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A Bidirectional Relationship between Smoking and HIV in the Era of Antiretroviral Therapy (ART)

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Abstract

Background: The potential effect of smoking on HIV and response to antiretroviral therapy has been explored. Yet, the interactions between smoking and HIV, particularly, the impact of antiretroviral (ARTs) to variability in biochemical markers of cigarette smoking is currently unknown.

Methods: A longitudinal study was conducted to determine interactions between smoking and HIV, the impact of antiretroviral, and the variability in the biochemical markers of cigarette smoke exposure. Four hundred and twenty people living with HIV (PLWH) were recruited into 4 equal groups based on HIV and smoking status.

Findings: Half of the participants were smokers. Analyses confirmed that smokers had higher viral loads compared to non-smokers. Unsurprisingly, cotinine levels between ART and non-ART recipients tended to differ (233 ± 22 vs. non-ART=200 ± 36 ng/ml, p=0.09). Females with irregular menstrual cycles exhibited higher cotinine levels (410 ± 85 vs. 202 ± 32 ng/ml, p=0.02). Multivariate analyses confirmed that ARTs, females with irregular cycles, and number of packs predict cotinine levels.

Conclusion: To our knowledge, this is the first study to identify a plausible interaction between HIV medication and nicotine metabolism. However, findings agree with the concept that both are metabolized by the CYP1A2 and CYP3A4 enzyme system.

Keywords:

Smoking; HIV/AIDS; ART; Cotinine; Viral load

Introduction

While substantial progress has been made in reducing the prevalence of smoking to approximately 20% among the general population, these statistics are still grimmer for People living with HIV (PLWH) in the US [1]. The smoking rates among this population are two to four times higher (40-80%), increasing the risks of numerous diseases and threatening health gains achieved with antiretroviral treatment (ART) [1]. These days PLWH receiving ART lose more life-years to smoking than to HIV, with mortality tripling compared to the general population [1, 2].

Examinations of the relationship between cigarette smoking and course of the HIV disease have rendered inconsistent findings. Many articles suggested that smoking may not impact HIV disease, T cell counts, or viral load [3]. Yet those findings need to be considered with the caveat that they were done near the beginning of the HIV epidemic. More recently, our group, along with others, started questioning such results because the immune response associated with tobacco related diseases should exacerbate viral replication [4]. In support with our initial paper and postulates, a recent study, the Women's Health Initiative and the Ryan White Part A services in the New York Eligible Metropolitan Area, found a strong association between smoking and the effectiveness of treatment [5].

While several of those studies examined the effect of tobacco on ART and HIV, to our knowledge no prior studies have examined the impact of ART on nicotine. Yet the nicotine present in tobacco is predominantly metabolized by hepatic cytochrome P450 2A6 (CYP2A6) and CYP3A4, which metabolizes approximately half of the commercially available drugs including ART [4]. The proposed analyses is also critical in light of studies indicating that, for an unknown reason, smoking cessation treatments seem to be less successful among PLWH. We therefore conducted a study to analyse this bi-directional relationship.

Methods

Study population

Participants were enrolled into one of four groups based on smoking and HIV sero-status (HIV+ smoker, HIV+ non-smoker, HIV- smoker and HIV- non-smoker). This cohort study consists of 200 PLWH and 200 PLWOH smokers and non-smokers chosen to represent relatively "pure" smokers with minimal drug use, and without major confounding factors. Subjects were ineligible if they possessed a significant history of medical and immunological illnesses (that is liver cirrhosis, myopathies, malignancies and congenital or acquired immunosuppressive conditions, such as recipients of transplants, corticoids and autoimmune diseases). Older individuals (>50 years) were excluded to avoid the effects of immune-senescence. The study was approved by Florida International University's and the University of Miami School of Medicine's Committee for the Protection of the Rights of Human Subjects. All subjects signed both written informed consent and HIPAA forms.

The 15% that were lost to follow-up, and those with missing data, were excluded from the analyses.

Participants assessment protocol

Trained interviewers conducted in-person, computer based interviews that were followed by a brief physical exam and collection of blood specimen.

Smoking

The Fagerström Test for Nicotine Dependence is an extensively used instrument that provides a wealth of information regarding the quantity of cigarette consumption, the compulsion to use, and dependence [6]. Type of tobacco used (cigarettes, length, mentholated or not, use of filters, cigars, pipes, etc.) was also collected.

We followed the National Health Interview Survey (NHIS) guidelines to classify a subject as current smoker or a non-smoker [7]. In order to control for bias in participants' reports, nicotine plasma levels were used to confirm tobacco use.

Biological confirmation

Cotinine concentrations were quantitatively determined by using the solid phase, competitive ELISA BK kits. Inc. (San Diego, CA, US). Intensity of color is inversely proportional to the concentration of cotinine in the samples. The cotinine concentrations were expressed in ng/mL.

