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Journal

J AIDS Journal of Acquired Immune Deficiency Syndromes, 91(5)

ISSN

1525-4135

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Publication Date

2022-12-15

DOI

10.1097/qai.0000000000003089

Peer reviewed



HHS Public Access

Author manuscript

J Acquir Immune Defic Syndr. Author manuscript; available in PMC 2023 December 15.

Published in final edited form as:

J Acquir Immune Defic Syndr. 2022 December 15; 91(5): 497–501. doi:10.1097/

QAI.0000000000003089.

HIV Infection Does Not Explain Higher Nicotine Metabolism in People Living with HIV

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Research included in this manuscript was presented at the CROI 2022 Virtual Conference in February 12-16 by Dr. Robert Gross.

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Abstract

Background: Smoking contributes to significant morbidity and mortality in people with HIV (PWH). PWH have relatively high nicotine metabolism rates, as measured by the nicotine metabolite ratio (NMR, 3-hydroxycotinine/cotinine). Higher NMR is associated with difficulty quitting smoking. We hypothesized that HIV infection might upregulate nicotine metabolism.

Setting: Retrospective study of male current smokers in the Multicenter AIDS Cohort Study who HIV seroconverted between 1985–1993.

Methods: Eligibility included having plasma stored prior to and after confirmed HIV seroconversion and current tobacco use. Samples were selected from the closest available visits prior to (median 3.3 months) and after (median 9.4 months) seroconversion. Antiretroviral therapy use was exclusionary. Cotinine and 3-hydroxycotinine were measured using liquid chromatography-tandem mass spectrometry. We compared NMR from plasma pre- and post-HIV infection using signed rank tests. We targeted a sample size of 71 pairs to achieve 80% power to detect a 0.1 unit increase in NMR with $p=0.05$.

Results: We analyzed paired samples from 78 participants; median age was 34.5 years (IQR 29, 40). Median NMR pre- and post-HIV was 0.45 (IQR 0.32, 0.54) and 0.46 (IQR 0.34, 0.56), respectively. Median change in NMR post seroconversion was +0.01 (IQR -0.05, +0.09), $p=0.25$. Stratification of median change in NMR by timing between samples or time since HIV seroconversion did not alter this finding.

Conclusion: Acquiring HIV had no measurable effect on NMR. We postulate that upregulation of the NMR may be due to direct pharmacologic effects of HIV medications or metabolic changes in response to HIV infection.

Keywords

HIV; smoking; nicotine; nicotine metabolite ratio

Introduction:

In the antiretroviral therapy (ART) era, smoking contributes to more life years lost among people with HIV (PWH) than HIV itself.¹ Rates of cigarette smoking among PWH are two

to three times higher than the general population, and quit rates among PWH are lower compared to people without HIV (PWOH).²⁻⁶

The nicotine metabolite ratio (NMR) is an important biomarker of nicotine clearance and thus impacts smoking cessation and tobacco-related phenotypes.⁷ Nicotine is largely metabolized in the liver to cotinine (COT) and then to 3-hydroxycotinine (3-HC) exclusively via the CYP2A6 enzyme. Measurement of single plasma NMR has shown high reliability when tested over time and with samples stored at different temperatures.⁸⁻¹⁰ Previous studies have shown that a faster rate of nicotine metabolism, as measured by a higher NMR, is associated with increased nicotine dependence, greater number of cigarettes smoked, and lower quit rates.^{11,12} Prior work suggests that PWH who smoke may have higher NMRs compared to PLWOH,¹²⁻¹⁴ though the mechanism for this difference is unclear. Higher rates of nicotine metabolism among PWH may be due to direct viral effects of HIV itself, metabolic effects on the liver due to HIV infection or viral hepatitis, or pharmacologic effects of ART.¹³⁻¹⁶ Direct virologic effects may induce CYP2A6 activity and thus increase NMR. CYP2A6 activity can be induced by inflammation and has been found to be higher in persons with hepatitis.¹⁷⁻¹⁹ As faster nicotine metabolism reduces smoking cessation, understanding the mechanism by which NMR may be higher among PWH can improve methods to achieve smoking cessation in this population. Therefore, we examined the effect of HIV seroconversion on NMR among PWH who reported smoking and who were not on ART.

