
Commentary

The United States National Cancer Institute's Coordinated Research Effort on Tobacco Use as a Major Cause of Morbidity and Mortality among People with HIV

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Abstract

The use of antiretroviral therapy for people with HIV (PWH) has improved life expectancy. However, PWH now lose more life-years to tobacco use than to HIV infection. Unfortunately, PWH smoke at higher rates and have more difficulty maintaining abstinence than the general population, compounding their risk for chronic disease. In this Commentary, we describe a United States National Cancer Institute-led initiative to address the relative lack of research focused on developing, testing, and implementing smoking cessation interventions for PWH. This initiative supports seven clinical trials designed to systematically test and/or develop and test adaptations of evidence-based smoking cessation interventions for PWH (eg, combination of behavioral and pharmacological). We summarize each project, including setting/recruitment sites, inclusion/exclusion criteria, interventions being tested, and outcomes. This initiative provides critical opportunities for collaboration and data harmonization across projects. The

knowledge gained will inform strategies to assist PWH to promote and maintain abstinence, and ensure that these efforts are adaptable and scalable, thereby addressing one of the major threats to the health of PWH. Reducing smoking behavior may be particularly important during the COVID-19 pandemic given that smokers who become infected with SARS-CoV-2 may be at risk for more severe disease.

Implications: This Commentary describes a National Cancer Institute-led initiative to advance the science and practice of treating tobacco use among PWH, which is now responsible for more life years lost than HIV. We describe the scope of the problem, the objectives of the initiative, and a summary of the seven funded studies. Harmonization of data across projects will provide information related to treatment mediators and moderators that was not previously possible. Stakeholders interested in tobacco cessation, including researchers, clinicians and public health officials, should be aware of this initiative and the evidence-base it will generate to advance tobacco treatment among this high-risk population.

Smoking Among People with HIV Is a Significant Health Issue

Antiretroviral therapy (ART) has improved life expectancy for people with HIV (PWH), with some showing a life expectancy similar to the general population.¹ This public health achievement has increased the need to address modifiable health risk behaviors, most notably tobacco use. PWH now lose more life-years to tobacco use than to HIV¹ and almost one-quarter of all deaths among PWH on antiretroviral therapy is attributed to smoking.² Although evidence is still emerging, tobacco use may be predictive of COVID-19 disease progression,³ making PWH who smoke particularly vulnerable to the current pandemic.

Unfortunately, the prevalence of tobacco use among PWH remains disproportionately higher than the general population.^{4,5} In 2014, the smoking rate among PWH in the United States was estimated to be 34%—two times greater than the general population (17%).⁶ Global prevalence is also high: 27 low- and middle-income countries surveyed in 2015 indicated ~24% of PWH smoke.⁷ Moreover, smoking cessation rates among PWH are lowest among those with a higher prevalence of health disparities including women, non-Hispanic blacks, those with lower educational attainment, and those living below poverty levels.⁶

State of the Science for Treating Tobacco Use Among PWH in the USA

In 2007, the NIH convened a workshop entitled, “Current Issues in Cigarette Smoking and HIV/AIDS” to bring together a multidisciplinary group of experts in tobacco use and HIV/AIDS (<https://archives.drugabuse.gov/meetings/2007/10/current-issues-in-cigarette-smoking-hiv-aids-workshop>). This workshop produced two Funding Opportunity Announcements (FOAs; PA-09-253, PA-08-254) led by the National Institute on Drug Abuse and a supplement in *AIDS Education and Prevention: An Interdisciplinary Journal*.⁸ This initiative highlighted understudied research areas and the importance of supporting future research.

While most PWH are interested in stopping smoking,⁴⁻⁶ particularly when cessation treatment is integrated with HIV care,⁹ there has been a relative lack of research focused on developing and testing smoking cessation interventions specifically for PWH.⁴ Reviews conclude that there are insufficient data to indicate that cessation interventions, which are efficacious in the general population, are similarly efficacious for PWH.^{5,10,11} For example, while mobile

behavioral treatments have demonstrated feasibility among PWH, abstinence rates for these interventions remained low at 3 months (10–12%).^{12,13} Pilot studies of behavioral interventions that incorporated motivational interviewing, contingency management, and strategies to address negative affect^{10,14} have shown promise for PWH, but fully powered trials are lacking.

