Characterising the immunometabolic profile of HIV/TB co-infection in cohorts untreated and treated for HIV

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The synergy between HIV and *Mtb* during co-infection is well-established. The immunological deterioration and metabolic mechanisms that drive this synergy are poorly understood. Although ART suppresses viral replication, it gives rise to metabolic disruptions and adaptations beyond that induced by infection. Here, the serum cytokine and metabolic profiles of untreated HIV/TB co- infected, HIV/TB co-infected on ART, and HIV-negative TB-positive patients, as well as healthy controls, were measured and compared using multiplexed cytokine measurements and untargeted gas chromatography mass spectrometry. There was no significant difference between the cytokine levels of the diseased groups when compared to each other, however, the co-infected individuals were characterised by increased IL-6 and IFN-γ when compared to controls. These suggested a failure of immunoregulation, resulting in an increased disease burden. Metabolites indicative of cachexia, intestinal mucosa damage, and microbiome dysbiosis characterised co-infected individuals from the TB-positive population, while co-infected individuals were additionally distinguished from healthy controls by more extensive amino acid changes. Loss of gut integrity and subsequent microbial translocation results in increased inflammation and immune activation, culminating in a reduced appetite and malabsorption, causing exacerbated wasting in co-infected individuals. Treating HIV in the co-infected group revealed a metabolic return to values comparable to the healthy or the TB- positive population. It is unclear whether this represents a return to a more healthy state, as treatment exacerbated other metabolic alterations. These results suggest that HIV partially augments the HIV- *Mtb* synergy through its detrimental effects on gut health, affecting energy availability.