Title

Nicotine Metabolite Ratio Decreases After Switching Off Efavirenz-Based Therapy in People With HIV Who Smoke

Journal

Clinical Pharmacology & Therapeutics, 115(1)

ISSN

0009-9236

Authors

Medaglio, Dominique
Bilker, Warren B
Han, Xiaoyan
et al.

Publication Date

2024

DOI

10.1002/cpt.3068

Peer reviewed

HHS Public Access

Author manuscript

Clin Pharmacol Ther. Author manuscript; available in PMC 2024 January 01.

Published in final edited form as:

Clin Pharmacol Ther. 2024 January ; 115(1): 80–85. doi:10.1002/cpt.3068.

Nicotine Metabolite Ratio Decreases After Switching Off Efavirenz-Based Therapy in People With HIV Who Smoke

Dominique Medaglio[1], **Warren B. Bilker**[1,2], **Xiaoyan Han**[1], **Jessica S. Merlin**[3], **Michael Plankey**[4], **Jeffrey Martin**[5], **Heidi M. Crane**[6], **Leila S. Hojat**[7], **Laura Bamford**[8], **Robert Schnoll**[2], **Rachel F. Tyndale**[9,10,11], **Rebecca L. Ashare**[12,†], **Robert Gross**[1,*,†]

[1]Department of Epidemiology, Biostatistics & Informatics, University of Pennsylvania, Philadelphia, Pennsylvania, USA

[2]Department of Psychiatry, University of Pennsylvania, Philadelphia, Pennsylvania, USA

[3]Department of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania, USA

[4]Department of Medicine, Georgetown University, Washington, DC, USA

[5]Department of Epidemiology and Biostatistics, University of California San Francisco, San Francisco, California, USA

[6]Department of Medicine, University of Washington, Seattle, Washington, USA

[7]Department of Medicine, Case Western Reserve University, Cleveland, Ohio, USA

[8]Department of Medicine, University of California San Diego, San Diego, California, USA

[9]Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada

[10]Department of Pharmacology & Toxicology, University of Toronto, Toronto, Ontario, Canada

[11]The Centre for Addiction and Mental Health, Toronto, Ontario, Canada

[12]Department of Psychology, State University of New York at Buffalo, Buffalo, New York, USA.

Abstract

Rates of cigarette smoking in people with HIV (PWH) are two to three times higher than in people without HIV. Nicotine is metabolized by CYP2A6 and the nicotine metabolite ratio (NMR; 3-hydroxycotinine/cotinine) is a measure of nicotine clearance. Higher NMR has been observed in PWH and is associated with lower quit rates. Efavirenz, a mainstay antiretroviral therapy (ART) globally, partially upregulates its own metabolism through CYP2A6. We hypothesized that efavirenz also upregulates nicotine metabolism by CYP2A6, resulting in a higher NMR,

*Correspondence: Robert Gross (grossr@pennmedicine.upenn.edu).
†These authors contributed equally to this work.

AUTHOR CONTRIBUTIONS

D.M., W.B.B., X.H., J.S.M., M.P., J.M., H.M.C., L.S.H., L.B., R.S., R.F.T., R.L.A., and R.G. wrote the manuscript. J.S.M., R.L.A., and R.G. designed the research. J.S.M., R.F.T., R.L.A., and R.G. performed the research. W.B.B. and X.H. analyzed the data.

CONFLICT OF INTEREST

The authors declared no competing interests for this work.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

and switching to non-efavirenz ART would decrease the NMR, potentially leading to improved quit rates. We compared the NMR during and after efavirenz use among PWH in a longitudinal, multisite cohort. Eligibility criteria included: (i) active cigarette smoking, (ii) ART switched from efavirenz-based to non-efavirenz-based regimen, (iii) plasma available at pre- and post-ART switch, and (iv) viral suppression during study period. Plasma cotinine and 3-hydroxycotinine were measured by liquid chromatography–tandem mass spectrometry. *T*-tests compared the NMR on and off efavirenz. Samples were collected between 2010 and 2019 in 72 PWH. The mean NMR difference after switching to a non-efavirenz-based regimen was −0.24 (SD: 0.37, $P < 0.001$); 44 PWH had at least a 0.1 decrease in NMR. Effect modification by race was present; Black PWH had a larger mean decrease. Our findings suggest that previously observed higher NMR among PWH may be due to direct pharmacologic effects of ART. Assessing the effect of ART on the NMR suggests that avoiding nicotine metabolism inducers could potentially increase quit rates.