Most studies that have examined the impact of tobacco treatment medications in PWH have utilized NRT, although a few examined varenicline.^{10,14} Recently, an algorithm-based approach for selecting smoking cessation medication demonstrated feasibility and reduced smoking behavior, but abstinence was not examined.¹⁵ Two randomized placebo-controlled trials conducted among PWH found that varenicline significantly increased quit rates, compared with placebo.^{16,17} However, cessation rates among varenicline-treated participants (28–29%)^{16,17} were lower than the general population (44%¹⁸). The limited available research indicates that behavioral interventions and medications yield moderate effects on cessation, but abstinence rates among PWH are generally lower than in the general population.^{5,11} There is also a lack of robust literature regarding strategies for switching treatments when smokers are not responsive to the initial treatment.

Despite evidence that current treatments are better than no treatment, implementation of evidence-based treatments for smoking cessation among PWH remains low, and recommended treatments are inconsistently provided.¹⁹ Recent data from the Veterans Aging Cohort Study found that PWH were less likely to receive NRT than veterans without HIV.¹⁹ Moreover, <4% of PWH use varenicline, and only 20% of HIV clinicians recommend varenicline to their patients who smoke.⁹ Digital interventions have taken on greater significance during the COVID-19 pandemic. However, a review of smoking cessation apps revealed that only two were developed for PWH.²⁰ Thus, there is an urgent need to identify novel and scalable strategies that meet the needs of the patients and setting (ie, community and clinic), including the need to deliver treatments remotely when face-to-face interactions pose health risks, such as during the COVID-19 pandemic. There is also a need for simultaneous evaluation of the patient, clinician, and community/organizational level factors that may impact intervention delivery.

The US National Cancer Institute-Led Research Initiative

The Office of AIDS Research, part of the NIH Office of the Director, is legislatively mandated to coordinate, evaluate, and budget for

the NIH AIDS research program. To address this tobacco-related health disparity among PWH, and the paucity of studies on tobacco use, the United States National Cancer Institute (NCI), in conjunction with the NIMHD, the Office of AIDS Research and the Office of HIV and AIDS Malignancy, issued two FOAs in 2018, entitled “Improving Smoking Cessation Interventions among People Living with HIV.” The emphasis was on “rigorous studies that propose to systematically test existing evidence-based smoking cessation interventions (eg, combination of behavioral and pharmacological) and/or to develop and test adaptations of evidence-based smoking cessation interventions...” for PWH (<https://grants.nih.gov/grants/guide/rfa-files/RFA-CA-18-027.html>, <https://grants.nih.gov/grants/guide/rfa-files/RFA-CA-18-028.html>); reissued as RFA-CA-20-035, RFA-CA-20-036). Six studies were funded: four R01 research project grants and two R21 exploratory/developmental grants. Another R01 consistent with the RFA was awarded nearly simultaneously and is included here. As required by the FOAs, all studies are clinical trials. **Supplementary Table 1** provides project summaries: the setting/sites, a description of subjects and the interventions, and primary and secondary outcomes (additional information here: <https://cancercontrol.cancer.gov/brp/tcrb/hiv.html>). All studies incorporate behavioral interventions, including: motivational interviewing, cognitive-behavioral skills training, peer navigation social support, contingency management, and managed problem solving for adherence. Four studies provide a smoking cessation medication (eg, NRT or varenicline) and the other three encourage PWH to utilize medication. Treatment delivery modes include in-person counseling, telephone counseling, mobile health applications, and video-assisted treatments. The primary outcome for the R01 grants is biochemically verified point-prevalence abstinence, whereas the R21 grants are focused on feasibility and acceptability of novel interventions. Several studies include implementation outcomes, including program reach, barriers, and facilitators of intervention delivery, and indices of cost-effectiveness as secondary outcomes. Finally, several studies plan to disseminate effective interventions to HIV clinics or national Quitlines.

