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**Title: Multi-layered, multifaceted role of CD4 T cell immune responses in HIV infection**

**Abstract**

CD4 T cells are the major target of HIV and progressively lost during the infection. However, emerging data suggest that HIV-specific CD4 T cell responses majorly contribute to the antiviral immune response. Indeed, the breadth and magnitude of HIV-specific IFN $\gamma$ + CD4 T cells have been associated with better disease outcome. Moreover, HIV-specific cytolytic CD4 T cells have been shown to directly inhibit viral replication and drive viral escape mutations at a fitness cost to the virus, while IL21+HIV-specific CD4 T cell responses have been implicated to provide help for HIV-specific CD8 T cells. The complexity of the anti-HIV CD4 T cell immunity becomes apparent in the finding that a small subset of anti-HIV IL-4+ IL-2+ CD40L+CD4 T cell responses is a strong correlate of protection in the modestly protective RV144 HIV vaccine trial. We recently discovered that there are several additional layers of CD4 T cell immunity that have not only different functions but also target different parts of HIV's proteome. Thus, these different layers of CD4 T cell immunity may have an underappreciated and unprecedented role in the antiviral immune response against HIV and may be critical to understand for HIV vaccine design.