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The unique challenges facing HIV-infected patients who smoke cigarettes: HIV viremia, ART adherence, engagement in HIV care, and concurrent substance use

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Abstract

Evidence suggests that smoking may have negative associations with HIV health outcomes. The smoking rate in our sample of people living with HIV (*N* = 333) was triple that of the general population (57% v. 19%). Regression analyses revealed that smokers (v. non-smokers) reported lower medication adherence (unstandardized beta = 9.01) and were more likely to have a detectable viral load (*OR* = 2.85, 95%CI [1.53–5.30]). Smokers attended fewer routine medical visits (β = −0.16) and were more likely to report recent hospitalization (*OR* = 1.89, 95%CI [0.99, 3.57]). Smokers ranked "health" as less important to their quality of life (β = −0.13) and were more likely to report problematic alcohol (*OR* = 2.40, 95%CI [1.35, 4.30]), cocaine (*OR* = 2.87, 95%CI [1.48–5.58]), heroin (*OR* = 4.75, 95%CI [1.01, 22.30]), or marijuana use (*OR* = 3.08, 95%CI [1.76–5.38]). Findings underscore the need for integrated behavioral smoking cessation interventions and routine tobacco screenings in HIV primary care.

Keywords

HIV/AIDS; smoking; adherence; substance use; engagement in care

INTRODUCTION

Given the widespread negative effect of cigarette smoking on health, many researchers have called for public health initiatives to reduce smoking among individuals living with chronic medical conditions [1]. People living with HIV, specifically, have been identified as a medical population that may be at particularly high risk for smoking-related illnesses, given the high rates of smoking and substantial related co-morbidity and mortality in this group

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[2]. In fact, one study found that 70% of HIV-positive outpatients are daily smokers [3], compared to an estimated 19% of the U.S. general population[4]. Given that mental health problems have been associated with an increased likelihood of smoking across disease populations [5,6], it is likely that the disproportionally high rates of mental health problems observed among people living with HIV [7–9] may be one way to understand these alarming rates of smoking.

Smoking, in the context of HIV, increases the risk for pneumocystis pneumonia (PCP), bacterial pneumonia, chronic obstructive pulmonary disease (COPD), cardiovascular disease, and non-AIDS cancer [10–16]. These types of comorbidities likely lead to poorer HIV health outcomes, including death. Accordingly, a recent population-based study of HIV-positive individuals in Denmark revealed that the attributable risk of death associated with smoking was 61.5% among HIV-positive individuals versus 34.2% among demographically matched HIV-negative controls [17]. These data are consistent with findings from a smaller study demonstrating a three-fold increase in hazard ratio for death among HIV-positive smokers compared to HIV-positive non-smokers living in San Francisco [18].

In addition to poorer HIV health outcomes from smoking-related co-morbidities, there is preliminary evidence to support associations between smoking and HIV health behaviors, including disease management behaviors. For example, preliminary evidence supports that HIV-positive smokers are less likely to be adherent to their medications, and less likely to benefit from the medications they are taking [19–22]. Results from a longitudinal study of over 900 women indicated that HIV-positive smokers experienced virologic failure sooner than HIV-positive non-smokers [19]. The relation between smoking and virological failure held true even after controlling for adherence, suggesting that there may be a direct biological pathway between smoking and impaired response to antiretroviral medications beyond the role of adherence [19].

Although a handful of previous studies have demonstrated relations between HIV disease management and increased morbidity and mortality among smokers, few studies have been able to identify a smoking-related vulnerability for health behaviors associated with HIV health outcomes. To address this gap, we aim to examine healthcare utilization and co-morbid substance use as additional factors in the relation between smoking and poorer HIV health. We hypothesized that, compared to non-smokers, smokers would evidence sub-optimal engagement in preventive medical care and, relatedly, place lower importance on "health" in evaluating their overall quality of life. We also hypothesized that smokers would be more likely to engage in concurrent alcohol or substance use that may buttress associations between smoking and HIV health variables. Finally, we examined the relations between smoking behavior, electronically captured medication adherence, and viral load among people living with HIV who were recruited for and screened for a psychotherapy intervention study for depression and adherence.