Antiretroviral therapy (ART) has transformed prognosis for people with HIV (PWH). However, even in high-income countries, life expectancy in PWH lags behind that of uninfected individuals, often due to comorbidities associated with, and exacerbated by, tobacco use.[1] The prevalence of smoking in PWH in the United States is estimated to be 40%, nearly 3 times that of uninfected individuals; the difference may be higher in low- and middle-income countries.[1–4] Despite availability of smoking cessation pharmacotherapy, quit rates among PWH remain low.[5]

A potential explanatory mechanism for the disparity in quit rates may lie in nicotine metabolism. Nicotine is primarily metabolized to cotinine and cotinine to 3-hydroxycotinine (3-HC) by the hepatic enzyme CYP2A6.[6] The ratio of 3-HC to cotinine, known as the nicotine metabolite ratio (NMR), is a validated biomarker of CYP2A6 activity and nicotine clearance.[6] In the general population, greater CYP2A6 activity results in faster nicotine clearance and higher NMR values. It is hypothesized that people who metabolize nicotine faster smoke more cigarettes per day to minimize withdrawal symptoms, leading to higher nicotine dependence, greater severity of withdrawal symptoms, and reduced cessation rates.[7] In PWH, the relationship between the NMR and smoking outcomes is similar, although the NMR has been found to be significantly higher compared with the general population.[8] Data from 2 independent smoking cessation trials found that mean NMR in smokers with HIV was 0.47 and in non-infected smokers was 0.34 ($P < 0.001$).[8] Whereas this finding points to a potential explanation underlying the lower smoking cessation rates among PWH, there is limited evidence regarding the mechanism for higher NMR among PWH and its downstream effects.

Differences in the NMR may be affected by HIV infection or its treatment, among other factors. We previously demonstrated that HIV acquisition had no discernable effect on the NMR.[9] In contrast, specific ART medications may alter the NMR through effects on CYP2A6. Efavirenz, a key component of ART globally, may upregulate CYP2A6[10] (CYP2A6 contributes to efavirenz metabolism) as it does CYP2B6, the primary enzyme involved in its metabolism.[11] A recent study found that in PWH who achieved viral suppression on ART, those who took ART regimens including efavirenz had a higher mean NMR increase than those on regimens without efavirenz.[10] Given the likely effect

of efavirenz on CYP2A6 activity, we hypothesized stopping efavirenz-based therapy would result in decreases in the NMR.

METHODS

Study design, population, and specimens

We conducted a study of PWH who smoke during and after efavirenz use. Data and specimens collected between January 2010 and November 2019 were obtained from the Centers for AIDS Research (CFAR) Network of Integrated Clinical Systems (CNICS) database and specimen bank. CNICS is a longitudinal cohort of PWH in care at 10 academic HIV care sites in the United States.[12] CNICS data includes clinical data, biological specimens, and patient-reported outcomes data. Seven of the 10 CNICS sites had the necessary data and were included in these analyses. Active ART regimens were reported with the collection of plasma samples rather than reporting initiation and discontinuation dates for each medication. Time on any given ART regimen was calculated based on sample collection dates where the ART regimen remained consistent for at least 3 months between samples to minimize the possibility of misclassifying the ART regimen at the time of NMR measurement. PWH in CNICS completed a clinical assessment of patient-reported outcomes on touch screen tablets approximately every 6 months as part of routine clinical care, including measures of drug, alcohol, and smoking status.

Inclusion criteria of plasma specimens were available both before and after switching from efavirenz in combination with two nucleoside analog reverse transcriptase inhibitors (NRTIs) to either an integrase strand transferase inhibitor (INSTI) or non-nucleoside analog reverse transcriptase inhibitor (NNRTI) in combination with the same two or different NRTIs, the participant took the efavirenz-based and non-efavirenz-based regimens for a minimum of 3 months and the participant self-reported currently smoking on both specimen dates. Participants were also limited to individuals with HIV RNA concentrations < 400 copies/mL at the times of both specimen collections to control for any potential effects of HIV viremia.

