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**Polygenic analysis of genome-wide genotype data reveals genetic overlap between HIV acquisition and addiction traits**

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Polygenic approaches using genome-wide data have been hugely successful in confirming and quantifying the heritability of complex human traits. Here, we hypothesize that polygenic approaches can identify novel HIV risk variants by assessing pleiotropic effects in genetically overlapping phenotypes. We used LD Score Regression in a sample of 6,315 people living with HIV and 7,247 population controls to test for genetic overlap between HIV acquisition and 27 previously unrelated traits. Using LD Hub, a web tool that performs LD Score Regression, we identified inflammatory, behavioral and addiction traits that significantly overlapped with HIV acquisition. Inflammatory traits included ulcerative colitis and Crohn's disease, supporting the known relationship between increased inflammation and increased HIV susceptibility. We also observed an overlap between number of sexual partners, age at first sex and schizophrenia suggesting that genetic influences on behavior and development of psychiatric disease play a role in infection. Finally, we observed a strong relationship between the genetics of cannabis use (genetic correlation  $\sim 0.30$ ;  $p < 0.05$ ) and a weak overlap with smoking behavior (genetic correlation  $\sim 0.18$ ) and HIV acquisition. This relationship has not been previously reported and suggests that genetic predisposition to some forms of addiction may also lead to enhanced susceptibility to infection. Analysis of additional addiction traits and larger studies of HIV susceptibility can potentially uncover further shared etiologies. These results highlight the ability to use polygenic methods to gain new insights into complex diseases and add to the evidence for the role of risk taking behavior in HIV acquisition.