METHOD

Participants and Procedures

Data for this study were gathered as part of a baseline assessment, the purpose of which was to determine eligibility for a randomized controlled trial of an intervention designed to address adherence and depression among people living with HIV. Participants were recruited from three HIV primary care clinics in New England (February 2009 – May 2012) via 1) research assistant recruiters and 2) advertisements at the study sites. Recruitment materials (i.e. mini-fliers) specified that the study was for individuals who struggle with depression. During HIV primary care visits, clinic providers obtained permission from patients to allow a study staff member to approach a potential participant, discuss the components of the study, and invite participation.

To be eligible to participate in the baseline assessment, individuals needed to meet the following criteria: a) report an HIV-positive serostatus, b) be between the ages of 18 and 65, c) have been prescribed antiretroviral medication for at least 2 months, and d) have screened positive for depression on the PHQ-2, a two-item diagnostic screening instrument that inquires about depressed mood and anhedonia over the previous two weeks [23]. One participant who demonstrated poor comprehension when reviewing the informed consent, and therefore was unable to provide consent, was excluded. Self-report assessments were read to participants who were able to provide informed consent, yet exhibited reading difficulties.

Baseline assessments took place at one of three HIV clinics. Study clinicians obtained written informed consent prior to beginning the assessment. The assessment included questionnaires on demographics, smoking behavior, and quality of life, as well as an introduction to the electronic pill cap for measuring adherence (MEMS; Medication Event Monitoring System; AARDEX), and clinician administered questionnaires assessing for depression, substance use, and health care utilization. In addition, viral load (i.e., HIV plasma RNA counts) was obtained by blood draw or by extraction from their medical record. Participants received $50.00 for their participation in the baseline assessment. Participants then returned two weeks later for a randomization visit where they returned the MEMS cap and were informed of their eligibility status for the clinical trial. All study procedures were approved by Institutional Review Boards at Massachusetts General Hospital, Fenway Health, and The Miriam Hospital.

Measures

Demographics—Participants completed a paper-and-pencil questionnaire containing items regarding their age, sex, sexual orientation, disability status, and educational history. Race and ethnicity was also assessed based on NIH-defined categories.

Depression—Study clinicians administered the Montgomery-Asberg Depression Rating Scale (MADRS) [24] to assess for depressive symptoms. The MADRS is a widely used clinical measure of depression in psychiatric research with strong psychometric reliability and validity. The measure is comprised of ten items that are rated on a Likert scale (0–6),

yielding an overall score from 0–60. Higher scores on this scale indicate more severe depression. To ensure consistency across study clinicians, the MADRS scores were regularly reviewed through audiotape supervision by an independent assessor.

Smoking behavior—Smoking behavior was assessed via self-report during the baseline assessment using three questions. Participants reported their current smoking status, how many cigarettes they typically smoke per day, and the number of years they have been smoking (lifetime). These data were used to describe the smoking behaviors of the sample. A dichotomous variable was created for use in regression analyses; smokers were coded as 1 and non-smokers were coded as 0.

Adherence—Antiretroviral medication adherence was monitored using the MEMS cap, which recorded each time the participant opened the bottle. In our analyses, adherence was operationalized as the percentage of on-time MEMS-based adherence in the two weeks following the baseline assessment. Adherence was adjusted to account for doses that participants may have taken without opening the pill cap (e.g., "pocketed doses"); these doses were only counted if the participant could recall specific instances (day, time, circumstance) when they took their medications but did not use the cap [25–27]. A dose was considered missed if it was not taken within a 2-hour window of the designated time. Participants also provided self-reported adherence for this time period. When discrepancies between self-report and MEMs data on adherence emerged, either a research assistant or study clinician would interview the participant to resolve this discrepancy, thus ensuring the most accurate capture of medication adherence.

Biological Markers of HIV—Viral load and CD4 data were obtained either through clinical chart review (if a test had been done in the month prior to the visit) or, for those who did not have a recent assay, directly through the study. Patients without recent assays had two tubes (10cc of blood each) drawn by a phlebotomist at the time of the baseline assessment. One tube was used for HIV viral load measurements and another for CD4. To assess for viral load, we used an ultra-sensitive quantitative assay, the AMPLICOR HIV-1 MONITOR Test (Roche Diagnostics), with a lower limit of detection of 50 RNA copies/ml plasma and an upper limit of 75,000 copies/ml plasma. Thus, undetectable viral load was operationalized as <50 RNA copies/ml plasma. The blood samples for the CD4 tests were first analyzed for CBCs, which were performed on an AdviaTM 120 Hematology System (Bayer Corporation, Tarrytown, NY), following the laboratory's standard operating procedure. Blood samples were then analyzed for CD4 enumeration in the Flow Cytometry Laboratory.