Outcome and covariate measurement and definitions

Standard liquid chromatography–tandem mass spectrometry was used to measure cotinine and 3-HC.[13] Plasma specimens were stored at −80°C until cotinine and 3-HC analyses were performed. The laboratory was blinded to the efavirenz status of the specimens. NMR was calculated as the ratio 3-HC:cotinine. A cotinine value > 15 ng/mL was used to confirm current smoking status. To assess the hypothesis that the effect of efavirenz, specifically as a CYP2A6 substrate, increases NMR, we chose comparator drugs in the INSTI and NNRTI class that are not known to induce or inhibit CYP2A6.

We examined demographic characteristics, including age, race, ethnicity, and birth sex, and days between collection of specimens. Other potential confounding variables included alcohol and stimulant use (methamphetamine/amphetamines and/or cocaine/crack), presence of liver disease, and other concurrent medications that might affect CYP2A6 function (www.pharmgkb.com).

Alcohol use was assessed using the Alcohol Use Disorders Identification Test (AUDIT-C).[14,15] PWH were categorized as “at-risk alcohol use” or “not at-risk alcohol use” based on AUDIT-C score thresholds. Two AUDIT-C thresholds were used in this study: the higher score threshold was ≥ 5 if male or ≥ 4 if female subjects, and the lower score threshold was ≥ 4 if male or ≥ 3 if female subjects. Stimulant use was assessed using the World Health Organization (WHO) Alcohol, Smoking and Substance Involvement Screening Test (ASSIST)[16]; only methamphetamines/amphetamines and cocaine/crack were considered.

The presence of liver disease was assessed using International Classification of Disease-9th revision (ICD-9) and ICD 10th revision (ICD-10) codes for cirrhosis, ascites, varices, hepatitis B, hepatitis C, unspecified hepatitis, and fatty liver (see Table S1). Known CYP2A6 inducer medications included amlodipine, azithromycin, clotrimazole, conjugated estrogens, dexamethasone, ketoconazole, and methylprednisolone.[17] Isoniazid was the only CYP2A6 inhibitor included.[17]

Statistical analyses and sample size

The mean change in NMR between efavirenz-based and non-efavirenz-based regimens was assessed using *t*-tests (all continuous variables were dichotomized at the median). Individuals were compared with respect to whether their NMR decreased by a clinically significant level after switching off efavirenz, which we defined as ≥ 0.1 based on prior studies.[18–20] Effect modification was evaluated using linear mixed models, including interactions between specimen samples and select PWH characteristics. Pearson’s correlations were conducted to measure the correlation of the mean change of cotinine and 3-HC to the mean change in NMR.

We targeted enrollment of 71 individuals to detect a 0.1 difference in NMR between specimens obtained on and post-efavirenz use with 80% power at a P value of 0.05, assuming a standard deviation of NMR of 0.25.

Ethics statement

All participants provided informed consent for collection of data and specimens for inclusion in the CNICS database. All data and specimens were anonymized prior to release by CNICS to the study team. The University of Pennsylvania and University of Toronto institutional review board approved the study protocol.

RESULTS

A total of 72 actively smoking PWH who switched from efavirenz to either an INSTI or other NNRTIs while maintaining HIV suppression were included. Samples collected while on an efavirenz-based regimen were primarily from 2012 to 2016 and samples collected while on a non-efavirenz-based regimen were primarily from 2015 to 2019. Participants were predominantly male sex at birth, nearly evenly divided between Black and White race, and had a median time of ~ 2.5 years between the efavirenz and non-efavirenz regimen specimens (Table 1). Differences in mean NMR between covariate levels were only found for race, with Black PWH having a larger change in the NMR. Whereas mean NMR on an efavirenz-based regimen was similar between the two race groups (Black: 0.75, SD: 0.39;

White: 0.78, SD: 0.36, $P = 0.73$), there was a greater difference in the mean NMR on a non-efavirenz-based regimen (Black: 0.40, SD: 0.22; White: 0.64, SD: 0.35, $P < 0.001$). Due to insufficient numbers, ethnicity, CYP2A6 inhibitor use, amphetamine use, and cocaine use were excluded as covariates.