To foster collaboration and data harmonization across projects, the NCI and NIMHD hosted a kick-off grantee meeting in October 2019. Several working groups were formed: (1) Data Harmonization; (2) Treatment Moderators; and (3) Non-Tobacco Substance Use. The Data Harmonization group created a core set of measures common across all studies, which will provide a unique opportunity to pool data. In addition to cigarette use, all studies will assess electronic cigarette use, marijuana use, and HIV-related outcomes (CD4 count, HIV viral load). In response to the SARS-CoV-2 pandemic, COVID-19-specific items were added to all assessment batteries. The Treatment Moderators Group will help guide the selection of participant-level factors that may influence treatment response such as psychiatric comorbidity or variation in the rate of nicotine metabolism. The Non-Tobacco Substance Use Group will utilize baseline data to characterize patterns of nontobacco substance use, such as unhealthy alcohol, marijuana and opioid use, among a diverse population of PWH, allowing the evaluation of nontobacco substance use moderators of smoking cessation treatment efficacy. As demonstrated by previous collaborative efforts in tobacco research²¹ and other populations of smokers (<https://cancercontrol.cancer.gov/brp/tcrb/scale-collaboration.html>), pooling these data will provide the most comprehensive description of smokers with HIV to date and will lay the foundation for a toolkit for use in future studies with similar populations in the United States and abroad.

Importantly, the studies will be conducted in diverse geographic locations and will recruit PWH through various sites (eg, VA hospitals, community HIV clinics, academic medical centers, and social media). These studies will accumulate a large, diverse population that is more representative of the population of PWH who smoke than any single study could have achieved. In addition to enhancing reach, this will enable consideration of health disparities by racial/ethnic groups, socioeconomic status, gender, and sexual orientation. The sum of knowledge obtained from cross-project measures will also facilitate evaluation of effective interventions (vs. control) and critically, which aspects are most valuable (eg, pharmacotherapy vs. behavioral; in-person vs. remote; clinical vs. community vs. remote samples). Finally, another NCI-led FOA on Tobacco Use and HIV in Low- and Middle-Income Countries (<https://grants.nih.gov/grants/guide/pa-files/par-18-023.html>, <https://grants.nih.gov/grants/guide/pa-files/par-18-022.html>) will allow investigators to link parallel on-going and future research in geographic areas where HIV and tobacco use are major threats.

Because of the success of HIV treatment, we are faced with the need to address the major threat of tobacco dependence to the health of PWH. By supporting the rigorous evaluation of the adaptation and implementation of evidence-based treatments for PWH who smoke, this NCI-led initiative will provide critical knowledge about how to promote abstinence and ensure that these efforts are scalable. These NCI-supported studies will provide an opportunity to disseminate findings to key stakeholders to enhance reach and sustainability, thereby expanding the impact of the NIH’s investment. Although additional research is needed, tobacco use likely exacerbates the effects of COVID-19 infection.³ Physical distancing recommendations have made identifying creative strategies for delivering smoking cessation interventions without face-to-face interactions a priority. The current studies are well-positioned to provide critical information about the impact of COVID-19 on PWH who smoke. Stakeholders interested in tobacco cessation should be aware of this initiative and the rich evidence-base it will provide.

Supplementary Material

A Contributorship Form detailing each author’s specific involvement with this content, as well as any supplementary data, are available online at <https://academic.oup.com/ntr>.

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Declaration of Interests

Dr. Ashare has an investigator-initiated grant from Novo Nordisk for a drug unrelated to the current study. Dr. Hitsman has served on scientific advisory boards for Pfizer and received varenicline and placebo free of charge from Pfizer for use in NIH-funded trials. Dr. Schnoll received medication and placebo free of charge from Pfizer for clinical trials and has provided consultation to Pfizer, GlaxoSmithKline, and Curaleaf. Dr. Gross serves on a Pfizer Data and Safety Monitoring Board for a drug unrelated to smoking or HIV. The remaining co-authors report no conflict of interest.

