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

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MULTICENTER AIDS COHORT STUDY

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Abstract

Methods: We compared NMR from plasma pre- and post-HIV infection in smokers who seroconverted and remained smokers in the MACS cohort. Any antiretroviral therapy (ART) use was exclusionary. Cotinine and 3-hydroxycotinine were measured in stored plasma using liquid chromatography-tandem mass spectrometry. We used signed rank tests to compare NMR pre- and post-HIV infection with a target sample size of 71 pairs to have 80% power to detect a clinically meaningful 0.1 unit increase in NMR with p=0.05.
Results: We analyzed samples between May 1984 and December 1993 in 78 men, median age 34.5 years (range: 24-53) who seroconverted with a median pre-HIV plasma cotinine of 267 ng/ml (range: 14- 649) and median post-HIV plasma cotinine of 252 ng/ml (15-267). The median NMR pre-HIV infection was 0.45 (IQR 0.32, 0.54) and post-HIV infection was 0.46 (IQR 0.34, 0.56) with a mean difference of 0.01 increase (IQR 0.05 decrease, 0.09 increase), p=0.25. The largest changes were a decrease in NMR of 0.55 units and an increase of 0.23 units. There was no evidence of differences when analyses were stratified by: a) > or ≤ 1 year between an individual's samples or b) HIV+ sample obtained > or ≤ 180 days after HIV infection.
Conclusions: HIV acquisition had no measurable effect on NMR. Since prior work consistently showing higher NMR in PWH included only individuals on ART, these results suggest that upregulation of the NMR may be due to direct pharmacologic effects of medications used to treat HIV (e.g., ARVs) or metabolic changes in response to HIV infection and its treatment over time. If follow-on studies show pharmacologic effects, changing the choice of ART to managing HIV infection in HIV+ smokers to decrease NMR may help increase quit rates.

Background

- People with HIV (PWH) ~3x > smoking than gen pop
- Nicotine metabolized by CYP2A6 to cotinine (COT) and 3-hydroxycotinine (3HC)
- Nicotine metabolite ratio (NMR)= 3HC/COT
  - Validated biomarker
- NMR associated with greater tobacco use & dependency
- Rate of NMR repeatedly shown higher in PWH on ART
- Effect of HIV infection on NMR unknown

Objectives

- We investigated whether HIV infection increases NMR

Methods

- Retrospective study of adult smokers in MACS Cohort who acquired HIV between 5/1985 and 12/1993
- Paired plasma pre- and post-HIV infection
- No ART before or after confirmed HIV seroconversion
- Analysis: signed rank test; significance level 0.05
- Subgroup analysis: stratified by time between specimen and seroconversion dates
- Change in NMR of 0.1 units clinically relevant
- Target sample size=71 pairs; 80% power

Results

Baseline Characteristics of HIV Seroconverters (N = 78)

▪ Male sex:	78 (100%)
▪ Median age (range), years	34.5 (24, 53)

Plasma NMR and Cotinine Pre- and Post- HIV Infection

NMR

- ❖ Median NMR pre-infection: 0.45 (IQR 0.32, 0.54)
- ❖ Median NMR post-infection: 0.48 (IQR 0.32, 0.56)

Cotinine

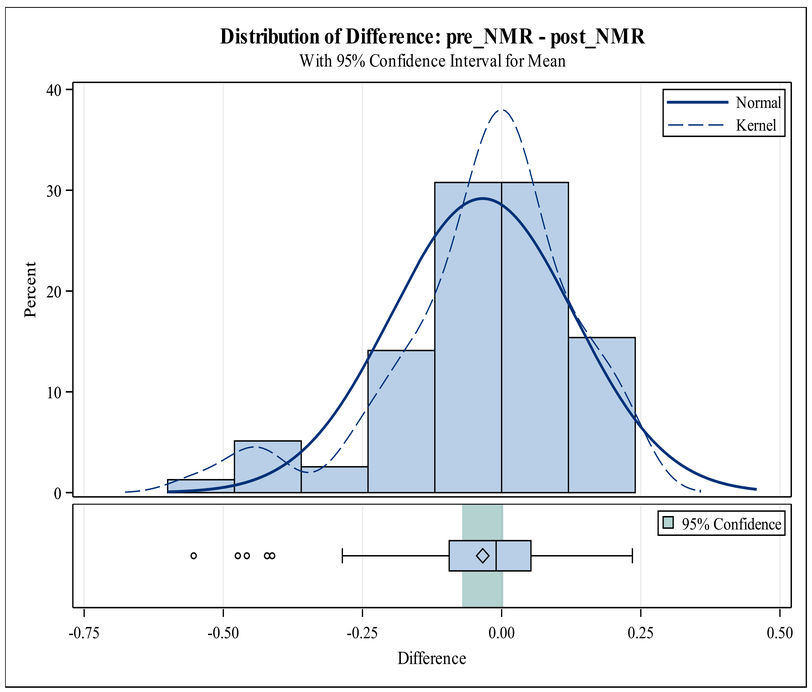
- ❖ Median COT pre-infection: 267 ng/ml (IQR 182, 321)
- ❖ Median COT post-infection: 252 ng/ml (IQR 147, 323)