HIV outcomes

Our HIV outcomes were biomarkers of HIV disease progression, which included unsuppressed viral load (viral load >200 copies/mL) and low CD4 cell count (<200 cells/mm^3). To achieve this goal blood was drawn and flow cytometry was used to obtain T lymphocyte phenotypic analysis. Viral load was quantified using the ultrasensitive Amplicor HIV monitor test (Roche Diagnostic System). The lower threshold for this kit detection is 20 copies/ml, with a reported linear range of 20–10,000,000 cp/ml. Virological success was defined as achieving undetectable VLs.

Treatment and adherence

Following national protocols, the usual ART regimen combines three or more different drugs, such as two nucleoside reverse transcriptase inhibitors (NRTIs) and a protease inhibitor (PI), two NRTIs and a non-nucleoside reverse transcriptase inhibitor (NNRTI), or other such combinations.

An AIDS Clinical Trial Group (ACTG, self-reported adherence questionnaire was used to calculate the percentage of adherence and triangulated the information with both pharmacy and medical records [8]. If discordant, we endorsed medical/pharmacy reports.

Covariates

Structured questionnaires were used to obtain information on variables that could impact our analyses including socio-demographics. Gender (male vs. female or transgender) was obtained and information regarding menstrual cycles and oral contraceptives was obtained. Other variables deemed important were adherence, body mass index, dietary intakes, drug and alcohol abuse.

Results

Table 1 shows the descriptive characteristics in the total sample, including smoking status. No significant differences were found across the groups at baseline in two measurements of social inequalities, education and income. Participants were on average 39.8 years old; the majority of participants were African American or Hispanic.

Table 1 Sample characteristics and smoking status (Mean values (SD) for continuous variables and n (%) for categorical variables. Except for age and education, the groups were very similar. Please note that even in these cases groups differed only by 2 years).

	Smokers	Non-Smoker	P value
Age (years)	40.4 ± 8.2	38.7 ± 9.6	0.06
Gender			

Male	61%	55%	0.37
Female	39%	45%	
>$49,999	2%	4%	
Education (years)	11.3 ± 2.3	11.8 ± 2.3	0.06
Body Mass Index	29.7 ± 7.4	29.8 ± 6.9	0.92
Albumin (mg/dl)	4.3 ± 0.3	4.2 ± 0.3	0.22
SGOT (IU/L)	32.2 ± 13	33 ± 17	0.85
SGPT (IU/L)	32.6 ± 18	35.9 ± 29.6	0.39

Smoking and HIV outcomes

As seen in **Table 2**, subjects smoked as little as 1 cigarette per day and as much as 4.5 packs. The average level of cumulative tobacco exposure was 10 pack-years; with our typical participant was a smoker, on average, for half of their life (approximately two decades).

The mean CD4 cell counts (cells/µL) tended to differ between smokers and non-smokers (317.3 ± 43) and HIV positive smokers (260.6 ± 24). Despite similar medication adherence (90% vs. 80%), there was a significant increase in the viral burden in smokers compared with non-smokers (37179.0 ± 10121.0 vs. 10797.5 ± 3123 copies). Additional analyses indicated that smokers were two times more likely to fail at achieving undetectable viral loads (OR=1.4; 95% CI 1-2.1, p=0.04).

Table 2 Tobacco outcomes. Mean values (SD) for continuous variables and n (%) for categorical variables. Despite smoking similar number of cigarettes per day and start smoking at similar age, HIV positive individuals exhibited significantly higher levels of cotinine.

HIV Status	Mean		Std. Deviation	P value
Smoking Quantity	Positive	7.58	0.95	
	Negative	7.79	0.81	0.813
Cotinine ng/ml	Positive	224.4	19.85	0.09
	Negative	199.89	16.58	
Years Smoking	Positive	24.87	8.91	0.008
	Negative	19.77	10.25	
Age Start Smoking	Positive	17.23	5.39	0.84
	Negative	17.08	5.84	

HIV, antiretroviral treatment and biomarkers of smoking

Our analyses revealed that HIV positives and negatives smoked similar quantities per day (7.5 ± 0.6 Vs 7.8 ±8.3 cigarettes/day). Yet, the circulating levels of cotinine were slightly higher in HIV positives compared to their seronegative counterparts (224.4 ± 198 vs. 190.8 ± 164 ng/ml, p=0.09). After multivariate adjustment, cotinine levels were an average of 40 ng/ml higher among PLWH receiving ART than those without it (p=0.05).

Female smokers had slightly higher serum cotinine concentrations than the males (220.8 ± 22 versus 208 ± 15 ng/ml, p=0.6). However, while PLWOH's cotinine levels were lower in females than in males, HIV-infected females had significantly higher cotinine levels than HIV infected males. Indeed, despite smoking similar amounts (males=8.0 ± 0.7 vs. 6.9 ± 0.9 cigarettes/day) cotinine values in HIV-infected females almost doubled compared to their non HIV-infected counterparts (283 ± 36 vs. 155.7 ± 19 ng/ml, p=0.01). Since prior studies have evidence that hormonal changes can affect nicotine metabolism we proceeded with analyses regarding their menstrual cycles [9]. In the descriptive analyses 19% of females had irregular menstrual cycles, 7% had been submitted to hysterectomy, and the remaining females (74%) reported normal menstrual cycles. Among HIV-infected females, those with irregular menstrual cycles exhibited the highest cotinine levels (410 ± 85 vs. 202 ± 32 ng/ml, p=0.02).

