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The Potential Impact of a Low Nicotine Product Standard for Cigarettes in Smokers Living With HIV

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Estimates of smoking prevalence among people living with HIV (PLWH) in the United States range between 40% and 84%, which is considerably greater than the smoking prevalence in the general U.S. population of 15.5% (Cooperman, 2016; Jamal et al., 2018). In PLWH, cigarette smoking is associated with an increased risk of all-cause mortality and contributes to approximately 24% of all non-HIV-related deaths (Helleberg et al., 2013; Lifson et al., 2010). Smokers living with HIV have a higher risk of developing smoking-related cancers compared with those without HIV. In general, PLWH have an increased cancer mortality risk compared with cancer patients without HIV (Engels et al., 2017). Lung cancer deaths account for approximately 10% of all non-HIV-related deaths, and smokers living with HIV develop lung cancer 20–30 years earlier than smokers without HIV (Winstone, Man, Hull, Montaner, & Sin, 2013). A recent study modeled the impact of smoking-attributable lung cancer mortality among PLWH in the United States (Reddy et al., 2017), and it found that of those who were adherent to antiretroviral therapy regimens, smokers living with HIV were 10 times more likely to die of lung cancer than of causes related to HIV. The model predicted that without changes to the smoking prevalence among PLWH in the United States, approximately 9% of this population, or roughly 59,900 people, will die of lung cancer (Reddy et al., 2017). Additionally, a recent North American cohort study of PLWH found that cigarette smoking likely contributed to 19% of all incident cancer

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diagnoses, including an estimated 94% of lung cancer diagnoses, suggesting that reducing smoking in this population could greatly improve health outcomes (Altekruse et al., 2018).

Smokers living with HIV are generally motivated to quit, but most are unsuccessful during cessation attempts (Cooperman, 2016). To date, there have been relatively few smoking cessation trials specifically targeting PLWH (Pacek & Crum, 2015), and some evidence suggests that conventional smoking cessation interventions have limited effectiveness in this population (Niaura, Chander, Hutton, & Stanton, 2012). Given the high smoking rates and low cessation rates, innovative approaches for reducing the public health burden of smoking in PLWH are critically needed.

One strategy proposed by tobacco control researchers was to reduce the overall burden of smoking in the general population. This could be achieved by limiting the amount of nicotine in commercially available cigarettes to a minimally addictive level (Donny et al., 2014). The U.S. Food and Drug Administration (FDA) currently has the authority to implement product standards for cigarettes, including setting a maximum allowable nicotine level, if such an action is likely to benefit population-level public health outcomes (Gottlieb & Zeller, 2017). Nicotine is the primary reinforcing constituent in cigarettes responsible for developing and sustaining smoking behavior. By mandating that all cigarettes sold in the United States have very low nicotine levels, nicotine dependence would likely be reduced, and smokers might have more success during quit attempts (Donny et al., 2014). Although very low nicotine content (VLNC) cigarettes still contain harmful combustible tobacco with similar toxicants as conventional cigarettes, they have lower addictive potential due to dramatically reduced nicotine levels (Richter et al., 2016). Thus, the primary mechanism by which a very low nicotine product standard for cigarettes may improve population-level public health outcomes would be via changes in smoking behaviors (e.g., quitting smoking) that result in reduced exposure to harmful tobacco toxicants.

Previous clinical trials of smokers using VLNC cigarettes have found significant reductions in urinary nicotine and toxicant exposure, decreases in the number of cigarettes smoked per day, lower nicotine-dependence levels, and increases in the number of quit attempts or quitting success (Donny et al., 2015; Hatsukami et al., 2013, 2018). Notably, many of these trials enrolled smokers not intending to quit, indicating that the effectiveness of this approach did not depend on the smoker's level of motivation. These findings suggest that a nicotine-reduction policy for cigarettes could have a major impact at the population level on smoking-related morbidity and mortality. A recent modeling study found that if a very low nicotine product standard for cigarettes were to be enacted in the United States by 2020, approximately 5 million people would quit smoking within the first year of policy implementation and 2.8 million smoking-related deaths would be averted by 2060 (Apelberg et al., 2018). Due to these promising findings, the FDA recently issued an Advanced Notice of Proposed Rulemaking regarding its intention to move forward with a very low nicotine product standard for cigarettes (Gottlieb & Zeller, 2017). If enacted, this tobacco control policy has the potential to be one of the most significant public health achievements in the 21st century.

