



## Marijuana Smoking in Men with HIV Infection: A Cause for Concern

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Marijuana is the second most widely smoked substance in our society after tobacco and interest in its medicinal applications is growing. Cannabis and comparable quantities of tobacco include similar amounts of volatile constituents and qualitatively similar tar components [1]. Despite the presence of these harmful substances, epidemiologic studies have generally failed to demonstrate significant and consistent associations between marijuana smoke and measures of chronic lung disease in HIV-uninfected persons [2].

However, people living with HIV (PLWH) may be at unique risk for the negative pulmonary health effects of marijuana exposure, as differences in lung biology in PLWH may increase susceptibility to pulmonary complications. Nearly 1 in 3 men with HIV infection smoke marijuana actively and since 1984 the prevalence of *daily* marijuana use among *current users* has increased significantly from 14% in 1984 to 32% in 2013 [3]. Marijuana has been linked to impairments in host defense [4,5] including abnormal responses of alveolar macrophages, which notably are also impacted by HIV infection. The intersection of increasing prevalence of marijuana use, increased risk of pulmonary disease and impaired host immune responses highlights the need to investigate possible enhanced susceptibility to long term harmful effects of marijuana exposure in PLWH.

In one of the first longitudinal cohort studies to address the relationship between marijuana use and pulmonary disease in HIV-infected

men, Lorenz et al. [6] have performed a sub-analysis of the Multicenter AIDS Cohort Study (MACS), a robust observational cohort collecting medical and health outcomes data for HIV-infected and uninfected men who have sex with men in the U.S. since 1984. Importantly, they excluded participants with daily or weekly heroin or cocaine use for one or more years during follow-up to minimize confounding due to concomitant other drug use in their analyses. They found that in HIV-infected participants, daily or weekly marijuana smoking was more common than in HIV-uninfected, and was associated with increased risk of infectious pulmonary diagnoses and self-reported chronic bronchitis after adjusting for tobacco smoking (modeled as status or as pack-years) and other risk factors. Tobacco smoking was also significantly associated with these outcomes, and the effect of marijuana and tobacco smoking was additive. These associations with marijuana were not statistically significant in HIV-uninfected individuals with similar demographic characteristics. Not surprisingly, low CD4 T cell count, <200 vs.  $\geq 350$  cells/ $\mu$ l, was strongly associated with increased risk of infectious disease when marijuana exposure was modeled as either a dichotomous categorical variable (current daily or weekly marijuana smoking vs. less than weekly or no marijuana use) or as a continuous variable (HR 3.37 [95% CI 2.58–4.41],  $p < 0.0001$  and HR 3.38 [95% CI 2.59–4.41],  $p < 0.0001$ , respectively) in the HIV-infected men. However, these findings remained statistically significant when analysis was restricted to clinical visits in those with CD4 > 200 cells/ $\mu$ l, suggesting that differences in host characteristics beyond immunodeficiency alone may mediate differential findings in HIV-infected and uninfected persons. Constitutive immune cell activation from infectious colonization [7], decreased phagocytic activity of alveolar macrophages [8], and reduced oxidative stress response to smoke [9] have been observed in HIV infection, but further pre-clinical studies are necessary to better understand the cellular biology that distinguishes HIV-infected and uninfected persons.

Questions remain about the long-term risk of marijuana use across multiple domains of lung health. One of the challenges has been how to model marijuana exposure to best assess risk of chronic use. Multiple studies have shown associations between *current* marijuana use and increased respiratory symptom burden, but it is reasonable to assume that cumulative marijuana exposure, synonymous to tobacco pack years, may play a more germane role in the development of other chronic lung diseases, notably emphysema and lung cancer. Unfortunately, observational studies are challenged to accurately calculate cumulative marijuana exposure given differences in the methods of use (joint, pipe, vaporized), differences in inhaling pattern, and differences in the

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quantity and quality of marijuana used among individuals, along with other factors [10]. Giving the recent legalization of marijuana for recreational use in many state jurisdictions, long term use of marijuana is likely to increase; with legalization, reporting of use may improve in accuracy as well. Future prospective studies can thus hopefully be more robust in informing our understanding of the effect of marijuana across a broader range of pulmonary disease.

The study by Lorenz and colleagues in this issue of *EClinicalMedicine* [6] takes an important first step in identifying marijuana smoking as a possible modifiable risk factor for lung disease in PLWH, independent of tobacco smoking and other drugs such as cocaine and heroin. These findings can inform healthcare providers who specialize in the care of HIV-infected patients. Their results support caution in the use of smoked forms of cannabis before further research on the relative risks and benefits in HIV-infected persons is undertaken, and may suggest the importance of counseling for best health practices among current users of marijuana. Finally, their findings also underscore the need for continued efforts at smoking cessation of tobacco cigarettes.

#### Authors' Contributions

D.W. and K.C. contributed equally to the design and writing of this commentary. The views represented are those of the authors and not necessarily those of the Department of Veterans Affairs.

#### Conflict of Interest

There is no conflict of interest present for the authors of this commentary.

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