Alcohol and Substance use—A clinician-administered measure, the NIDA-CTN Addictions Severity Index—Lite (ASI-Lite) [28,29] was used to assess the number of days of substance use in the past 30 days. These items were dichotomized to reflect 0 (*no use*) or 1 (*any use*) in the past 30 days. In order to ensure sufficient variability, relations with smoking status were examined for the seven most frequently used substances in the past 30 days. These were alcohol, alcohol (to intoxication), marijuana, cocaine, and non-prescribed sedative, heroin, and "other opiate" (i.e., non-heroin) use.

Health care visits—As part of a clinician-administered questionnaire to assess health care utilization, participants were asked to report the number of outpatient health care visits (not including mental health care) and whether or not they had an overnight hospital stay for medical issues in the past four months. Routine HIV primary care visits were not included in these totals. Outpatient health care visits in our analyses indicate the number of health care visits attended by participants, with lower numbers indicating under-engagement in care. Inpatient hospitalization was operationalized as 0 (*no overnight hospital stay*) or 1 (*at least one overnight hospital stay*) in the past four months.

Importance of health—We used one item from the Quality of Life Inventory (QOLI) [30], a self-report measure which focuses on life-satisfaction, to assess the importance of their health (i.e., "being physically fit, not sick, and without pain or disability") to their happiness. Clinicians asked participants to indicate the level of importance health had in their overall quality of life. Response choices included: 1 (*not important*), 2 (*important*), or 3 (*extremely important*).

Data Analysis

Univariate procedures were run on demographics, as well as independent and dependent variables to obtain descriptive statistics for the sample. Next, bivariate correlations were run for smoking variables and all dependent variables. A t-test was used to determine if there were group differences in depression between smokers and non-smokers. Finally, six separate logistic and linear regression models were run using smoking status as the dependent variable and detectable viral load, medication adherence, health care visits, inpatient visits, importance of health to quality of life, substance use, and alcohol use as independent variables. A priori determined covariates of age, race, education, and gender were included in each of these models. Although sexual orientation was significantly related to smoking status, it had high colinearity with gender (i.e., only 18.4% of the men in the sample identified as being exclusively heterosexual). The pattern and significance of the main findings remain unchanged when sexual orientation replaces gender in the regression models below.

RESULTS

Demographic and Smoking Characteristics

Demographic information and smoking characteristics of the sample are presented in Table I. The mean age was 47.2 years (SD = 8.3) and the majority of participants were Caucasian (55.1%). A large minority of participants were on disability (39.3%). In terms of education, the sample was diverse; 19.5% reported less than a high school degree; 23.8% reported high school degree; 26.6% reported some college; and 30.0% reported having a college degree. Approximately 57% of the sample identified as current smokers. Further, participants reported smoking an average of 7.5 cigarettes per/day (SD = 9.2) and an average smoking history of 15 years (SD = 14.7). Overall, smokers were more likely to be male (p = .005), to identify as gay or bisexual (p = .005), have lower education (p < .001), and to report as a racial minority (p = .03). A t-test revealed that depression scores of smokers (M = 22.6, SD

= 9.6) did not differ significantly from the depression scores of non-smokers (*M* = 22.7, *SD* = 10.4) in our sample (*p* = .27).

The average viral load (log10) for the sample as a whole was 5.71 (*SD* = 0.55) and the average CD4 cell number was 574.66 (*SD* = 279.00) identifying the average patient in this sample as being in the mid-range of HIV disease course with considerable individual variability. All regression models were adjusted for age, race, education, and gender, logistic regression analysis (see Table II) revealed that smokers were almost three times as likely to have a detectable viral load compared to non-smokers (*OR* = 2.85, 95%CI [1.53 – 5.30]).

A series of linear and logistic regression models were used to assess the impact of smoking status on three dependent variables including: MEMS-assessed adherence, number of health care visits, inpatient hospitalization (yes/no), and self-reported importance of health to quality of life. The average MEM-assessed adherence for all those screened at baseline was 84.81% (*SD* = 22.57). Results indicate that smokers have significantly poorer MEMS-assessed adherence (unstandardized beta = −9.01, *p* = .004), such that smokers had 9% poorer adherence compared to non-smokers. Further, relative to non-smokers, smokers reported attendance to fewer routine outpatient healthcare visits (β = −0.13, *p* =.01) and were more likely to report inpatient hospitalization (*OR* = 1.89, 95%CI [0.99, 3.57]) in the previous 4 months. Smokers also ranked "health" as less important to their quality of life (β = −0.13, *p* = .02) compared to non-smokers.

