6 Vesikari T, Karvonen A, Prymula R, et al. Efficacy of human rotavirus vaccine against rotavirus gastroenteritis during the first 2 years of life in European infants: randomised, double-blind controlled study. *Lancet* 2007; **370:** 1757–63.

7 Global Advisory Committee on Vaccine Safety, 11–12 December 2013. *Wkly Epidemiol Rec* 2014; 89: 53–60.

8 Soares-Weiser K, Maclehose H, Bergman H, et al. Vaccines for preventing rotavirus diarrhoea: vaccines in use. *Cochrane Database Syst Rev* 2012; **11:** cd008521.

9 Grant LR, Watt JP, Weatherholtz RC, et al. Efficacy of a pentavalent human-bovine reassortant rotavirus vaccine against rotavirus gastroenteritis among American Indian children. *Pediatr Infect Dis J* 2012; **31:** 184–88.

10 Gladstone BP, Ramani S, Mukhopadhya I, et al. Protective effect of natural rotavirus infection in an Indian birth cohort. *New Engl J Med* 2011; **365:** 337–46.

11 Bar-Zeev N, Kapanda L, Tate JE, et al. Effectiveness of monovalent rotavirus vaccine in infants in Malawi after programmatic roll-out: an observational and case-control study. *Lancet Infect Dis* 2014; published online Jan 29. http://dx.doi.org/10.1016/S1473-3099(14)71060-6.

12 Groome MJ, Page N, Cortese MM, et al. Effectiveness of monovalent human rotavirus vaccine against admission to hospital for acute rotavirus diarrhoea in South African children: a case-control study. *Lancet Infect Dis* 2014; **14:** 1096–104.

Tuberculosis-associated immune reconstitution inflammatory syndrome: a manifestation of adaptive or innate immunity?

Published Online
February 9, 2015
http://dx.doi.org/10.1016/
S1473-3099(15)70026-5

See Articles page 429

In *The Lancet Infectious Diseases,* Shruthi Ravimohan and colleagues[1] investigate whether immunological profiles before and after antiretroviral therapy (ART) can distinguish patients co-infected with HIV and tuberculosis who develop tuberculosis-associated immune reconstitution inflammatory syndrome (IRIS) from those who do not develop this disorder and those who have early mortality. The investigators noted decreased pre-ART concentrations of several pro-inflammatory cytokines in patients with tuberculosis-associated IRIS (eg, interleukin [IL]-6 adjusted odds ratio [OR] per 1 $\log_{10}$ increase 0·40 [95% CI 0·18–0·89]), which resurged during the disease. After ART initiation, the most prominent changes in patients with tuberculosis-associated IRIS were reported for cytokines related to innate immunity (eg, IL-6: adjusted OR 1·7 [95% CI 1·2–2·5] and tumour necrosis factor [TNFα: 1·5 [1·0–2·2]), whereas recovery of the CD4 T-cell compartment was similar to that shown in control participants who survived without a diagnosis of tuberculosis-associated IRIS.

Elisabeth Schneider/Look At Sciences/Science Photo Library

These findings seem to challenge the fundamental role of T cells in patients with tuberculosis-associated IRIS. Findings from early key reports pointed towards an overproduction of inflammatory T-helper-1 cytokines, such as interferon-γ, as being the driving force behind tuberculosis-associated IRIS.[2] Lately, however, increasing evidence is emerging implicating the innate immune system in this syndrome.

Why is it that so many studies of tuberculosis-associated IRIS report different or even conflicting observations? In truth, tuberculosis-associated IRIS is a disease with many faces. Even when guidelines proposed by the International Network For The Study of HIV-Associated IRIS are used,[3] patients diagnosed with tuberculosis-associated IRIS still present with symptoms that widely vary in type, severity, and timing.[4] As such, the clinical picture of this disease might not be uniform across different studies, which could lead to observations becoming just as heterogeneous as the disease itself. For example, Ravimohan and colleagues now show the importance of the study of tuberculosis-associated IRIS during the actual IRIS event, when the inflammatory process is peaking. The increase in IL-6 concentrations between baseline and 4 weeks of ART in patients with tuberculosis-associated IRIS was much more pronounced

in patients who developed IRIS between weeks 2 and 4 of ART (early tuberculosis-associated IRIS) than in those who developed IRIS later than 4 weeks of ART (late disease). Of note, patients with early disease had their IRIS event closer to the 4 week timepoint than those with late disease. This finding shows the complex cytokine kinetics in tuberculosis-associated IRIS, whereby a phase of increasing and subsequently decreasing cytokine concentrations flank the cytokine peak during the IRIS event. Studies measuring cytokines on the slopes of this so-called cytokine storm might therefore be underestimating their importance. This drawback restricts the comparability between different studies, emphasising the kind of effect that the heterogeneous nature of tuberculosis-associated IRIS can have on our observations.