The mean NMR difference was −0.24 (SD: 0.37), with NMR differences ranging from −1.35 to 0.76; this overall mean decrease was statistically significant ($P < 0.001$). Forty-four (61%) study individuals had an NMR decrease of > 0.1, 12 (17%) had an NMR decrease 0–0.1 and 16 (22%) had an increase in the NMR (see Table S2 for individual characteristics by change in NMR). Figure 1 displays individual-level NMRs on efavirenz-based and after switching to non-efavirenz-based regimens. The first timepoint represents an individual's NMR while on an efavirenz-based regimen and the second timepoint while on a non-efavirenz-based regimen. Individual changes are represented by the lighter lines and the bolded line connects the mean NMR on an efavirenz-based regimen to the mean NMR while on a non-efavirenz-based regimen.

The mean difference in cotinine levels was 52.99 ng/mL (SD: 122.67) higher and the mean difference in 3-HC was 26.56 ng/mL (SD: 76.87) lower after switching off efavirenz. The correlation between change in NMR and change in cotinine ($r = −0.39$, $P < 0.001$) and change in 3-HC ($r = 0.34$, $P = 0.003$) were of similar magnitude, although, as expected, in opposite directions. Linear mixed models were used to examine interactions by race, age, time between specimens, and birth sex for the NMR. The interaction term between race and specimen sample was found to be statistically significant ($P = 0.015$). Interactions by age ($P = 0.855$), time between specimens ($P = 0.325$), and birth sex ($P = 0.154$) were not found to be significant.

DISCUSSION

In this sample of PWH who smoke who were virologically suppressed on efavirenz-based regimens and remained suppressed after switching to non-efavirenz regimens, the magnitude of decrease in NMRs was both clinically and statistically significant. Most individuals had decreases, although a few had increases in their NMR. Race appeared to be an effect modifier, with Black PWH having a significantly larger decrease in the NMR.

Our team has previously found that PWH who smoke have a higher NMR than those without HIV who smoke.[8] Although we found that HIV infection itself (i.e., pre- vs. post-HIV infection change in NMR) does not appear to be the mechanism responsible for the higher NMR in PWH who smoke,[9] we did find a small increase in the NMR after viral suppression (0.14, $P = 0.002$). However, there was a marked increase for those taking efavirenz-based regimens (0.53, $P < 0.001$).[10] The present data add to our understanding of how ART can affect nicotine metabolism and, in turn, smoking behaviors among PWH.

Differences in NMR decrease were found by race, with Black PWH having a similar mean NMR while on an efavirenz-based regimen as White PWH, yet had a larger NMR decrease after efavirenz discontinuation. In populations where CYP2A6 is not induced, Black smokers have a lower mean NMR than White smokers; this is consistent with our

findings after efavirenz discontinuation.[21–24] Similarly, wide CYP2A6 heterogeneity in Black PWH has been found to influence efavirenz pharmacokinetics, particularly when the primary metabolic pathway, mediated predominantly by CYP2B6, is also slower.[25] The mechanism of this race by NMR effect of efavirenz is unclear and warrants further investigation. It is important to note that race is a social construct, and when used in epidemiologic studies, frequently reflects the treatment of people of color in various systems and sectors rather than as a characterization of their genetic background.[26] Thus, our finding of difference by race warrants replication with precise genetic measurement to determine if efavirenz metabolism differences can account for this finding.

