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# Physiological and Immunomodulatory Effects Of Δ-9-Tetrahydrocannabinol Depend on HIV Serostatus

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Pharmacokinetics (PK) and pharmacodynamics of Δ-9 tetrahydrocannabinol (THC) in people with HIV (PWH) is unclear. We aimed to understand if THC has altered metabolism and physiological effects in PWH. Twenty people without HIV (PWoH) and 4 PWH were administered THC (0.32mg/kg) intravenously and blood samples were collected before, 70 minutes (T1), and 5 hours (T2) after infusion. Plasma THC and metabolites (11-OH-THC, THC-COOH) were detected by Waters™ Xevo LC-MS-MS. Plasma cytokines were measured by Ella™ (Bio-Techne).

Compared to PWoH, PWH had elevated levels of circulating THC at T1 (1064.5±413.5 vs 80.8±35.2 pg/ml) and T2 (224.3±94.3 vs 33.0±14.7 pg/ml) while there were no differences in metabolite levels between the groups. This altered metabolism was accompanied by changes in THC's effect on heart rate, systolic blood pressure (SBP), and inflammation. THC increased heart rate more in PWoH than in PWH (average peak increase 39.9.3±3.5 and 12.25±3.1 bpm, respectively). THC had a dimorphic effect on SBP depending on HIV status: in PWoH SBP had an average peak increase of 18.3±2.4 mmHg, whereas in PWH SBP had an average peak decrease of -19.25±3.5 mmHg. THC reduced circulating pro-inflammatory cytokines (TNF, CXCL10/IP-10, CCL2/MCP-1, CCL3/MIP-1α, and CCL4/MIP-1β; ps<0.05), and increased IL-6, which has pro- and anti-inflammatory functions. PWH had higher levels of CXCL10 and IL-6, and there was an HIVxTHC interaction trend for CCL3 (p=.051).

These results reveal compelling differences in the exposure to and the physiological effects of THC in PWH, which may enhance THC's psychoactive and immunomodulatory effects, and risk of cannabis use disorder.