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Rate of Nicotine Metabolism and Tobacco Use among Persons with HIV: Implications for Treatment and Research

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Abstract

Background: The nicotine metabolite ratio (NMR) is a biomarker that represents individual variation in the speed that nicotine is metabolized. The rate of nicotine metabolism alters smoking behavior (e.g., amount) and has been validated for personalizing tobacco dependence medication selection to increase treatment efficacy and reduce treatment side effects in the general population of smokers. While smoking rates are extremely high among those with HIV, the NMR has not been evaluated in this underserved population.

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Conflicts of Interest

Methods: We used baseline data from a smoking cessation clinical trial for smokers with HIV (N = 131) to examine associations between NMR and demographic, smoking, disease-related, and psychological characteristics. Pearson r and ANOVA were used to identify univariate correlates of NMR, which were then entered into a multiple linear regression model.

Results: In univariate analyses, a higher NMR (faster nicotine metabolism) was associated with being Caucasian, and more cigarettes per day, nicotine dependence, exhaled carbon monoxide, and symptoms of depression and anxiety, and using efavirenz. In a multiple regression model, a higher NMR was associated with more cigarettes per day, higher anxiety symptoms, and efavirenz use.

Conclusions: As in other populations, faster nicotine metabolism was associated with use of more cigarettes and higher anxiety symptoms. Notably, efavirenz use was associated with faster metabolism, which might make it harder to quit smoking for people with HIV treated with that medication. These findings could help guide further study and the clinical use of the NMR to personalize nicotine dependence treatment in this underserved population.

Keywords

Nicotine metabolite ratio; Tobacco; HIV; Smoking; Efavirenz; Anxiety

Introduction

Tobacco use remains a critical public health problem in the US [1]. When an individual smokes a cigarette, nicotine is metabolized by hepatic cytochrome P450 2A6 (CYP2A6) [2] and functional polymorphisms in the *CYP2A6* gene that affect enzyme activity - and nicotine metabolism - have been identified [3, <https://www.pharmvar.org/>]. Individuals with reduced or loss of function *CYP2A6* variants, genetically slow nicotine metabolizers, smoke fewer cigarettes each day, are less nicotine dependent, and are more likely to quit smoking [4-6]. The nicotine metabolite ratio (NMR; 3-hydroxycotinine/cotinine) is a widely used phenotype measure of CYP2A6 activity, which incorporates genetic and environmental influences on nicotine metabolism [7].

Higher NMR values are associated with smoking more cigarettes each day, a higher level of nicotine dependence, and higher rates of nicotine withdrawal [8]. More recently, several studies [e.g., 9], including a large, prospectively NMR-stratified pharmacogenetic smoking cessation clinical trial [10], showed that the NMR could be used to personalize nicotine dependence treatment and increase treatment efficacy. Using an NMR cut-point of 0.31 to differentiate slow from fast nicotine metabolizers, this landmark study validated a personalized treatment model, whereby slow nicotine metabolizers are treated with the transdermal nicotine patch and fast nicotine metabolizers are treated with varenicline to improve quit rates and reduce medication side effects [10]. Studies have shown that faster nicotine metabolism is associated with greater subjective nicotine reward [11], increased nicotinic receptor availability [12], and increased brain activity in response to smoking cues [13,14], suggesting mechanisms of this effect. Taken together, the NMR is poised to become an important clinical tool to improve treatment efficacy through personalizing treatment selection, thereby reducing smoking rates and tobacco morbidity.

To date, NMR studies have largely focused on the general population of smokers and, thus, the generalizability of this literature to important sub-groups of smokers remains unclear. Certain sub-populations, such as people living with HIV (PLWH), report smoking rates that are 2-3 times greater than the general population [15-19] and other clinical populations (e.g., major depression; [20]). Moreover, while the advent of modern antiretroviral therapy (ART) has greatly increased life expectancy among PLWH, the high rates of smoking in this population has led to cancer and cardiovascular disease rising to be the main causes of death in this population [21-23]. A recent study showed that HIV-infected smokers lose more life-years due to tobacco use than they do to their HIV infection [24]. Further, some data indicate that, as CYP2A6 is involved in efavirenz metabolism, variation in CYP2A6 activity is associated with concentrations of this ART [25], and also that CYP2A6 variation can affect HIV pathogenesis through oxidative stress pathways [26]. Thus, understanding unique aspects of tobacco use, including the potential role of the NMR, among PLWH is critical to developing and testing smoking cessation treatments for this group of smokers.