Although the scientific literature supports the feasibility of a nicotine-reduction policy for cigarettes in the general population, there are potential concerns regarding unintended consequences of this regulatory approach, especially for priority populations such as PLWH (Donny et al., 2014; Gottlieb & Zeller, 2017). Potential negative consequences may include compensatory smoking to achieve desired nicotine levels, exacerbation of psychiatric symptoms, weight gain due to reduced nicotine exposure, and increased drug and alcohol consumption to substitute for nicotine (Donny et al., 2014). Although public health officials need to consider these potential unintended consequences, research has provided little evidence for concern. However, it is important to examine how certain subpopulations of smokers will respond to VLNC cigarettes to minimize unintended consequences of a nicotine-reduction policy.

To date, evidence from the general population of smokers suggests that switching to VLNC cigarettes does not lead to compensatory smoking because reductions, rather than increases, in daily cigarette consumption have been noted (Donny et al., 2015; Hatsukami et al., 2013, 2018). Furthermore, smoking topography studies (i.e., assessing per cigarette smoking intensity) have found that overall smoke exposure is lower when smoking VLNC cigarettes compared to a usual brand cigarette or conventional nicotine research cigarettes (Donny & Jones, 2009; Tidey et al., 2018). In general, data have indicated that smokers do not compensate for lower nicotine levels by smoking more cigarettes each day or by modifying the manner in which they smoke. However, it is unknown whether smokers living with HIV will respond differently.

With regard to potential unintended consequences of VLNC cigarettes, several secondary analyses from a large, 6-week trial of VLNC cigarettes in the general population of smokers (Donny et al., 2015) examined changes in depressive symptoms, substance use, and body weight. Smoking VLNC cigarettes for 6 weeks did not lead to significant increases in self-reported depressive symptoms; rather, participants with elevated depressive symptoms at baseline had significant decreases in depressive symptoms after 6 weeks of using VLNC cigarettes, which was an unexpected positive result (Tidey et al., 2017). In addition, no significant increases were observed in alcohol or cannabis consumption by smokers using VLNC cigarettes for 6 weeks (Dermody et al., 2016; Pacek et al., 2016). However, participants smoking VLNC cigarettes gained significantly more weight, similar to amounts commonly observed during smoking cessation, when compared to those smoking conventional nicotine cigarettes (Rupprecht et al., 2017). In sum, evidence suggests that the potential benefits of a very low nicotine product standard for cigarettes will likely outweigh the potential risks.

Previous VLNC cigarette trials primarily recruited healthy individuals from the general population of smokers (Donny et al., 2015; Hatsukami et al., 2013, 2018). Under the new public health regulatory standard for tobacco, the FDA must weigh the risks and benefits to the population as a whole before implementing tobacco product standards (Family Smoking Prevention and Tobacco Control Act, 2009). Therefore, as the FDA moves forward with enacting a very low nicotine product standard for cigarettes, it needs to consider the effects of smoking VLNC cigarettes in a broader population of smokers. Several VLNC cigarette trials are currently underway enrolling priority smoking populations, including people with

serious mental illness, substance use disorders, and those with low socioeconomic status (Tidey et al., 2018). During previous acute laboratory studies involving these priority smoking populations, smoking VLNC cigarettes did not result in more intense smoking topography characteristics, indicative of compensatory smoking, compared to smoking conventional cigarettes (Tidey et al., 2018). Also, VLNC cigarettes suppressed nicotine craving and withdrawal symptoms. Furthermore, participants reported less satisfaction and reward from VLNC cigarettes (Tidey et al., 2018). Overall, the initial results from the extant laboratory studies of VLNC cigarettes are encouraging, and data from ongoing clinical trials will eventually provide regulators with vital information about potential unintended consequences in these priority smoking populations.