Although our study did not find any other sources of effect modification, the study covariates were selected due to prior evidence of effecting the NMR. Regarding alcohol use, two studies investigated the change in the NMR after people who smoke received psychotherapy for alcohol use disorder; one study focused on alcohol abstinence only in men[27] and the other focused on changes in alcohol consumption in men and women.[28] In both studies, the NMR significantly decreased for men after completing treatment, but this decrease was not seen in the second study for women. Of note, the second study also found much higher alcohol use and a larger decrease in alcohol use in men compared with women. Studies have also shown an association with age and NMR levels, with older individuals having modestly higher NMRs.[29,30]

Our findings have several implications given the established relationship between the NMR and smoking cessation outcomes.[18,30] The use of efavirenz as first-line ART remains common worldwide and is a mainstay in low- and middle-income countries.[31] Medication effects on CYP2A6 activity like those of efavirenz likely affects smoking cessation while on these regimens. Additionally, individuals who metabolize nicotine faster are less likely to respond to nicotine replacement therapy as a component of cessation strategies.[32] In lieu of measuring the NMR or attempting to quit using nicotine replacement therapy, PWH on efavirenz who smoke might have better outcomes with a non-nicotine-based pharmacotherapy, such as varenicline.[33] Additionally, PWH who smoke may be switched to ART that will not increase CYP2A6 activity.

Our study has several strengths. The repeated measures design allowed PWH to serve as their own control and therefore, confounding by time-invariant personal characteristics was eliminated. Thus, only time-varying confounders were considered, such as alcohol use, stimulant use, and other CYP2A6 medications. Insufficient frequencies of each prevented these analyses from being done, making them unlikely to cause large-magnitude confounding. Furthermore, there is a lack of a theoretical reason why a change in ART regimen among PWH with an undetectable viral load would be accompanied by a change in lifestyle factors.

The results of this study should be interpreted given certain limitations. This study was retrospective in nature, so the plasma levels used to calculate the NMR were collected at different points in time. The active ART regimen at the time of sample collection was provided rather than specific start and stop dates of efavirenz; this lack of certainty of the exact time exposure to efavirenz may have increased misclassification of drug exposure,

which would bias the results toward the null. We decided to only include samples where the ART regimen remained constant for at least 3 months to prevent including samples where efavirenz was recently initiated or discontinued. Because misclassification of this type would have biased our results to the null, the true NMR change after efavirenz discontinuation may be even larger than our study found. Smoking in PWH is a notoriously difficult and complex problem, with several well-known medical and mental health comorbidities that affect cessation.[34] Although we know from prior work that the NMR is associated with differences in smoking topography, quit potential, and lung cancer risk,[7,18,35] we did not directly measure these clinical outcomes or cessation behaviors themselves. Given the large amount of variation in the NMR, there is likely a large heterogeneous effect of the NMR on smoking outcomes, which warrants future prospective studies.

Given the enormous and growing burden smoking has on the health of PWH internationally, the findings of this project provide necessary clinical information that can guide providers and PWH through smoking cessation intervention and potentially ART regimen selection decisions. Additionally, it raises the question of whether other concomitant medications that affect CYP2A6 activity are associated with lower quit rates and worse outcomes for PWH who smoke.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

FUNDING

This work was supported by a National Heart, Lung, and Blood Institute grants (R01 HL151292 and R01 HL126538), by the University of Pennsylvania Center for AIDS Research (P30 AI 045008) and Penn Mental Health AIDS Research Center (P30 MH 097488), and a Canadian Institutes of Health Research Foundation grant (FDN-154294). Additional support came from the National Institute of Allergy and Infectious Diseases/CFAR Network of Integrated Clinical Sciences (R24 AI067039), University of Washington Center for AIDS Research (P30 AI027757), University of California San Francisco Bay Area Center for AIDS Research (P30 AI027763), and the National Institutes of Alcohol Abuse and Alcoholism (P01 AA029544). D.M. was supported by a training grant from the National Institute of General Medical Sciences (T32 GM075766). R.T. was funded in part by the Canada Research Chairs program (Chair in Pharmacogenomics). J.S.M. has received research grant support from the Cambia Health Foundation.

