé MM, Manabe YC, Worodria W, Mazakpwe D, Luzinda K, et al. Urinary lipoarabinomannan as predictor for the tuberculosis immune reconstitution inflammatory syndrome. *J Acquir Immune Defic Syndr* 2011;**58**:463–8.
37. Kim TS, Hufford MM, Sun J, Fu YX, Braciale TJ. Antigen persistence and the control of local T cell memory by migrant respiratory dendritic cells after acute virus infection. *J Exp Med* 2010;**207**:1161–72.
38. Andrade BB, Singh A, Narendran G, Schechter ME, Nayak K, Subramanian S, et al. Mycobacterial antigen driven activation of CD14++CD16-monocytes is a predictor of tuberculosis-associated immune reconstitution inflammatory syndrome. *PLoS Pathog* 2014;**10**:e1004433.
39. Perrin FM, Breen RA, Lipman MC, Shorten RJ, Gillespie SH, McHugh TD. Is there a relationship between *Mycobacterium tuberculosis* strain type and TB paradoxical reaction? Thorax 2005;60:706–7.
40. Simonney N, Dewulf G, Herrmann JL, Gutierrez MC, Vicaut E, Boutron C, et al. Anti-PGL-Tb1 responses as an indicator of the immune restoration syndrome in HIV–TB patients. *Tuberculosis (Edinb)* 2008;**88**:453–61.

41. Price P, Morahan G, Huang D, Stone E, Cheong KY, Castley A, et al. Polymorphisms in cytokine genes define subpopulations of HIV-1 patients who experienced immune restoration diseases. *AIDS* 2002;**16**:2043–7.
42. Beck JS, Potts RC, Kardjito T, Grange JM. T4 lymphopenia in patients with active pulmonary tuberculosis. *Clin Exp Immunol* 1985;**60**:49–54.
43. Roberts T, Beyers N, Aguirre A, Walzl G. Immunosuppression during active tuberculosis is characterized by decreased interferon-γ production and CD25 expression with elevated forkhead box P3, transforming growth factor-β, and interleukin-4 mRNA levels. *J Infect Dis* 2007;**195**:870–8.
44. Barber DL, Mayer-Barber KD, Antonelli LR, Wilson MS, White S, Caspar P, et al. Th1-driven immune reconstitution disease in *Mycobacterium avium*-infected mice. *Blood* 2010;**116**:3485–93.
45. Guihot A, Bourgarit A, Carcelain G, Autran B. Immune reconstitution after a decade of combined antiretroviral therapies for human immunodeficiency virus. *Trends Immunol* 2011;**32**:131–7.
46. Autran B, Carcelain G, Li TS, Blanc C, Mathez D, Tubiana R, et al. Positive effects of combined antiretroviral therapy on CD4+ T cell homeostasis and function in advanced HIV disease. *Science* 1997;**277**:112–6.
47. Pakker NG, Notermans DW, De Boer RJ, Roos MT, Wolf FD, Hill A, et al. Biphasic kinetics of peripheral blood T cells after triple combination therapy in HIV-1 infection: a composite of redistribution and proliferation. *Nat Med* 1998;**4**:208–14.
48. Imami N, Antonopoulos C, Hardy GA, Gazzard B, Gotch FM. Assessment of type 1 and type 2 cytokines in HIV type 1-infected individuals: impact of highly active antiretroviral therapy. *AIDS Res Hum Retroviruses* 1999;**15**:1499–508.
49. Zamir E, Hudson H, Ober RR, Kumar SK, Wang RC, Read RW, et al. Massive mycobacterial choroiditis during highly active antiretroviral therapy: another immune-recovery uveitis? *Ophthalmology* 2002;**109**:2144–8.
50. Bourgarit A, Carcelain G, Martinez V, Lascoux C, Delcey V, Gicquel B, et al. Explosion of tuberculin-specific Th1-responses induces immune restoration syndrome in tuberculosis and HIV co-infected patients. *AIDS* 2006;**20**:F1–7.
51. Wilkinson KA, Meintjes G, Seldon R, Goliath R, Wilkinson RJ. Immunological characterisation of an unmasking TB-IRIS case. *South Afr Med J* 2012;**102**:512–7.
52. Meintjes G, Wilkinson KA, Rangaka MX, Skolimowska K, van Veen K, Abrahams M, et al. Type 1 helper T cells and FoxP3-positive T cells in HIV–tuberculosis-associated immune reconstitution inflammatory syndrome. *Am J Respir Crit Care Med* 2008;**178**:1083–9.
53. Mahnke YD, Greenwald JH, Dersimonian R, Roby G, Antonelli LR, Sher A, et al. Selective expansion of polyfunctional pathogen-specific CD4+ T cells in HIV-1-infected patients with immune reconstitution inflammatory syndrome. *Blood* 2012;**119**:3105–12.
54. Tadokera R, Meintjes G, Skolimowska KH, Wilkinson KA, Matthews K, Seldon R, et al. Hypercytokinaemia accompanies HIV–tuberculosis immune reconstitution inflammatory syndrome. *Eur Respir J* 2011;**37**:1248–59.
55. Tadokera R, Meintjes GA, Wilkinson KA, Skolimowska KH, Walker N, Friedland JS, et al. Matrix metalloproteinases and tissue damage in HIV–tuberculosis immune reconstitution inflammatory syndrome. *Eur J Immunol* 2014;**44**:127–36.
56. Tobin DM, Roca FJ, Oh SF, McFarland R, Vickery TW, Ray JP, et al. Host genotype-specific therapies can optimize the inflammatory response to mycobacterial infections. *Cell* 2012;**148**:434–46.