Methods

Participants

Data for this study were from a smoking cessation clinical trial for PLWH (NCT01710137), approved by the University of Pennsylvania IRB, and conforming to US Federal Policy for the Protection of Human Subjects. The trial began in October 2012 and ended June 2018. Written informed consent was obtained from each participant. Prospective participants were recruited through Penn's health system, media advertisements, and through a community-based HIV clinic. To be eligible, individuals had to be age ≥ 18 , have a confirmed HIV diagnosis and be treated with ART with HIV viral loads <1000 copies/ml and CD4+ counts >200 cells/mm³, report daily smoking, ALT and AST <2 times upper limit of normal, and creatinine clearance >50 mL/min. Potential participants were excluded if they reported a lifetime history of psychosis or a suicide attempt, reported a current or planned pregnancy, reported current use of smoking cessation medications, and showed unstable or untreated alcohol/substance abuse. For this study, the 131/179 enrolled participants who provided blood for NMR analyses were included. Providing a blood sample was optional, and not all attempts at collecting the sample were successful, most often due to complications resulting from past drug use. Participants who did not provide a sample were more likely to have acquired HIV through needle use and showed higher levels of anxiety, vs. participants who provided a sample (p 's $< .05$).

Measures

Data were collected at eligibility screening. Demographic information (e.g., race, sex) were ascertained from self-report. Disease-related characteristics, including current HIV viral load (proportion ≥ 50) and CD4+ count (within the past 6 months), were collected from medical records. Mode of HIV acquisition and current ART and ART adherence (i.e., proportion of medications prescribed that were taken over the 2 weeks prior to the assessment) were collected through self-report. Because efavirenz is a substrate of CYP2A6, we identified those taking efavirenz [25]. Smoking-related data included self-reported smoking (e.g., smoking rate, number of previous quit attempts, years smoked), the Fagerström Test for

Cigarette Dependence (FTCD) [27], a breath carbon monoxide (CO) measure, the Minnesota Nicotine Withdrawal Scale [28], and the brief Questionnaire of Smoking Urges [29]. Current depression and anxiety symptoms [30] and current negative and positive mood [31] were assessed using the Hospital Anxiety and Depression Scale (HADS) and the Positive and Negative Affect Schedule, respectively. The HADS has been shown to be a reliable and valid assessment of anxiety and depression symptoms among those with HIV [32]. Plasma samples were examined for nicotine, cotinine, and 3-hydroxycotinine (3-HC), to identify NMR, using liquid chromatography-tandem mass spectrometry [10].

Data Analysis

Sample characteristics, including plasma nicotine, cotinine, 3-HC, and NMR, were assessed. Pearson r and ANOVA were used to examine univariate correlates of NMR. Variables associated with NMR ($p < .10$) were included in a multiple linear regression model to control for potential confounding. Analyses were conducted using SPSS (IBM Corporation, Armonk, NY).

Results

Sample Characteristics (Table 1)

78.6% of the sample were African American, 68.9% were male, and 69.4% reported earning <\$20,000/year. On average, participants smoked 13.0 cigarettes per day ($SD = 7.0$), had a breath CO of 14.3 ppm ($SD = 9.7$), and reported smoking for 30.91 years ($SD = 10.7$); 88.2% of participants acquired HIV through sexual contact, viral loads were very low (80.2% of the sample < 50), and 99.4% of participants reported taking prescribed ART. Mean nicotine was 11.2 ng/ml ($SD = 35.4$), mean cotinine was 173.6 ng/ml ($SD = 127.5$), mean 3-HC was 73.1 ng/ml ($SD = 59.3$), and mean NMR was 0.47 ng/ml ($SD = 0.29$).

