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Baseline humoral antibody repertoires in HIV-1 infected KS patients against Kaposi sarcoma herpesvirus (KSHV) using high-resolution antibody profiling

Kaposi sarcoma-associated herpesvirus (KSHV, or HHV-8) is the aetiologic agent of Kaposi Sarcoma (KS) and other rare lymphoproliferative diseases. KS is one of the most common cancers among people living with HIV (PLWH). In the era of antiretroviral treatment (ART), KS still occurs in PLWH despite complete suppression of HIV-1 viral load and with reconstituted CD4+ T cell counts. While HIV-1 co-infection increases the risk of KS onset ~600-fold, individuals infected with KSHV often remain asymptomatic, making it difficult to identify surrogate immune markers of protection against KS. Moreover, more than half of KS patients in sub-Saharan Africa (SSA) fail to achieve complete resolution with chemotherapeutic treatment, and 20-40% experience disease relapse within a year. These findings underscore the need to define prognostic indicators, such as the antibodies (Ab) against different KSHV viral antigenic determinants, or repertoire, at baseline upon KS diagnosis, and how they relate to longitudinal clinical factors and disease trajectory. Phage immunoprecipitation sequencing (PhIP-seq) enables high-throughput, peptide-level profiling of patient Ab repertoires against the human virome using the VirScan phage display library. Such profiles support broad and unbiased characterization of prior and ongoing antiviral humoral immune responses. Our preliminary data showed high similarity between patient antiviral Ab repertoires identified at baseline and post-chemotherapy; however, Ab repertoires identified segregated between responders and non-responders. These findings support the hypothesis that the presence of baseline Ab repertoires could serve as biomarkers to predict KS treatment outcomes. In this study, we profiled the Ab repertoires of treatment-naïve (baseline) plasma samples from 28 Zambian PLWH with KS, as a validation set for our main longitudinal study (n=260, Uganda). Viral Ab repertoires were quantified (breadth and magnitude), at the peptide, protein, and organism-level. These baseline serologic data will be integrated with longitudinal laboratory and clinical metadata, including HIV-related parameters, immune status, and clinical assessments. Our study establishes a framework for combining high-resolution Ab profiling with longitudinal clinical metadata to identify candidate immune biomarkers of KS progression and treatment response. Findings from this cohort may inform future studies aimed at improving risk stratification and monitoring KS clinical settings.