The geographical overlap of HIV and malaria pandemics in Sub-Saharan Africa results in a considerable frequency of co-infections. Worldwide, *Plasmodium* species alone are responsible for 300-600 million clinical malaria episodes and 1.2 million deaths annually, most attributed to infection with *P. falciparum* which is prevalent in Sub-Saharan Africa, also the epicenter of the HIV pandemic with more than 20 million HIV-1 infected patients. Consequently, it is imperative to understand how both HIV and malaria interact and alter host immune responses in co-infected individuals. Clinical studies suggest that HIV-1 infected patients are at greater risk for severe malaria, and conversely, that malaria episodes in HIV-1 infected patients result in increased viremia and morbidity.

To understand the underlying pathology and immune mechanisms that lead to disease exacerbation observed in HIV-malaria co-infections, we have developed a rhesus macaque SIV-*P. fragile* co-infection model to mimic human HIV-1-*P. falciparum* co-infection. In our initial studies, we identified that co-infected animals exhibited a transient, but significant, 1-2 log increase in viremia during acute parasitemia. This elevation in viremia coincided temporally with an increase in systemic and CD4+ T cell immune activation. We hypothesize that acute parasitemia induced immune activation is driving virus replication. Furthermore, we observed that this period of acute malaria was also marked by an increase in parasite transmission from macaques to mosquitoes in co-infected animals. This data, in conjunction with the aforementioned elevation in viremia, suggests that in a clinical setting, co-infection would, at least transiently, elevate the risk of transmission of both HIV and malaria. When studying the immune responses present during persistent co-infection, we observed that myeloid dendritic cells (mDC) from SIV-*P. fragile* co-infected macaques became hyporesponsive to TLR4 stimulation. This hyporesponsiveness coincided temporally with failure to control parasite levels. Dysfunction of mDC and monocytes has been documented in both HIV and malaria infections, including inhibition of phagocytosis, mDC maturation, and antigen presentation function. We hypothesized that in co-infection, the combination of host and pathogen factors that mDC and monocytes are exposed to during maturation shape their subsequent TLR responsiveness and may affect the development of an effective adaptive immune response. To further delineate the immunopathogenesis of SIV-*P. fragile* co-infection, we aimed to: 1) determine the responsiveness of mDC and monocytes to TLR ligands via an *ex vivo* stimulation assay that measured the ability of the aforementioned cells to make appropriate cytokines, and 2) determine the *in vivo* circulating levels of inflammatory and immunosuppressive cytokines. We found that monocytes from *P. fragile*-only infected animals exhibited a TLR hyperresponsiveness during acute malaria infection. However, this effect was not as evident in co-infected animals and the cytokine production was dominated by IL10, an immunosuppressive cytokine. In addition, we found that plasma cytokine levels followed the observed *ex vivo* results. These results suggest that co-infected animals may experience immunosuppression during acute malaria which could explain the clinical outcome of exacerbated disease in co-infected animals.