57. Barber DL, Andrade BB, Sereti I, Sher A. Immune reconstitution inflammatory syndrome: the trouble with immunity when you had none. *Nat Rev Microbiol* 2012;**10**:150–6.
58. Grant PM, Komarow L, Lederman MM, Pahwa S, Zolopa AR, Andersen J, et al. Elevated interleukin 8 and T-helper 1 and T-helper 17 cytokine levels prior to antiretroviral therapy in participants who developed immune reconstitution inflammatory syndrome during ACTG A5164. *J Infect Dis* 2012;**206**:1715–23.
59. Wood R, Middelkoop K, Myer L, Grant AD, Whitelaw A, Lawn SD, et al. Undiagnosed tuberculosis in a community with high HIV prevalence: implications for tuberculosis control. *Am J Respir Crit Care Med* 2007;**175**:87–93.
60. Von Reyn CF, Kimambo S, Mtei L, Arbeit RD, Maro I, Bakari M, et al. Disseminated tuberculosis in human immunodeficiency virus infection: ineffective immunity, polyclonal disease and high mortality. *Int J Tuberc Lung Dis* 2011;**15**:1087–92.
61. Rana FS, Hawken MP, Mwachari C, Bhatt SM, Abdullah F, Ng'ang'a LW, et al. Autopsy study of HIV-1-positive and HIV-1-negative adult medical patients in Nairobi, Kenya. *J Acquir Immune Defic Syndr* 2000;**24**:23–9.
62. Nambuya A, Sewankambo N, Mugerwa J, Goodgame R, Lucas S. Tuberculous lymphadenitis associated with human immunodeficiency virus (HIV) in Uganda. *J Clin Pathol* 1988;**41**:93–6.
63. Rivoisy C, Amrouche L, Carcelain G, Séréni D, Bourgarit A. Paradoxical exacerbation of tuberculosis after TNFα antagonist discontinuation: beware of immune reconstitution inflammatory syndrome. *Joint Bone Spine* 2011;**78**:312–5.
64. Britton WJ, Lockwood DN. Leprosy. *Lancet* 2004;**363**:1209–19.
65. Teles RM, Graeber TG, Krutzik SR, Montoya D, Schenk M, Lee DJ, et al. Type I interferon suppresses type II interferon-triggered human anti-mycobacterial responses. *Science* 2013;**339**:1448–53.
66. Roca FJ, Ramakrishnan L. TNF dually mediates resistance and susceptibility to mycobacteria via mitochondrial reactive oxygen species. *Cell* 2013;**153**:521–34.
67. Meintjes G, Wilkinson RJ, Morroni C, Pepper DJ, Rebe K, Rangaka MX, et al. Randomized placebo-controlled trial of prednisone for paradoxical TB-associated immune reconstitution inflammatory syndrome. *AIDS* 2010;**24**:2381–90.
68. Meintjes G, Skolimowska KH, Wilkinson KA, Matthews K, Tadokera R, Conesa-Botella A, et al. Corticosteroid-modulated immune activation in the tuberculosis immune reconstitution inflammatory syndrome. *Am J Respir Crit Care Med* 2012;**186**:369–77.
69. Mayer-Barber KD, Andrade BB, Oland SD, Amaral EP, Barber DL, Gonzales J, et al. Host-directed therapy of tuberculosis based on interleukin-1 and type I interferon crosstalk. *Nature* 2014;**511**:99–103.
70. Barber DL, Andrade BB, McBerry C, Sereti I, Sher A. Role of IL-6 in *Mycobacterium avium*-associated immune reconstitution inflammatory syndrome. *J Immunol* 2014;**192**:676–82.
71. Antonelli LR, Mahnke Y, Hodge JN, Porter BO, Barber DL, DerSimonian R, et al. Elevated frequencies of highly activated CD4+ T cells in HIV+ patients developing immune reconstitution inflammatory syndrome. *Blood* 2010;**116**:3818–27.
72. Bourgarit A, Carcelain G, Samri A, Parizot C, Lafaurie M, Abgrall S, et al. Tuberculosis-associated immune restoration syndrome in HIV-1-infected patients involves tuberculin-specific CD4 Th1 cells and KIR-negative gamma-delta T cells. *J Immunol* 2009;**183**:3915–23.
73. Bekker LG, Maartens G, Steyn L, Kaplan G. Selective increase in plasma tumor necrosis factor-α and concomitant clinical deterioration after initiating therapy in patients with severe tuberculosis. *J Infect Dis* 1998;**178**:580–4.
74. Tran HT, Van den Bergh R, Loembé MM, Worodria W, Mayanja-Kizza H, Colebunders R, et al. Modulation of the complement system in monocytes contributes to tuberculosis-associated immune reconstitution inflammatory syndrome. *AIDS* 2013;**27**:1725–34.
75. Tan DB, Lim A, Yong YK, Ponnampalavanar S, Omar S, Kamarulzaman A, et al. TLR2-induced cytokine responses may characterize HIV-infected patients experiencing mycobacterial immune restoration disease. *AIDS* 2011;**25**:1455–60.
76. Pean P, Nerrienet E, Madec Y, Borand L, Laureillard D, Fernandez M, et al. Natural killer cell degranulation capacity predicts early onset of the immune reconstitution inflammatory syndrome (IRIS) in HIV-infected patients with tuberculosis. *Blood* 2012;**119**:3315–20.
77. Conradie F, Foulkes AS, Ive P, Yin X, Roussos K, Glencross DK, et al. Natural killer cell activation distinguishes *Mycobacterium tuberculosis*-mediated immune reconstitution syndrome from chronic HIV and HIV/MTB coinfection. *J Acquir Immune Defic Syndr* 2011;**58**:309–18.