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Differences in the Rate of Nicotine Metabolism among Smokers with and without HIV

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Abstract

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Contributors

Rebecca Ashare helped to conceptualize the present study, led the data analysis, and co-drafted the manuscript. Morgan Thompson oversaw data collection. David Metzger helped with sample recruitment. Karam Mounzer ensured participant safety and helped with participant recruitment. Robert Gross ensured participant safety, helped with participant recruitment, and assisted with interpreting results and conclusions. Rachel Tyndale oversaw the NMR analyses. Robert Schnoll, Martin Mahoney, Paul Cinciripini, and Tony P. George served as site Principal Investigators for NCT01314001 and provided feedback on the manuscript. Caryn Lerman and Rachel F Tyndale were Principal Investigators for NCT01314001, obtained funding, led the trial and data acquisition, and provided feedback on the manuscript. Ronald Collman facilitated access to participants and helped draft the manuscript. Robert Schnoll is the overall study Principal Investigator for NCT01710137, helped to conceptualize the present study, and co-drafted the manuscript. All authors edited the manuscript for content and have approved the final version.

Conflicts of Interest: Dr. Schnoll receives 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. Dr. Ashare has an investigator-initiated grant from Novo Nordisk for a drug unrelated to the current study. Dr. Tyndale has consulted for Quinn Emmanual, Apotex and Ethismos.

Objective—HIV-infected smokers lose more life years to tobacco use than to HIV infection. The nicotine metabolite ratio (NMR), a biomarker of CYP2A6, represents individual variation in the rate at which nicotine is metabolized and is associated with response to smoking cessation treatments. We evaluated whether HIV-infected smokers metabolize nicotine faster than HIV-uninfected smokers, which may contribute to the disproportionate smoking burden and may have important treatment implications.

Design: We analyzed baseline data from two clinical trials (NCT01710137; NCT01314001) to compare the NMR in HIV-infected smokers (N=131) to HIV-uninfected smokers (N=199).

Methods—Propensity scores were used to match the groups 2:1 on characteristics that influence NMR: sex, race, body mass index, and smoking rate. Nicotine metabolites were assessed via LC-MS methods and the ratio of 3-hydroxycotinine:cotinine was used to compute the NMR.

Results—HIV-infected smokers had significantly higher NMR (mean=0.47, SEM=0.02) and were more likely to be in the highest NMR quartile compared to HIV-uninfected smokers (mean=0.34, SEM=0.02; *p*s<0.001).

Conclusions—The higher NMR observed among HIV-infected smokers may partially explain higher smoking rates and lower response to transdermal nicotine therapy. Understanding the mechanisms by which HIV and/or ART contribute to faster nicotine metabolism may guide the use of the NMR to personalize tobacco cessation strategies in this underserved population.

Keywords

Nicotine metabolite ratio; HIV; Tobacco; Biomarkers; Smoking

Introduction

People living with HIV (PLWH) smoke tobacco at higher rates [1–5] and have more difficulty quitting smoking than the general population. HIV-infected smokers lose more life-years to tobacco use than to HIV infection [6, 7]. One plausible mechanism that may underlie smoking behavior among PLWH may be differences in nicotine metabolism rates. Nicotine is primarily metabolized by the cytochrome P450 liver enzyme CYP2A6 into cotinine, which is further metabolized to 3´-hydroxycotinine (3HC) [8]. The ratio of 3HC to cotinine – nicotine metabolite ratio (NMR) – is a well-validated biomarker of nicotine metabolism, and in non-HIV populations higher NMR values (i.e., faster nicotine clearance) are associated with smoking more cigarettes/day, greater nicotine dependence, and more severe nicotine withdrawal symptoms [9]. The NMR can also optimize nicotine dependence treatment [10–12], as shown in a large clinical trial using prospective NMR stratification [13].

The NMR is influenced by biological and environmental factors. Although genetic variation in the *CYP2A6* gene affects enzyme activity – and therefore nicotine metabolism ([14]; https://www.pharmvar.org/), African-Americans are more likely to have reduced function variants vs. Caucasians [15] and NMR values parallel these differences. Moreover, higher NMR is associated with being female, older, lower BMI, non-menthol smokers, and greater alcohol consumption [9, 16]. Medications that are substrates, inhibitors, or inducers of

CYP2A6 activity may also impact nicotine metabolism. Concentrations of the antiretroviral (ART) efavirenz, which is a substrate of CYP2A6 (among other enzymes), may affect variation in CYP2A6 activity [17].

