Naive CD4+ T cells (Th0) interact with dendritic cells in the T cell zone of secondary lymphoid organs. Depending on the type of cytokine stimulation by dendritic cells, Th0 T cells can differentiate into Th1, Th2, Th17 or Treg phenotypes. Th1 and Th17 T cells secrete INF-γ and IL-17, respectively, which promote pro-inflammatory immune responses. Conversely, Th2 and Treg T cells secrete IL-10/IL-4 and IL-10, respectively, which antagonise pro-inflammatory immune responses by suppressing Th1 and Th17 T cell development. It is thought that IRIS may be due to an imbalance of pro-inflammatory and anti-inflammatory immune responses during the immune reconstitution phase that occurs shortly after initiation of ARV therapy.
Preferential replication of HIV in secondary lymphoid tissue results in accumulation of viral gp120, which interacts with CD4 receptors expressed on CD4+ T cells. CD4 receptor stimulation promotes retention of CD4+ T cells in the lymph node by interference with lymph node homing and exit receptor regulation. ARV therapy inhibits viral replication and reverses the sequestration of CD4+ T cells. The first phase of immune reconstitution following ARV therapy is the redistribution of sequestered CD4+ T cells from the lymph nodes to peripheral blood and tissues. It has been shown that the majority of these cells are of a memory phenotype that may initiate uncontrolled pro-inflammatory immune responses to recall antigens.
Soon after initiation of ARV therapy, a large reduction in levels in virus replication in lymphoid tissue leads to a reversal of CD4+ T cell sequestration in lymph nodes resulting in their redistribution to peripheral blood and tissues. The majority of these cells are of a memory phenotype that may initiate pro-inflammatory immune responses to recall antigens. In IRIS, it is thought that Th1 and Th17 T cells responding to recall antigens derived from living/dead organisms or antigens in tissue may result in uncontrolled inflammation due to an unbalanced anti-inflammatory response by Treg and Th2 T cells.