Methods:

We performed a retrospective analysis of male smokers participating in the Multicenter AIDS Cohort Study (MACS). Participants in the MACS were enrolled from four sites (Pittsburgh, PA; Baltimore, MD/Washington, DC; Chicago, IL; Los Angeles, CA) over four time periods (1984/85, 1987/90, 2001/03, 2010+), and completed a semi-annual study visit including a standardized medical history interview, clinical evaluations, laboratory tests and storage of specimens.²⁰ The MACS is a cohort of sexual minority men living with or without HIV. This study cohort was chosen for the present investigation due to the availability of plasma specimens among smokers before and after HIV seroconversion.

Being a smoker was defined as having self-reported currently smoking cigarettes on at least two consecutive time points a minimum of a year apart and at all intervening time points (if assessed). Participants were included in the analysis if they 1) had a stored plasma sample available for NMR testing at a time when they reported currently smoking and were known to be HIV aviremic (defined as having no detectable HIV RNA and were HIV antibody negative, “pre-infection” specimen) and 2) had a stored plasma sample after HIV seroconversion (“post-infection” specimen) when they were known to have HIV viremia (defined as having detectable HIV RNA) and reported currently smoking. Antiretroviral therapy (ART) use at the time of either sample collection was an exclusion criterion, as the aim of this study was to assess the effect of newly acquired HIV on nicotine metabolism.

Nicotine metabolites were measured from plasma pre- and post-HIV infection among participants with paired samples available. Samples were selected from the closest available

visits prior to and after seroconversion. Samples were stored at -80 degrees Celsius and analyzed in author R.T.'s laboratory at the University of Toronto in Toronto, Canada. The laboratory was blinded to the pre- and post-HIV infection status of the samples. Plasma COT and 3-HC levels were measured in stored samples using liquid chromatography-tandem mass spectrometry.^{8–10} NMR was obtained by calculating the ratio of 3-HC/COT.

A change in NMR of 0.1 was considered clinically meaningful based on previous work.^{21–23} To achieve 80% power to detect a change in NMR of 0.1 with significance level of 0.05, we estimated requiring a sample size of at least 71 paired specimens. Given that COT and NMR were not normally distributed, we calculated the median and interquartile range for both measures. For the primary analysis, we used the Wilcoxon signed-rank test to compare the median NMR between the paired pre- and post-infection samples. Subgroup analyses included stratifying by the amount of time between pre- and post-infection specimen collection (>365 days vs. ≤ 365 days) and by time since HIV seroconversion to post-infection specimen collection of >180 days vs. ≤ 180 days. Mixed-effects linear regression analysis using square-root transformation for non-normality was used to assess whether differences in NMR pre- and post-HIV seroconversion differed by viral hepatitis status or reported alcohol use, or if change in reported alcohol use confounds the relationship between NMR pre- and post-HIV seroconversion. Viral hepatitis status was defined as reactive Hepatitis B surface antigen or Hepatitis C antibody at either timepoint. Self-reported alcohol use was defined as low (two or fewer drinks per day) or high (three or more drinks per day) at either timepoint.

Institutional review boards at University of Toronto as well as each study site approved the MACS study protocols and informed consent was obtained from all participants.

Results:

We identified 78 participants with paired pre- and post-HIV infection plasma samples. Samples meeting all study criteria were identified from 1985 to 1993. The median age of participants at time of post-HIV infection specimen collection was 34.5 (IQR 29, 40, range 24, 53); 65 (83%) were non-Hispanic White, 10 (13%) were non-Hispanic Black, and 3 (4%) were Hispanic White. Samples selected were taken a median 3.3 months (IQR 3.0–6.8) before and median 9.4 months (IQR 8.8–14.4) after seroconversion.

The median plasma COT levels and NMR pre- and post-HIV seroconversion are shown in Table 1. The median COT pre-infection was 267 ng/mL (IQR 182, 321) and post-infection was 252 ng/mL (IQR 147, 323) with a median difference of 14 ng/mL decrease (IQR 64 ng/mL decrease, 43 ng/mL increase), p -value= 0.17. The median NMR pre-infection was 0.45 (IQR 0.32, 0.54) and post-infection was 0.46 (IQR 0.34, 0.56) with a median difference of 0.01 increase (IQR 0.05 decrease, 0.09 increase), p =0.25. Figure 1 shows the change in NMR values for each pair. The range of changes in NMR between pre- and post- seroconversion specimens was an increase of 0.55 units and a decrease of 0.23 units. Considering a pre-post difference of at least 0.1 to be a significant change, there were 15 (19%) decreases, 19 (24%) increases, and 44 (56%) unchanged subjects.