However, such a relationship did not hold in female PLWOH **(Figure 1** and **Table 3)**.

Table 3 Regression analyses; predictors of cotinine levels (a: Dependent Variable: Cotinine), Model 1: Adjusted for age (years) alcohol consumption, body mass index (normal weight/overweight/obese), physical activity (inactive/low/medium or high); viral load. A pack-year was defined as having smoked 20 cigarettes per day.

	Coefficients				
Model	**Unstandardized Coefficients**		**Standardized Coefficients**	**t**	**Sig.**
	B	**Std. Error**	**Beta**		
(Constant)	219.064	164.9		1.328	0.19
Antiretroviral	80.426	39.192	0.266	2.052	0.05
Menopause/irregular cycles	-162.99	70.511	-0.3	-2.31	0.03
CD4 Absolute Counts	-0.01	0.022	-0.056	-0.44	0.66
Packs	119.028	50.055	0.304	2.378	0.02

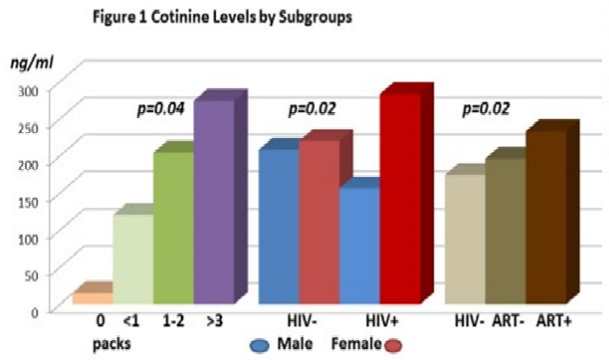

Figure 1 Cotinine levels by subgroups. As depicted in the figure cotinine levels significantly differed by number of cigarettes smoked per day (left in the figure), by HIV status and gender (middle part of the graph) and by therapy (right).

Discussion

In accord with prior *in vitro* and *in vivo* studies, our data demonstrated that smoking is associated with increased viral burdens and poor viral responses among those receiving antiretroviral therapy [9-12]. Our analyses expanded the literature in the field by demonstrating that after controlling for the amount and type of cigarettes smoked, HIV infected smokers had higher cotinine levels than non-HIV infected ones. This is the first clinical evidence of a bi-directional relationship. Differences in cotinine levels between seropositives and seronegatives are consistent with prior studies signifying that these at-risk populations experience more difficulty quitting [13]. Our study provides further information by demonstrating that antiretroviral therapy may be driving at least part of the increased levels of cotinine observed in this population. Findings were not unexpected when considering that tobacco is metabolized by hepatic cytochrome P4502A6 (CYP2A6) and CYP3A4 which metabolizes many antiretroviral. More specifically CYP is involved in the metabolism of protease inhibitors and non-nucleoside reverse transcriptase inhibitors [10]. Findings are clinically relevant as they highlight the need for Nicotine replacement therapy dose adjustments during pharmacological interventions to temper/match nicotine intake prior to quitting. The observed increases are also of concern because it can lead to increases in the production of reactive oxygen species oxidative stress and organ damage.

Notably, data also indicated that the association between HIV/ART and cotinine levels was stronger and statistically significant for women. Analyses have shown that gender differences in cotinine levels are not related to a greater number of cigarettes smoked, rather it is probably due to hormone driving differences [14]. Indeed, higher levels were evident among those self-reporting amenorrhea, changes in menstrual cycles, early menopause, or hysterectomy. Findings are of great concern in light of studies indicating that the health consequences of tobacco use are greater among female smokers [15]. Equally important, our results can partially explain prior observations indicating less favourable results among women trying to quit, which could reflect the need for higher NRT doses. Results also highlight the need of additional research and tailoring therapies, because the “one size fits all” approach clearly does not work for this study population.

This study has some limitations. First, the population was limited to those living in South Florida. Although we had dietary data, we cannot analyse differences in intakes of some dietary products such as tea, tomatoes, eggplants, and potatoes that have nicotine, but these should contribute minimal amounts.

In summary the data indicated the impact of HIV and antiretroviral therapy on cotinine levels and provided a potential explanation for why people living with HIV have additional difficulties quitting. The analyses highlight the impact of gender when studying behaviours and treatment

outcomes, in order to provide relevant and useful information to clinicians and health policymakers.

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Competing Interests

Authors received salary support from the James and Esther King Biomedical Research Program, Florida Health Department for the submitted work. There are no other relationships or activities that could influence the submitted work.

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