References

1. Helleberg M et al. Mortality attributable to smoking among HIV-1-infected individuals: a nationwide, population-based cohort study. Clin. Infect. Dis. 56, 727–734 (2013). [PubMed: 23254417]
2. Tesoriero JM, Gieryic SM, Carrascal A & Lavigne HE Smoking among HIV positive New Yorkers: prevalence, frequency, and opportunities for cessation. AIDS Behav. 14, 824–835 (2010). [PubMed: 18777131]
3. Mosepele M, Letsatsi V, Mokgatlhe L, Hudson FP & Gross R Cholesterol screening and statin prescription is low among HIV-infected patients on protease-inhibitor regimens in Botswana. Open AIDS J. 11, 45–51 (2017). [PubMed: 28839514]
4. Mdodo R et al. Cigarette smoking prevalence among adults with HIV compared with the general adult population in the United States. Ann. Intern. Med. 162, 335–344 (2015). [PubMed: 25732274]
5. 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 23, 10–23 (2015). [PubMed: 28529471]

6. Dempsey D et al. Nicotine metabolite ratio as an index of cytochrome P450 2A6 metabolic activity. Clin. Pharmacol. Ther.76, 64–72 (2004). [PubMed: 15229465]
7. Siegel SD, Lerman C, Flitter A & Schnoll RA The use of the nicotine metabolite ratio as a biomarker to personalize smoking cessation treatment: current evidence and future directions. Cancer Prev. Res. 13, 261–272 (2020).
8. Ashare RL et al. Differences in the rate of nicotine metabolism among smokers with and without HIV HHS public access. AIDS 33, 1083–1088 (2019). [PubMed: 30946162]
9. Arens Y et al. Brief Report: HIV infection does not explain higher nicotine metabolism in people living with HIV. J. Acquir. Immune Defic. Syndr. 91, 497–501 (2022). [PubMed: 36083509]
10. Bien-Gund CH et al. Brief Report: nicotine metabolism ratio increases in HIV-positive smokers on effective antiretroviral therapy: a cohort study. J. Acquir. Immune Defic. Syndr. 89, 428–432 (2022). [PubMed: 34879005]
11. Holzinger ER et al. Genome-wide association study of plasma efavirenz pharmacokinetics in AIDS Clinical Trials Group protocols implicates several CYP2B6 variants. Pharmacogenet. Genomics 22, 858–867 (2012). [PubMed: 23080225]
12. Kitahata MM et al. Cohort profile: the centers for AIDS research network of integrated clinical systems. Int. J. Epidemiol. 37, 948–955 (2008). [PubMed: 18263650]
13. Tanner J-A et al. Nicotine metabolite ratio (3-hydroxycotinine/cotinine) in plasma and urine by different analytical methods and laboratories: implications for clinical implementation. Cancer Epidemiol. Biomarkers Prev. 24, 1239–1246 (2015). [PubMed: 26014804]
14. Bush K, Kivlahan DR, McDonell MB, Fihn SD & Bradley KA The AUDIT alcohol consumption questions (AUDIT-C): an effective brief screening test for problem drinking. Arch. Intern. Med. 158, 1789–1795 (1998). [PubMed: 9738608]
15. Bradley KA et al. Two brief alcohol-screening tests from the alcohol use disorders identification test (AUDIT). Arch. Intern. Med. 163, 821–829 (2003). [PubMed: 12695273]
16. Humeniuk R et al. Validation of the alcohol, smoking and substance involvement screening test (ASSIST). Addiction 103, 1039–1047 (2008). [PubMed: 18373724]
17. Banerjee P, Dunkel M, Kemmler E & Preissner R SuperCYPsPred—a web server for the prediction of cytochrome activity. Nucleic Acids Res. 48(W1), W580–W585 (2020). [PubMed: 32182358]
18. Fix BV et al. Nicotine metabolite ratio (NMR) prospectively predicts smoking relapse: longitudinal findings from ITC surveys in five countries. Nicotine Tob. Res. 19, 1040–1047 (2017). [PubMed: 28387850]
19. Lerman C et al. Nicotine metabolite ratio predicts efficacy of transdermal nicotine for smoking cessation. Clin. Pharmacol. Ther. 79, 600–608 (2006). [PubMed: 16765148]
20. Schnoll RA, Patterson F, Wileyto EP, Tyndale RF, Benowitz N & Lerman C Nicotine metabolic rate predicts successful smoking cessation with transdermal nicotine: a validation study. Pharmacol. Biochem. Behav. 92, 6–11 (2009). [PubMed: 19000709]
21. Ho MK et al. Association of nicotine metabolite ratio and CYP2A6 genotype with smoking cessation treatment in African-American light smokers. Clin. Pharmacol. Ther. 85, 635–643 (2009). [PubMed: 19279561]
22. Mwenifumbo JC et al. Novel and established CYP2A6 alleles impair in vivo nicotine metabolism in a population of black African descent. Hum. Mutat. 29, 679–688 (2008). [PubMed: 18360915]
23. Fukami T, Nakajima M, Higashi E, Yamanaka H, McLeod HL & Yokoi T A novel CYP2A6*20 allele found in African-American population produces a truncated protein lacking enzymatic activity. Biochem. Pharmacol. 70, 801–808 (2005). [PubMed: 15993850]
24. Benowitz NL, St Helen G, Dempsey DA, Jacob P & Tyndale RF Disposition kinetics and metabolism of nicotine and cotinine in African American smokers: impact of CYP2A6 genetic variation and enzymatic activity. Pharmacogenet. Genomics 26, 340–350 (2016). [PubMed: 27035242]
25. Arab-Alameddine M et al. Pharmacogenetics-based population pharmacokinetic analysis of efavirenz in HIV-1-infected individuals. Clin. Pharmacol. Ther. 85, 485–494 (2009). [PubMed: 19225447]
26. Kaufman JS Commentary: considerations for use of racial/ethnic classification in etiologic research. Am. J. Epidemiol. 154, 291–298 (2001). [PubMed: 11495850]