Stratification of median difference in NMR by timing between pre- and post- specimens (> 365 days vs < 365 days, $p=0.88$) or by time since HIV seroconversion (> 180 days vs < 180 days, $p=0.63$) did not yield clinically or statistically significant changes. Mixed-effects models with and without square-root transformation adjusting for hepatitis B and hepatitis C infection status as well as self-reported alcohol use did not yield statistically or biologically significant changes in NMR (results not shown, all p values > 0.05.)

Discussion:

In this study comparing nicotine metabolism before and after HIV seroconversion among adult male current smokers not taking ART, we found no significant difference in NMR following acquiring HIV. Our findings suggest that the higher rates of nicotine metabolism seen in PWH^{13,14} are unlikely explained by HIV infection itself.

The overall mean NMR of 0.46 among male smokers with eventual HIV seroconversion in the present study was similar to that seen in previous studies of PWH. Ashare *et al.* found that mean NMR levels in PWH was 0.47, compared to 0.34 in PWOH; Schnoll *et al.* found that PWH not on efavirenz-containing ART had an NMR of 0.44.^{12,13} Our finding of similar NMR before and after HIV seroconversion – at levels consistent with other studies of PWH – may suggest that higher NMR reported in other studies of PWH reflects a higher baseline CYP2A6 activity in persons who acquire HIV, rather than a direct effect of HIV infection itself. These findings may suggest that higher CYP2A6 activity may be in the causal pathway for HIV acquisition, while ART may further increase the NMR. Interestingly, efavirenz is associated with higher NMR in PWH.^{12,16} Schnoll *et al.* found that NMR in PWH on efavirenz-containing regimens was 0.67 compared to 0.44 in those on non-efavirenz-containing ART. As efavirenz is known to induce CYP2A6²⁴ – the predominant liver enzyme responsible for nicotine metabolism – our study adds further evidence that ART associated with HIV treatment, rather than HIV itself, may explain the higher nicotine metabolism rates seen in other cohorts of PWH.

Our study has several strengths. The MACS cohort includes participant data prior to HIV seroconversion which allows for within-subject measurement of nicotine metabolism. As most observational cohorts lack data on PWOH, this is a unique advantage to the present study. In addition, the exclusion of subjects with ART exposure removes the potential confounding effect of pharmacologic agents or virologic suppression on nicotine metabolism in PWH. Further, the samples were collected as part of a well-characterized cohort with standardized laboratory protocols. Lastly, our study was adequately powered to detect a clinically meaningful difference in NMR following HIV seroconversion, though one was not detected.

Important limitations in the study include inability to control for all time-varying confounders. However, subgroup analysis of difference in NMR after HIV seroconversion stratified by time between pre- and post-specimen collection or time since HIV seroconversion did not yield a significant change in difference in nicotine metabolism, nor did change in alcohol use. In addition, only males were included, so these results may not be generalizable to women, who metabolize nicotine faster.²⁵ Another limitation is that our

sample was mostly of White race. This is notable as White smokers are less likely to smoke menthol cigarettes, which have been shown to inhibit nicotine metabolism and thus may lower the NMR.^{26,27} However, previous work by Jao *et al.* suggests that menthol cigarette use was not associated with short-term smoking abstinence, and there was no evidence of an interaction between cigarette type and NMR on the effect of short-term abstinence.²⁸

NMR, a biomarker of nicotine metabolism, can be used to guide quitting strategies among smokers.⁷ Future research to assess the impact of ART on NMR in PWH should include studying whether discontinuation of efavirenz-containing ART regimens reduces NMR or improves smoking cessation rates. Personalized quitting strategies that account for modifiable factors of nicotine metabolism, including changes in ART, may help reduce smoking rates among PWH.

Acknowledgments:

This research was supported by R01 HL151292 (Gross and Ashare), support from the Penn Center for AIDS Research (P30 AI 045008) and Penn Mental Health AIDS Research Center (P30 MH 097488), the T32-AI-055435 Infectious Diseases Epidemiology Training Grant (Arens), the Canada Research Chairs program (Tyndale, Chair in Pharmacogenomics) and a Canadian Institutes of Health Research Foundation grant (FDN-154294).

Data in this manuscript were collected by the Multicenter AIDS Cohort Study (MACS) and Women's Interagency HIV Study (WIHS), now the MACS/WIHS Combined Cohort Study (MWCCS), which is supported by the National Institutes of Health. [Full Acknowledgement may be found here](#). The authors gratefully acknowledge the contributions of the study participants and dedication of the staff at the MWCCS sites.