Correlates of NMR

In univariate analyses, NMR was associated with race, cigarettes per day, nicotine dependence, CO, depression and anxiety, and efavirenz use (p 's < 0.10). Caucasian participants had a higher NMR ($M = 0.57$), vs. African Americans ($M = 0.45$; $F[1,126] = 3.03$, $p = .084$). A higher NMR was associated with higher mean cigarettes per day ($r = .30$, $p = .001$), CO level ($r = .17$, $p = .052$), nicotine dependence ($r = .18$, $p = .045$), anxiety ($r = .26$, $p = .003$), and depression ($r = .19$, $p = .030$). Participants taking efavirenz had a higher NMR ($M = 0.62$) than participants not taking efavirenz ($M = 0.44$, $F[1,123] = 7.00$, $p = .009$); 82% of participants using efavirenz were fast nicotine metabolizers (i.e., NMR $< .31$), vs. only 59% of participants who were not taking efavirenz ($\chi^2[1] = 4.35$, $p = 0.053$). Efavirenz use was not associated with nicotine, cotinine, 3-HC, or cotinine+3-HC (p 's $> .05$) and NMR was not related to viral load, CD4+ count, or ART adherence.

In the multiple linear regression model (Table 2), a higher NMR was associated with smoking more cigarettes/day ($b = 0.188$, $p = 0.050$), higher anxiety symptoms ($b = 0.191$, $p = .054$), and taking efavirenz ($b = 0.221$, $p = .010$). These variables account for 11% unique variance in NMR ($F[3,115] = 5.01$, $p = .003$); taking efavirenz alone accounted for 5% unique variance in NMR ($F[1,115] = 6.84$, $p = .010$).

Discussion

Tobacco use is a serious concern for PLWH, now representing the primary source for life-years lost [24]. Yet, many PLWH continue to smoke and few studies have examined reasons for high smoking rates or evaluated tobacco cessation interventions in this population. In the general population, the NMR can be used to improve treatment efficacy [8]. This is the first study of the NMR among PLWH.

First, the NMR is higher among these HIV-infected smokers vs. the general population of (e.g., 0.47 vs. 0.34-0.39; [9,28]), suggesting that the proportion of smokers with HIV who are faster metabolizers of nicotine may be greater vs. the general population of smokers. This is consistent with a previous study that showed higher rates of the nicotine metabolite nornicotine but lower levels of nicotine among HIV positive vs. negative smokers [34]; NMR was not compared. The mean NMR of this sample resembles levels reported among those with opioid dependence [35]. While the nature of the relationship between NMR and HIV is uncertain, these results suggest that the nicotine patch would have limited therapeutic benefit for most smokers with HIV, which has been reported [36], and that varenicline would be more beneficial [8].

Second, these results indicate that the relationship between NMR and smoking rate holds among PLWH. Those with a higher NMR reported smoking more cigarettes each day, consistent with studies in the general population [see 7]. Nicotine dependence was not associated with the NMR in the multivariate model, consistent with a study among those dependent on opioids [35], and previous study in the general population [8]. The relationship between NMR and nicotine dependence is influenced by the gender and racial composition of the sample and the type of assessment used to determine nicotine dependence [33].

Third, higher NMR was associated, marginally, with higher levels of anxiety, which is consistent with studies with the general population of smokers that showed that higher NMR was prospectively associated with increased anxiety symptoms when individuals were trying to quit smoking [9,37]. Thus, among PLWH, addressing anxiety symptoms, using specific behavioral interventions that target anxiety [38], may be important to improve clinical outcomes.

Lastly, consistent with previous studies in the context of HIV [25], we found a significant relationship between NMR and taking efavirenz. Taking efavirenz was associated with higher NMR, rather than lower NMR as expected for a drug interaction (efavirenz would be predicted to inhibit CYP2A6), which needs to be understood further. This suggests efavirenz therapy should be considered when addressing tobacco use among PLWH. Further, demonstrating the use of the NMR as a marker for nicotine metabolism among PLWH supports use of the NMR to examine the influence of nicotine metabolism on HIV pathogenesis through oxidative stress or efavirenz metabolism [24,37]. However, since cotinine, 3-HC, and the combination of the two metabolites were not significantly different depending on efavirenz use, additional research is needed to more fully understand the complex relationship between HIV, efavirenz use, the rate of nicotine metabolism, NMR,

and smoking, including whether or not efavirenz use increases NMR and serves as a barrier to cessation in this population.

Study limitations include the small sample and use of cross-sectional data, which limit power and causal inference. Further, the clinical trial inclusion and exclusion criteria may limit generalizability. However, this is the first study to examine the NMR among smokers with HIV. Future studies are needed to directly compare the NMR among smokers with and without HIV in order to provide more clarity to the unique clinical implications of the NMR for HIV-infected smokers.