27. Gubner NR et al. Cessation of alcohol consumption decreases rate of nicotine metabolism in male alcohol-dependent smokers. Drug Alcohol Depend. 163, 157–164 (2016). [PubMed: 27107849]
28. Dermody SS, Hendershot CS, Andrade AK, Novalen M & Tyndale RF Changes in nicotine metabolite ratio among daily smokers receiving treatment for alcohol use disorder. Nicotine Tob. Res. 22, 256–263 (2020). [PubMed: 30561731]
29. Johnstone E et al. Determinants of the rate of nicotine metabolism and effects on smoking behavior. Clin. Pharmacol. Ther. 80, 319–330 (2006). [PubMed: 17015050]
30. Kaufmann A et al. Rate of nicotine metabolism and smoking cessation outcomes in a community-based sample of treatment-seeking smokers. Addict. Behav. 51, 93–99 (2015). [PubMed: 26240944]
31. World Health Organization. Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection Recommendations for a Public Health Approach (2016) <https://www.who.int/publications/i/item/9789241549684>.
32. Lerman C et al. Use of the nicotine metabolite ratio as a genetically informed biomarker of response to nicotine patch or varenicline for smoking cessation: a randomised, double-blind placebo-controlled trial. Lancet Respir. Med. 3, 131–138 (2015). [PubMed: 25588294]
33. Bauer A-M et al. Medication adherence and rate of nicotine metabolism are associated with response to treatment with varenicline among smokers with HIV. Addict. Behav. 112, 106638 (2021). [PubMed: 32911350]
34. Ledgerwood DM & Yskes R Smoking cessation for people living with HIV/AIDS: a literature review and synthesis. Nicotine Tob. Res. 18, 2177–2184 (2016). [PubMed: 27245237]
35. Murphy SE Biochemistry of nicotine metabolism and its relevance to lung cancer. J. Biol. Chem. 296, 100722 (2021). [PubMed: 33932402]

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

The nicotine metabolite ratio (NMR; 3-hydroxycotinine/cotinine) is a valid biomarker of CYP2A6 activity and nicotine clearance, and higher NMR values have been associated with lower smoking quit rates. In trials, people with HIV (PWH) have lower quit rates than expected compared with HIV-negative people. Antiretroviral therapy (ART) such as efavirenz upregulates its own metabolism, partially via CYP2A6.

WHAT QUESTION DID THIS STUDY ADDRESS?