Although there is limited recent evidence that HIV-infected smokers have higher rates of nicotine metabolism vs. HIV-uninfected smokers [18], the relationship between HIV infection, nicotine metabolism, and CYP2A6 activity warrants investigation in a larger, more representative sample. This study compared NMR values among HIV-infected smokers enrolled in a clinical trial of varenicline for smoking cessation (NCT01710137) to a matched sample of HIV-uninfected smokers who were screened for a large, multi-site smoking cessation clinical trial [13]. We hypothesized that HIV-infected smokers would exhibit faster nicotine metabolism. Understanding whether the NMR is a mechanism underlying tobacco use among PLWH may guide smoking cessation treatment in this population.

Methods

Samples

HIV-infected Participants—Data were from a smoking cessation clinical trial for smokers with HIV (NCT01710137) approved by the University of Pennsylvania IRB. Participants were recruited through Penn's health system, advertisements, and through a community-based HIV clinic. To be eligible, individuals had to be age ≥18, have a confirmed HIV diagnosis, be treated with ART with HIV viral loads <1000 copies/ml and CD4+ counts >200 cells/mm^3, smoke >1 cigarette/day, ALT and AST <2 times upper limit of normal, and creatinine clearance >50 mL/min. Exclusion criteria included history of psychosis or a suicide attempt, current/planned pregnancy, current use of smoking cessation medications, and unstable/untreated alcohol/substance abuse. For this study, the 131/179 enrolled participants who provided blood for NMR analyses were included.

HIV-uninfected Participants—Treatment-seeking smokers responded to advertisements for a smoking cessation clinical trial (NCT01314001). Smokers ages 18–65 who reported smoking ≥10 cigarettes/day for the past 6 months were included. Participants provided written informed consent. Those eligible provided a blood sample for NMR determination. See Supplemental Material for exclusion criteria. The study protocol, including NMR determination, has been described elsewhere [16, 19].

Measures

Demographic and Smoking-related Measures (Both Samples)—Demographic information was ascertained. Smoking-related data (e.g., current smoking rate, number of previous quit attempts), the Fagerström Test for Cigarette Dependence (FTCD; [20]), and a breath carbon monoxide (CO) measure were collected at baseline while individuals were still smoking (i.e., prior to the quit attempt). See Supplemental Material for subjective measures.

Nicotine metabolites (Both Samples)—Blood samples (10 ml) were collected at the eligibility visit and frozen until cotinine and 3′-hydroxycotinine (3-HC) were assessed by

liquid chromatography-tandem mass spectrometry (LC-MS) [21, 22]. The continuous measure of the NMR is the ratio of 3-HC:cotinine. Participants were categorized by NMR quartiles (e.g., lowest quartile equals 25% of people with the slowest nicotine metabolism, vs. highest quartile equals 25% of people with the fastest nicotine metabolism) [10]. The NMR quartile means, medians, upper and lower limits, and sample size were: (1) 0.18, 0.20 (<0.2591), 142; (2) 0.30, 0.30 (0.2592–0.3519) 142; (3) 0.40, 0.39 (0.352–0.466), 142; and (4) 0.63, 0.56 (>0.466), 142 [10].

HIV-related Health Outcomes (HIV-infected Sample Only)—Disease-related characteristics, including current HIV viral load and CD4+ count (within the past 6 months), were collected from medical records. Mode of HIV acquisition and current ART medications and adherence were collected through self-report. Because efavirenz is a substrate of CYP2A6 [23] and because liver diseases, such as hepatitis [24], may induce CYP2A6, exploratory analyses excluded those taking efavirenz and those with a history of hepatitis.