Despite such heterogeneity, the similar patterns emerging in research of tuberculosis-associated IRIS are intriguing. We previously linked tuberculosis-associated IRIS with reduced pre-ART concentrations of IL-6, which sharply increased during the IRIS event.[5] In concert, we noted the same pattern in the concentrations of lipopolysaccharide-binding protein (a well-known acute phase protein linked to IL-6 stimulation of the liver). Our findings are very similar to those of Ravimohan and colleagues', suggesting that tuberculosis-associated IRIS is paradoxically preceded by a relative decrease in inflammation—a calm before the cytokine storm. By contrast with this theory, a study reported increased concentrations of IL-18 in a group of patients with paradoxical and unmasking tuberculosis-associated IRIS, both before and during ART.[6] This contrast again shows the high degree of variability that accompanies the study of cytokines in tuberculosis-associated IRIS. Nonetheless, these seemingly conflicting studies do have some common ground. Both IL-6 and IL-18 were increased during tuberculosis-associated IRIS and both cytokines originate from cells of the innate immune system. In fact, perturbations in innate cytokines have become a recurring feature in research of tuberculosis-associated IRIS,[1,5,7,8] inviting researchers to reassess the role of the adaptive and innate immune system in patients with this disease. Monocytes, for example, have been associated with both predisposition to and development of tuberculosis-associated IRIS.[9] This viewpoint is supported by findings from independent studies showing that mycobacterial antigen-driven activation of a particular subset of monocytes is a predictor of tuberculosis-associated IRIS.[10] Therefore, the role of innate immunity in tuberculosis-associated IRIS might be much more elaborate than previously believed.

In conclusion, the amount of evidence suggesting that innate immunity is a driving mechanism behind tuberculosis-associated IRIS is steadily increasing. The fundamental role of T cells in this disease might therefore have to be reconsidered. Although we need to be mindful of the high degree of clinical heterogeneity when comparing different studies of tuberculosis-associated IRIS, present research might be heading towards a shift in our understanding of this disease.

*Odin Goovaerts, *Luc Kestens*
Immunology Unit, Department of Biomedical Sciences, Institute of Tropical Medicine, Nationalestraat 155, Antwerp B-2000, Belgium (OG, LK); and Department of Biomedical Sciences, University of Antwerp, Universiteitsplein 1, Antwerpen, Belgium (OG, LK)
lkestens@itg.be

We declare no competing interests.

1 Ravimohan S, Tamuhla N, Steenhoff AP, et al. Immunological profiles to distinguish tuberculosis-associated immune reconstitution inflammatory syndrome and non-immune reconstitution inflammatory syndrome death in HIV-infected adults with pulmonary tuberculosis starting antiretroviral therapy: a prospective observational cohort study. *Lancet Infect Dis* 2015; published online Feb 9. http://dx.doi.org/10.1016/S1473-3099(15)70008-3.

2 Bourgarit A, Carcelain G, Martinez V, et al. Explosion of tuberculin-specific Th1-responses induces immune restoration syndrome in tuberculosis and HIV co-infected patients. *AIDS* 2006; **20:** F1–7.

3 Meintjes G, Lawn SD, Scano F, et al. Tuberculosis-associated immune reconstitution inflammatory syndrome: case definitions for use in resource-limited settings. *Lancet Infect Dis* 2008; **8:** 516–23.

4 Worodria W, Menten J, Massinga-Loembe M, et al. Clinical spectrum, risk factors and outcome of immune reconstitution inflammatory syndrome in patients with tuberculosis-HIV coinfection. *Antivir Ther* 2012; **17:** 841–48.

5 Goovaerts O, Jennes W, Massinga-Loembé M, et al, for the TB-IRIS Study Group. LPS-binding protein and IL-6 mark paradoxical tuberculosis immune reconstitution inflammatory syndrome in HIV patients. *PLoS One* 2013; **8:** e81856.

6 Tan HY, Yong YK, Andrade BB, Shankar EM, et al. Plasma interleukin-18 levels are a biomarker of innate immune responses that predict and characterize tuberculosis-associated immune reconstitution inflammatory syndrome. *AIDS* 2015; published online Jan 5. DOI:10.1097/QAD.0000000000000557.

7 Conesa-Botella A, Meintjes G, Coussens AK, et al. Corticosteroid therapy, vitamin D status, and inflammatory cytokine profile in the HIV-TB immune reconstitution inflammatory syndrome (TB-IRIS). *Clin Infect Dis* 2012; **55:** 1004–11.

8 Meintjes G, Skolimowska KH, Wilkinson KA, et al. Corticosteroid-modulated immune activation in the tuberculosis immune reconstitution inflammatory syndrome. *Am J Respir Crit Care Med* 2012; **186:** 369–77.

9 Tran HT, Van den Bergh R, Vu TN, et al, for the TB-IRIS Study Group. The role of monocytes in the development of Tuberculosis-associated Immune Reconstitution Inflammatory Syndrome. *Immunobiology* 2014; **219:** 37–44.

10 Andrade BB, Singh A, Narendran G, 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.