Recent work in several fields of science has identified a bias in citation practices such that papers from women and other minority scholars are under-cited relative to the number of such papers in the field.^{29–37} Here we sought to proactively consider choosing references that reflect the diversity of the field in thought, form of contribution, gender, race, ethnicity, and other factors. Using previously described methods to predict author gender^{33,38} we estimate that our references contain 7.3% woman(first)/woman(last), 15.8% man/woman, 47.4% woman/man, and 29.5% man/man. Using previously described methods to predict author racial/ethnic category^{39,40}, we estimate that our references contain 9.1% author of color (first)/author of color(last), 19.2% white author/author of color, 21.0% author of color/white author, and 50.7% white author/white author. We look forward to future work that could help us better understand how to support equitable practices in science.

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Figure 1. Spaghetti Plot of NMR Pre- and Post- HIV Infection.

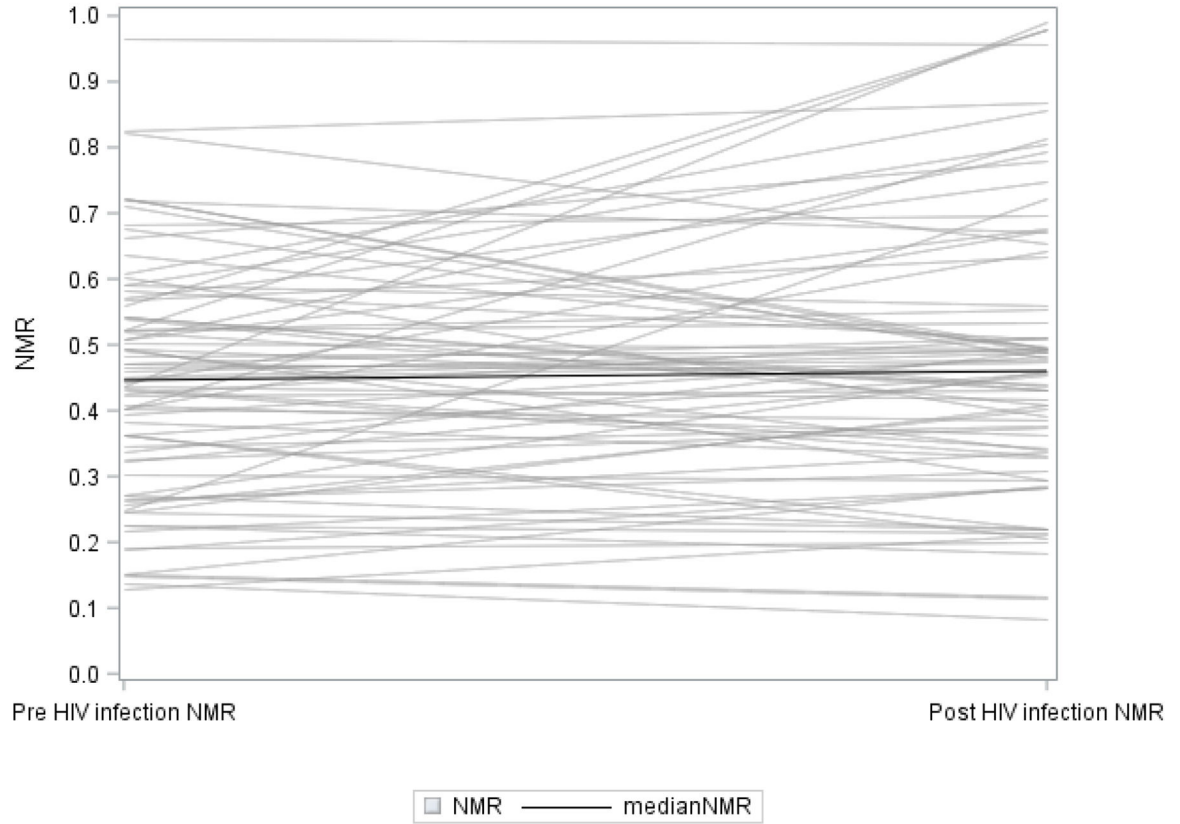


Figure 1. Spaghetti plot of paired NMR values pre- and post- HIV infection for study participants (N=78).

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Plasma cotinine (COT) and Nicotine Metabolite Ratio (NMR) Pre- and Post- HIV Infection ($N = 78$ paired samples).

Table 1.

	Pre-infection	Post-infection	Post-Pre Infection	<i>p</i> -value
Median COT, ng/mL (IQR)	267 (182, 321)	252 (147, 323)	-14 (-64, +43)	0.17
Median NMR (IQR)	0.45 (0.32, 0.54)	0.46 (0.34, 0.56)	+0.01 (-0.05, +0.09)	0.25