Data Analysis

Descriptive statistics were used to characterize the two samples and Pearson *r* and *t*-tests were used to examine univariate correlates of NMR (Supplemental Table 1). Propensity score matching was utilized to create a matched sample of HIV-uninfected smokers using variables associated with NMR (i.e., sex, age, race, body mass index (BMI), and smoking rate) and characteristics that differed between the groups (i.e., education). Subjects were matched using a 2:1 ratio [25, 26] and calipers equal to 0.2 [27]. A mixed model using the matched sample of 131 HIV-infected and 199 HIV-uninfected smokers (n=330) evaluated the effect of HIV on NMR with matching weight as a random effect. Thus, we had 80% power using a conservative α=0.01 to detect an effect size of d=0.39 between groups. Multinomial logistic regression was used to evaluate the relative risk of HIV-infected individuals being in the highest NMR quartile (fastest metabolizers), vs. the lowest NMR quartile (slowest metabolizers). See Supplemental Material for analysis of subjective measures.

Results

Sample Characteristics

Demographic and smoking-related characteristics are presented in Table 1. The matched samples did not differ on most characteristics except that the HIV-infected sample smoked fewer cigarettes per day and a greater proportion of the HIV-infected sample reported an annual income less than $35k.

Group differences in NMR by HIV status

HIV-infected smokers had significantly higher NMR vs. HIV-uninfected smokers (β=0.13, 95% CI: 0.07,0.19, p<0.001, d=0.48). The groups also differed when comparing the 1st quartile to the 4th quartile. HIV-infected smokers were significantly more likely to be in the 4th quartile (i.e., fastest metabolizers), relative to HIV-uninfected smokers (RR=3.1, 95% CI: 1.7,5.5, p<0.001; Figure 1). When individuals taking efavirenz (n=22) or those with a

history of hepatitis (n=12) were removed from analyses, results were not meaningfully different.

Discussion

PLWH lose more life-years to tobacco use than to HIV infection [6], highlighting the need to better understand the mechanisms that underlie high smoking rates in this population. We compared NMR values – a well-validated index of nicotine metabolism – in a relatively large sample of HIV-infected smokers to a matched sample of HIV-uninfected smokers. This is the first study to directly compare the NMR among PLWH to the general population of treatment-seeking smokers.

The NMR reflects genetic and environmental sources of variation in nicotine metabolism including race, sex, smoking rate, and BMI [16]. The HIV-infected smokers in this study were predominantly African American and male, had an average BMI in the overweight range, and smoked fewer cigarettes per day than the HIV-uninfected sample indicating it was plausible to expect that their NMRs would be *lower* than in the general population of smokers. Our data indicate the opposite – that, compared to the matched sample, HIV-infected smokers have significantly higher NMR values and were more likely to be characterized as fast metabolizers (4^{th} quartile), reflecting faster nicotine metabolism. Even after removing individuals taking efavirenz, an ART that plausibly might increase CYP2A6 activity, the group difference remained significant. Nevertheless, demographic and smoking-related variables do not capture all of the variance in NMR and future studies should include *CYP2A6* genotypes as markers of CYP2A6 activity [28].

CYP2A6 activity may also play a role in mediating HIV-1 pathogenesis by inducing reactive oxygen species (ROS), a marker and mediator of oxidative stress [29–31]. CYP enzymes (including 2A6) are expressed in monocytes [32], which play a role in the neurodegenerative effects of HIV [33]. If HIV-infected smokers have increased CYP2A6 activity, tobacco use and HIV may interact to increase oxidative stress [32]. Evidence that HIV-infected smokers (not on ART) may have higher viral loads vs. HIV-infected non-smokers was supported by *in vitro* models demonstrating increased viral replication in HIV-infected macrophages treated with cigarette smoke condensate [34]. Thus, CYP2A6 activity, faster nicotine metabolism, and smoking may synergistically contribute to HIV-1 pathogenesis and sequelae such as HAND.

These data raise several important questions. HIV itself may induce CYP2A6, thereby increasing the NMR, as the enzyme can be induced by inflammation and is found at higher levels in livers of hepatitis patients [24, 35–37]. Although our results were unchanged after excluding those with a history of hepatitis, it is possible that HIV-1 infection increases nicotine metabolism. Confirmation would require evaluating the NMR pre- and post-infection, which is challenging. Alternatively, although the higher NMRs persisted after excluding individuals taking efavirenz, one drug that is a known CYP2A6 substrate, other ARTs may influence CYP2A6 activity. The mechanisms through which HIV may increase CYP2A6 activity and nicotine metabolism warrant investigation.