Change in NMR

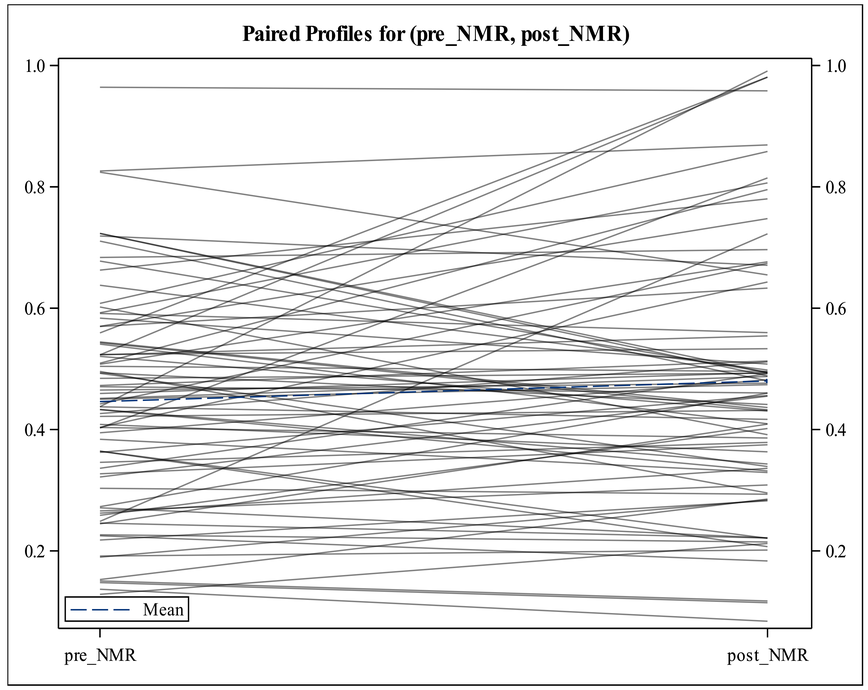
- ❖ Median change +0.01 (IQR -0.05, +0.09)

Stratified by Timing of Specimen Collection

- ❖ Results unchanged by timing of specimen collection:
  a) > vs. ≤365 days between pre- and post- specimens
  b) > vs. ≤180 days after seroconversion for post-specimen



Spaghetti Plot of NMR Pre-Post HIV Seroconversion



Limitations

- Only short term effect of HIV infection observable in cohort
- Given paired nature of samples, time-varying unmeasured confounders were not available to evaluate their effect

Conclusions

- No acute change in NMR after viral suppression among smokers who HIV seroconverted
- Cause of elevated NMR in PWH observed in previous studies remains unexplained
- Possible etiologies include: pharmacogenetic effects of ART (i.e., upregulation of CYP2A6) or metabolic effects of ART
- Further studies to determine etiology of higher NMR may yield targets to decrease nicotine metabolism and increase quitting

Data for this study were collected by the Multicenter AIDS Cohort Study (MACS), now the MACS/WIHS Combined Cohort Study (MWCCS). 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), by the Canada Research Chairs program (Tyndale, Chair in Pharmacogenomics) and a Canadian Institutes of Health Research Foundation grant (FDN-154294).