The findings show that the proportion of smokers with rapid nicotine metabolism may be relatively high in the HIV population vs. the general population and that this biomarker of nicotine metabolism is associated with smoking rate as seen in the general population and may covary with anxiety symptoms. Further, additional research is needed to more fully clarify the relationship between nicotine metabolism, as measured by the NMR, and efavirenz use in order to understand the clinical implications of this ART on efforts to promote smoking cessation. This issue may have particular relevance for HIV treatment in sub-Saharan Africa, where efavirenz use is common and smoking rates have been increasing; while use of efavirenz in the US will remain relatively low, lower expected prices suggests that it will see continued use in the US. The high NMR, suggesting rapid nicotine metabolism, may contribute to poor therapeutic benefits from transdermal nicotine patch and suggest the need for varenicline use in this population. Overall, these results can help guide continued examination of this biomarker of nicotine metabolism to understand and treat nicotine dependence in this important and under-served population of smokers.

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Table 1.

Demographic, smoking history, disease-related, and psychological characteristics, and nicotine metabolism (N = 131)

Variable	N [%] or M [SD]
<u>Demographic variables</u>	
Race [% African American]	105 [80.2]
Sex [% Male]	92 [70.2]
Level of Education [% High School Grad or less]	79 [60.3]
Annual Household Income [% 20K or less]	94 [71.8]
Age (Range = 21-70)	48.0 [9.9]
BMI (Range = 15.3-58.2)	27.2 [6.7]
Number of Beers in Past 7 Days (Range = 0-15)	2.8 [3.5]
Number of Shots of Liquor in Past 7 Days (Range = 0-21)	2.2 [4.1]
Number of Glasses of Wine in Past 7 Days (Range = 0-12)	0.84 [2.1]
<u>Smoking-related variables</u>	
FTCD (Range = 0-10)	4.7 [2.0]
Nicotine, ng/ml (Range = 0.99-390.37)	11.2 [35.4]
Cotinine, ng/ml (Range = 0.97-634.48)	173.6 [127.5]
3-HC, ng/mL (Range = 1.76-256.94)	73.1 [59.3]
3-HC/COT, ng/ml (Range = 0.054-1.42)	0.47 [0.29]
Cigarettes Per Day in Past 7 Days (Range = 3-40)	13.0 [7.0]
Breath Carbon Monoxide, ppm (Range = 1-60)	14.3 [9.7]
Number of Years Smoking (Range = 4-56)	30.9 [10.7]
Number of Times Quit Smoking for $\geq$ 24 Hours (Range = 0-500)	7.9 [44.4]
Nicotine Withdrawal Symptoms (Range 0-27)	9.4 [6.1]
Nicotine Craving (Range = 10-70)	33.7 [16.1]
<u>HIV-related disease characteristics</u>	
% of HAART Prescribed in Past 2 Weeks Taken (Range = .86-1.00)	0.99 [0.03]
Viral Load (% $\leq$ 50)	105 [80.2]
CD4+ (Range = 214-1932)	714.4 [341.6]
% Acquired HIV via Sex	111 [84.7]
Type of ART (% Efavirenz)	22 [16.8]
<u>Psychological measures</u>	
Negative Affect (Range = 10-50)	15.2 [6.3]
Positive Affect (Range = 10-50)	37.4 [8.3]
Anxiety Symptoms (Range = 0-16)	4.6 [3.3]
Depression Symptoms (Range = 0-10)	2.6 [2.3]

Note. FTCD = Fagerström Test for Cigarette Dependence; BMI = Body Mass Index.

Table 2.

Multiple linear regression model of factors associated with the nicotine metabolite ratio.

Variable	b	95% CI	p
Race	0.079	[-0.082, 0.212]	0.383
FTCD	0.060	[-0.018, 0.036]	0.514
Anxiety Symptoms	0.191	[0.000, 0.035]	0.054
Depression Symptoms	0.026	[-0.021, 0.028]	0.787
Cigarettes Per Day in Past 7 Days	0.188	[0.000, 0.016]	0.050
Breath Carbon Monoxide	0.067	[-0.003, 0.008]	0.448
Efavirenz Use	0.221	[0.043-0.314]	0.010

Note. FTCD = Fagerström Test for Cigarette Dependence.