Recent studies have investigated the mechanisms underlying the effects of the NMR on smoking behavior in the general population. Among abstinent smokers, faster nicotine metabolism was associated with increased cigarette craving, subjective nicotine reward, and physiological responses (e.g., increased heart rate) in response to intravenous nicotine [38]. Neuroimaging studies also suggest that NMR plays a role in brain responses to tobacco use. Slow metabolizers had reduced nicotinic receptor availability following overnight abstinence, vs. fast metabolizers [39] and fast metabolizers exhibit increased smoking cue-related brain activity [40, 41]. Therefore, the higher NMR among PLWH in the present study may contribute to increased nicotine reinforcement, nicotinic receptor availability, and cue-related neural responses among HIV-infected smokers. These data imply that HIV-infected smokers are strong candidates for varenicline, which has been shown to be more effective for fast metabolizers [13].

Several limitations warrant mention. First, these data were cross-sectional and mechanistic, prospective studies are needed to investigate the temporal relationship between HIV infection, ART use, and increased nicotine metabolism. Second, although none of the HIV-uninfected smokers self-reported an HIV diagnosis or taking ART, we did not have biological confirmation. Because the prevalence of HIV in the cities where the HIV-uninfected sample was recruited is <2% (Philadelphia, Toronto, Buffalo, and Houston), it is unlikely we misclassified HIV status [42–45]. Lastly, NMR may be elevated via alteration in UGT enzymes which glucuronidate cotinine and 3HC, including UGT2B7 which glucuronidates both 3HC and efavirenz [17, 46].

Conclusions

These findings suggest that HIV-infected smokers metabolize nicotine faster than HIV-uninfected smokers, even after controlling for relevant demographic and behavioral factors. Understanding the mechanisms that contribute to faster nicotine metabolism among PLWH is necessary to understand tobacco's role in undermining clinical outcomes in HIV, and identifying novel therapeutic interventions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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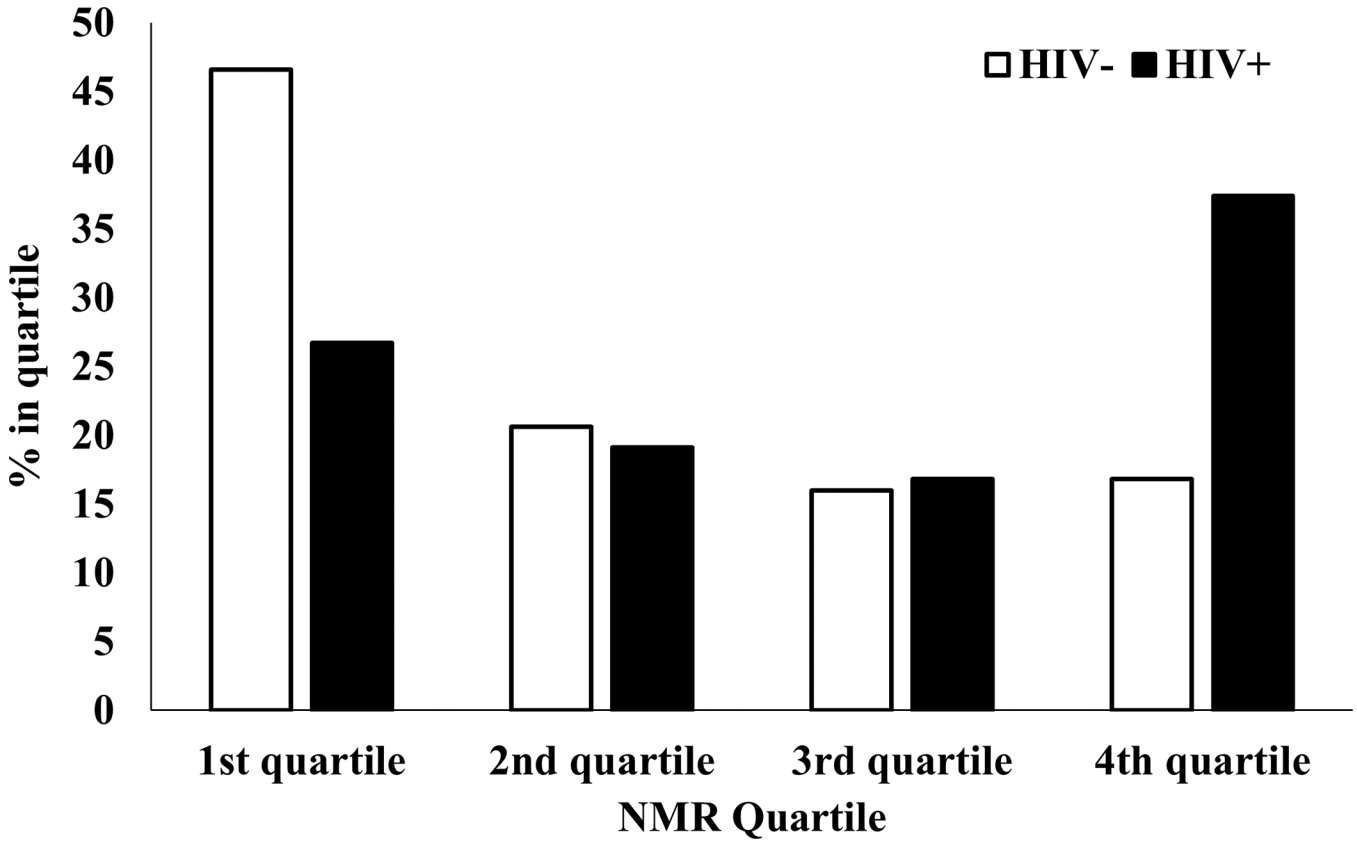

