HBsAg serotype modulates HIV-1 replication and genome architecture in macrophages

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Despite advances in antiretroviral therapy (ART), we remain unable to eradicate HIV-1 from the body. This is largely due to our inability to find and remove the integrated proviral HIV-1 that makes up latent viral reservoirs. These reservoirs persist across a variety of cell types and organ systems, including liver-resident macrophages. Hepatitis B virus (HBV), another hepatotropic virus, is a common comorbidity in people with HIV-1 (PWH). With an estimated 5-10% of individuals affected globally, HIV-1/HBV coinfection is associated with increased incidence of hepatocellular carcinoma and accelerated liver disease progression. However, the mechanism(s) by which HIV-1 and HBV interact to mediate this elevated risk are unclear. As likely mediators of HIV-induced liver immunopathology, liver macrophages represent an understudied cell population in this context. During chronic HBV infection, liver macrophages are persistently exposed to hepatitis B surface antigen (HBsAg), which circulates throughout the body. Multiple major HBsAg serotypes exist, with distribution linked to genotype and geography, but the role of HBsAg serotype in shaping HIV-1 coinfection dynamics remains largely unexplored. Here, we characterize the impact of HBsAg serotype (*adr*, *adw*, *ayw*) on HIV-1 replication and genetic architecture in primary human monocyte-derived macrophages (hMDMs) infected with HIV-1_{ADA}. hMDM cultures were monitored over nine days post-infection, with DNA samples collected at days 3, 5, 7 and 9 to undergo near full-length (NFL) amplification of the HIV-1 proviral genome. HBsAg serotype modulated HIV-1_{ADA} replication dynamics; *adr* and *ayw* exposure reduced p24 secretion, while *adw* exposure had no effect. Gel electrophoresis of PCR-amplified *ayw*-exposed viral genomes revealed discrete additional bands below the expected full-length product, consistent with a subpopulation of genomes carrying large deletions - a pattern not consistently observed with *adr* or *adw*. These results suggest that HBsAg serotype differentially affects both the efficiency and genomic architecture of HIV-1 replication in hMDM, with *ayw* particularly linked to genomic changes. Future work will employ long-read Nanopore sequencing to validate and map these deletion events at nucleotide resolution and further characterize HIV-1 genetic architecture across HBsAg serotype exposures, informing how coinfections shape HIV-1 evolution in individuals with chronic HBV.

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