Immune reconstitution inflammatory syndromes after commencement of antiretroviral therapy in HIV patients with severe immunodeficiency

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Approximately 20% of HIV patients who commence antiretroviral therapy (ART) with a $CD4^+$ T cell count of <100/μL will develop an immune reconstitution inflammatory syndrome (IRIS) irrespective of their country of origin. An IRIS results from the augmentation of immune responses against pathogens causing a recognised and treated infection (paradoxical IRIS) or an unrecognised infection (unmasking IRIS) that results in excessive and/or atypical inflammation. While commencement of ART before a recognised infection is optimally treated results in an overall survival benefit, an IRIS often results in hospitalisation and substantial morbidity and death when associated with infections of the central nervous system. It is therefore important to elucidate pathogenic mechanisms so that preventative and therapeutic strategies can be improved.

Increasing evidence indicates that development of an IRIS is not directly related to the rate of $CD4^+$ T cell increase or HIV viral load decline after ART is commenced. Rather, it is related to a high pathogen load and immune dysregulation before ART is commenced and the expansion of pathogen-specific T cells after ART commencement. In the case of tuberculosis-associated IRIS (TB-IRIS), the immune dysregulation before ART is characterised by abnormally activated innate immune responses in the context of severe $CD4^+$ T cell depletion. This particularly affects monocytes and macrophages and includes inflammasome activation in monocytes and production of pro-inflammatory cytokines, especially IFN-γ, TNF, IL-6 and IL-18. It seems likely that TNF contributes to neutrophil activation and that IL-18 contributes to the expansion of mycobacteria-specific $CD4^+$ T cells that are skewed towards a Th1 phenotype and activate monocytes/macrophages further.

Identification of patients at risk of an IRIS is facilitated by assessing inflammatory markers, particularly blood haemoglobin level and plasma levels of sCD14, D-dimers, IL-6 and CRP before ART is commenced. Prophylactic prednisolone therapy reduces the incidence of TB-IRIS in at-risk patients.