Figure 1. NMR Quartile by HIV Status in Matched Sample.

There were significantly more HIV-infected smokers (35%) characterized as fastest metabolizers (4th quartile) compared to HIV-uninfected smokers (17%). In contrast, 47% of HIV-uninfected smokers were characterized as the slowest metabolizers compared to 29% of HIV-infected smokers.

Table 1.

Demographic Characteristics and Smoking-related Variables

Variable	HIV- (full sample; n=1,807)	HIV- (matched sample; n=199)	HIV+ (n=131)	Total Matched Sample (N=330)	*p*-value [b]
Demographic variables					
Female sex (n, %)	801, 44% [a]	51, 26%	39, 30%	90, 27%	0.41
African American race (n, %)	608, 34% [a]	143, 72%	103, 79%	246, 75%	0.17
Education HS/GED or less (n, %)	545, 30% [a]	112, 56%	79, 60%	191, 58%	0.47
Income ≤ $35,000 (n, %)	814, 46% [a]	124, 64%	113, 86%	237, 72%	<0.001
Age	45.4 (11.3) [a]	47.6 (10.2)	48.0 (9.9)	47.8 (10.0)	0.73
Body Mass Index	28.7 (6.3) [a]	28.2 (6.1)	27.9 (7.3)	28.1 (6.6)	0.72
Smoking-related variables					
Cigarettes per day	18.5 (7.4) [a]	14.9 (6.2)	12.7 (7.3)	14.1 (6.8)	0.003
Nicotine Dependence	5.2 (2.0) [a]	5.0 (1.9)	4.7 (2.0)	4.8 (1.9)	0.18
Cotinine, ng/ml	245.9 (116.8) [a]	255.7 (127)	174.9 (127.1)	223.6 (132.9)	<0.001
3-HC, ng/ml	89.4 (57.5) [a]	80.1 (57.7)	73.1 (59.3)	77.9 (58.4)	0.23
NMR, ng/ml	0.38 (0.21) [a]	0.34 (0.23)	0.47 (0.3)	0.39 (0.26)	<0.001
Characteristics for HIV sample only					
ART adherence past 2 weeks (%, range)			99%, 86–100%		
% Undetectable Viral Load (<50 copies/ml; n, %)			105 (80%)		
Plasma CD4 Count (cells/mm3)			714.4 (341.6)		
Mode of HIV transmission (n, % sex)			121, 92%		
History of HCV (n, %)			12, 9%		

Note: Unless otherwise noted, values are mean (SD); BMI = Body Mass Index.

[a] $p<0.05$ when comparing full sample to HIV-infected sample;

[b] *p*-value is for the comparison between the matched HIV-infected and –uninfected samples