What is the effect of switching from efavirenz-based ART to non-efavirenz-based ART on the NMR in virally suppressed PWH who smoke?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

The results of this repeated measures study showed that switching to non-efavirenz-based ART was associated with a decrease in the NMR in PWH who smoke.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

The use of efavirenz as first-line ART remains common worldwide and is a mainstay in low- and middle-income countries. Although the effect of efavirenz on smoking behavior is still under investigation, providers may consider switching PWH who smoke to non-efavirenz based regimens or choosing non-nicotine-based pharmacotherapy.

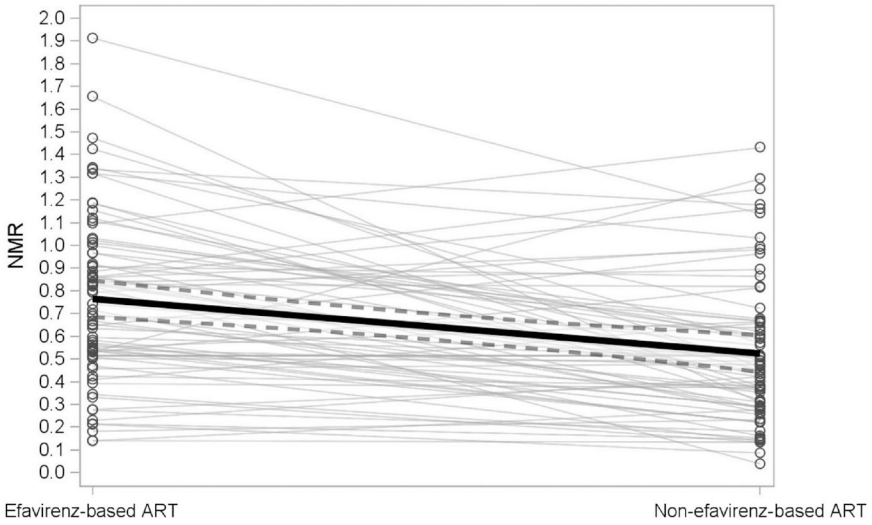

Figure 1.

Spaghetti plot of change in NMR from efavirenz-based to non-efavirenz-based regimen. The gray lines depict the change in each individual's NMR from efavirenz-based to non-efavirenz-based ART. The black bar depicts the mean change in NMR and the dotted bars depict the 95% confidence interval. ART, antiretroviral therapy; NMR, nicotine metabolite ratio.

Table 1

Mean difference in the nicotine metabolite ratio after discontinuing an efavirenz-based regimen by characteristics of people with HIV

Variable	*n*	Mean NMR difference post-efavirenz (95% CI)	*P* value for interaction
Age			
<= median (51 years)	36	−0.24 (−0.37 to −0.11)	0.98
> median (51 years)	36	−0.24 (−0.36 to −0.12)	
Sex at birth			
Male	63	−0.22 (−0.30 to −0.13)	0.15
Female	9	−0.41 (−0.79 to −0.02)	
Race			
Black	34	−0.35 (−0.48 to −0.23)	0.01
White	38	−0.14 (−0.26 to −0.02)	
Liver disease[3]			
Yes	9	−0.26 (−0.54 to 0.03)	0.91
No *Missing = 1*	62	−0.24 (−0.34 to −0.15)	
Days between specimen samples			
≤ median (628.5 days)	36	−0.16 (−0.28 to −0.04)	0.07
> median (628.5 days)	36	−0.32 (−0.44 to −0.19)	
Post-efavirenz medication			
INSTI	53	−0.19 (−0.29 to −0.10)	0.06
NNRTI	19	−0.38 (−0.58 to −0.18)	
CYP2A6 inducer use[a]			
Yes	12	−0.34 (−0.62 to −0.06)	0.30
No	60	−0.22 (−0.31 to −0.13)	
Alcohol use[a,b]			
At-risk	16	−0.29 (−0.44 to −0.14)	0.66
Not at-risk *Missing = 8*	48	−0.25 (−0.36 to −0.13)	

CI, confidence interval; INSTI, integrase strand transferase inhibitor; NMR, nicotine metabolite ratio; NNRTI, non-nucleoside analog reverse transcriptase inhibitor.

[a] All time-varying covariate frequencies reflect prevalence prior to efavirenz discontinuation.

[b] Based on lower AUDIT score thresholds.