Notably absent from the growing nicotine-reduction literature is the research assessing the potential impact of VLNC cigarette use by smokers living with HIV. Given the high smoking prevalence and increased risk for developing tobacco-related disease, a nicotine-reduction policy for cigarettes may be particularly beneficial to PLWH. Such a policy may increase successful quit attempts in smokers living with HIV, and thus reduce their risk of developing cardiac and pulmonary diseases. A modeling study in PLWH found substantial decreases in lung cancer mortality in PLWH when researchers included smoking cessation parameters in the model (Reddy et al., 2017). Additionally, smoking has been associated with poorer adherence and response to antiretroviral therapy (Miguez-Burbano et al., 2003), including unsuppressed viral load (Cioe et al., 2017; Cooperman, 2016; Cropsey et al., 2016) and lower CD4+ T-cell counts (Hile, Feldman, Alexy, & Irvine, 2016) in PLWH. Thus, by facilitating more successful quit attempts by PLWH, a very low nicotine product standard for cigarettes may also improve HIV-related health outcomes at a population level. Studies modeling the impact of a very low nicotine product standard for cigarettes on smoking cessation and viral suppression in PLWH could be highly informative to regulators.

Several concerns exist regarding the impact of a very low nicotine product standard for cigarettes on smokers living with HIV. First, similar to data gathered from the general population, research has indicated that the understanding of smokers living with HIV about the role that nicotine plays in smoking-related morbidity is inaccurate, such that nicotine is perceived as being a cause of smoking-related disease (Pacek, Rass, & Johnson, 2017). This misperception could have the unintended consequence that VLNC cigarettes are perceived as being safer than conventional cigarettes and could possibly delay quit attempts by PLWH. As a result, the development of education and mass media campaigns to clarify the risks associated with the use of VLNC cigarettes may be of particular importance for this population. Second, the prevalence of obesity among PLWH in the United States is now approximately that seen in the general population (Koethe et al., 2016), so the weight gain that has been observed as a result of using VLNC cigarettes (Rupprecht et al., 2017) is also a potential concern for smokers living with HIV. Providing access to alternative forms of nicotine (e.g., nicotine replacement therapy) may help to attenuate weight gain that results from the use of VLNC cigarettes. Additionally, the concurrent use of alternative nicotine sources and VLNC cigarettes may also help to curb withdrawal and craving symptoms that may occur when using VLNC cigarettes (Donny & Jones, 2009; Hatsukami et al., 2013).

Additional concerns for the potential impact of a nicotine-reduction policy on PLWH include exacerbation of any psychosocial comorbidities that disproportionately affect this population, such as psychiatric illness, substance use, and living in poverty. As noted previously, negative effects of VLNC cigarette use on psychiatric symptoms, drug use, and alcohol use have not been observed to date among smokers in general. Ideally, however, to assess the impact of this policy in PLWH, a VLNC cigarette trial targeting this population would be conducted. In such a trial, recruitment diversity (e.g., transgender women, men who have sex with men, sex workers, and homeless) would be important to ensure adequate representation of potentially vulnerable subgroups that may be experiencing one or more of these comorbidities. Data generated from such a trial would inform the FDA on the potential unintended consequences of a nicotine-reduction policy across subgroups of PLWH. In lieu of such a trial, results from the aforementioned priority smoking populations' VLNC cigarette trials can contribute meaningful information given the overlapping comorbidities with PLWH. Preliminary studies of the potential unintended consequences of a nicotine-reduction policy in the general population of smokers have been encouraging; nevertheless, additional research is needed to assure that a nicotine-reduction policy does not further exacerbate the smoking-related health disparities experienced by PLWH.

Due to the limited number of smoking cessation interventions in PLWH, and evidence for limited effectiveness of conventional smoking cessation interventions in this population, as well as the disproportionate prevalence of smoking and accompanying burden of disease, novel approaches to address the burden of tobacco use in this vulnerable population are vitally important. An FDA-mandated nicotine-reduction policy for all cigarettes sold in the United States is one strategy that may be particularly beneficial to PLWH. Tobacco control researchers and HIV health care providers must work together to ensure that PLWH benefit equitably from such a policy and to advocate for more evidence-based tobacco control strategies aimed at improving health outcomes in PLWH.

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