Authors' Contributions

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References

- Helleberg M, May MT, Ingle SM, et al. Smoking and life expectancy among HIV-infected individuals on antiretroviral therapy in Europe and North America. *AIDS*. 2015;29(2):221–229.
- Lifson AR, Neuhaus J, Arribas JR, van den Berg-Wolf M, Labriola AM, Read TR; INSIGHT SMART Study Group. Smoking-related health risks among persons with HIV in the Strategies for Management of Antiretroviral Therapy clinical trial. *Am J Public Health*. 2010;100(10):1896–1903.
- Karanasos A, Aznaouridis K, Latsios G, et al. Impact of smoking status on disease severity and mortality of hospitalized patients with COVID-19 infection: A systematic review and meta-analysis. *Nicotine Tob Res*. 2020;22(9):1657–9.
- Pacek LR, Crum RM. A review of the literature concerning HIV and cigarette smoking: morbidity and mortality, associations with individual- and social-level characteristics, and smoking cessation efforts. *Addict Res Theory*. 2015;23(1):10–23.
- Pacek LR, Cioe PA. Tobacco use, use disorders, and smoking cessation interventions in persons living with HIV. *Curr HIV/AIDS Rep*. 2015;12(4):413–420.
- Frazier EL, Sutton MY, Brooks JT, Shouse RL, Weiser J. Trends in cigarette smoking among adults with HIV compared with the general adult population, United States - 2009–2014. *Prev Med*. Jun 2018;111:231–234.
- Mdege ND, Shah S, Ayo-Yusuf OA, Hakim J, Siddiqi K. Tobacco use among people living with HIV: Analysis of data from Demographic and Health Surveys from 28 low-income and middle-income countries. *Lancet Glob Health*. 2017;5(6):e578–e592.
- Hoffman AC, Starks VL, Gritz ER. The impact of cigarette smoking on HIV/AIDS: Urgent need for research and cessation treatment. *AIDS Educ Prev*. 2009;21(3 Suppl.):1–2.
- Pacek LR, Rass O, Johnson MW. Positive smoking cessation-related interactions with HIV care providers increase the likelihood of interest in cessation among HIV-positive cigarette smokers. *AIDS Care*. 2017;29(10):1309–1314.
- Ledgerwood DM, Yskes R. Smoking cessation for people living with HIV/AIDS: a literature review and synthesis. *Nicotine Tob Res*. 2016;18(12):2177–2184.
- Keith A, Dong Y, Shuter J, Himelhoch S. Behavioral Interventions for Tobacco Use in HIV-Infected Smokers: A Meta-Analysis. *J Acquir Immune Defic Syndr*. 2016;72(5):527–533.
- Gritz ER, Danysh HE, Fletcher FE, et al. Long-term outcomes of a cell phone-delivered intervention for smokers living with HIV/AIDS. *Clin Infect Dis*. 2013;57(4):608–615.
- Shuter J, Kim RS, An LC, Abrams LC. Feasibility of a smartphone-based tobacco treatment for HIV-infected smokers. *Nicotine Tob Res*. 2020;22(3):398–407.
- Mann-Jackson L, Choi D, Sutfin EL, et al. A qualitative systematic review of cigarette smoking cessation interventions for persons living with HIV. *J Cancer Educ*. 2019;34(6):1045–1058.
- Cropsey KL, Bean MC, Haynes L, Carpenter MJ, Richey LE. Delivery and implementation of an algorithm for smoking cessation treatment for people living with HIV and AIDS. *AIDS Care*. 2020;32(2):223–229.
- Ashare RL, Thompson M, Serrano K, et al. Placebo-controlled randomized clinical trial testing the efficacy and safety of varenicline for smokers with HIV. *Drug Alcohol Depend*. 2019;200:26–33.
- Mercié P, Arsandaux J, Katlama C, et al.; ANRS 144 Inter-ACTIV study group. Efficacy and safety of varenicline for smoking cessation in people living with HIV in France (ANRS 144 Inter-ACTIV): a randomised controlled phase 3 clinical trial. *Lancet HIV*. 2018;5(3):e126–e135.
- Gonzales D, Rennard SI, Nides M, et al.; Varenicline Phase 3 Study Group. Varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. *JAMA*. 2006;296(1):47–55.
- Shahrir S, Crothers K, McGinnis KA, et al. Receipt and predictors of smoking cessation pharmacotherapy among veterans with and without HIV. *Prog Cardiovasc Dis*. 2020;63(2):118–124.
- Vilardaga R, Casellas-Pujol E, McClermon JF, Garrison KA. Mobile applications for the treatment of tobacco use and dependence. *Curr Addict Rep*. 2019;6(2):86–97.
- Fishbein H, Bauer D, Yu Q, et al. Harmonizing cigar survey data across tobacco centers of regulatory science, center for tobacco products, and population assessment of tobacco and health studies: The Cigar Collaborative Research Group [published online ahead of print October 29, 2019]. *Nicotine Tob Res*. 2019.