Logistic regression analyses controlling for age, race, education, and gender indicated that individuals who reported problematic alcohol use (to intoxication) were more than two times more likely to be smokers compared to those who did not report problematic alcohol use (*OR* = 2.40, 95%CI [1.35, 4.30]). Participants who reported problematic cocaine, heroin, or marijuana use in the past 30 days were approximately three times more likely (cocaine: *OR* = 2.87, 95%CI [1.48–5.58]; heroin: *OR* = 4.75, 95%CI [1.01, 22.30]; marijuana: *OR* = 3.08, 95%CI [1.76–5.38]) to be smokers compared to participants who did not report problematic cocaine, heroin, or marijuana use. Relative to non-smokers, smokers were no more likely to report the use of alcohol without intoxication (*OR* = 1.49, 95%CI [0.95–2.33]), "other opiates" (*OR* = 1.19, 95%CI [0.71–2.00]), or sedatives (*OR* = 1.18, 95%CI [0.70–1.99]) in the past 30 days. Full details of these analyses are presented in Table III.

DISCUSSION

Our study is the first of which we are aware to demonstrate a smoking-related vulnerability for HIV health and health behaviors critical to the effective management of HIV; most notably, we observed significant relationships between smoking and adherence to HIV medications, attendance to routine HIV medical appointments, and HIV viral suppression. In our sample, we observed smoking rates that were triple the rates observed in the general population (57% v. 19%) [4]. Our main findings are consistent with previous studies that have identified associations between smoking status and medication non-adherence among people living with HIV [19,21,22]. In the current sample, smokers were more likely than non-smokers to have a detectable viral load. This finding expands upon previous research suggesting that smokers experience virologic failure sooner than non-smokers [20].

In recent years, the relevance of health-related quality of life has been underscored by its associations with biological markers of HIV disease progression [31–33] as well as HIV survival [34–36]. In our study, we found that smokers endorsed lower importance of health to their overall quality of life relative to non-smokers. The relative low importance of health endorsed by smokers may be one of the factors associated with lower engagement in health protective behaviors. Given that it is unlikely that smokers have fewer medical complaints compared to non-smokers, our finding that smokers attended fewer non-HIV-related routine health visits likely suggests that smokers (v. non-smokers) are less likely to consult with their medical providers when experiencing medical issues. This finding may also indicate that, by assigning lower importance of health in their quality of life, smokers place lower importance in attending preventative medical care visits relative to non-smokers. Likely as a result of under-engagement in preventative care, we found that smokers were almost twice as likely as non-smokers to have reported a medical hospitalization in the previous four months. These findings concerning inpatient and outpatient health care utilization may suggest that smokers may be less likely to seek outpatient care and may, as a result, be more likely to undergo inpatient treatment due to less consistent outpatient care utilization.

Further, differences in the importance of health in quality of life may be key framework for understanding the high rates of additional health risk behaviors observed among HIV-positive smokers compared to non-smokers. For example, smokers evidenced poorer adherence to medication relative to non-smokers, suggesting lower engagement in health protective behaviors. In terms of concurrent health risk behaviors, we found that smokers were more likely than non-smokers to endorse problematic alcohol, cocaine, heroin, and marijuana use. These findings are consistent with previous research indicating that smokers engage in more health risk behaviors and fewer health promoting behaviors relative to non-smokers [37,38].

Although the pathways linking smoking to various HIV outcomes are largely unknown, some plausible mechanisms have emerged, including health behaviors, psychosocial factors, substance use, and biological pathways. Consistent with our findings, higher likelihood of non-adherence among smokers and lower engagement in a range of health-promoting behaviors, such as routine medical appointments, may place smokers at increased risk of poor disease management. Given that smokers in our study reported lower importance of health to their quality of life relative to non-smokers, smokers may be less likely to engage in health protective behaviors as well as more likely to engage in other health risk behaviors, thereby increasing the likelihood of adverse health outcomes. As a result, the relative importance of health in estimations of quality of life may well be an important target for behavioral smoking cessation programs for smokers living with HIV. Additionally, higher rates of alcohol and substance use among smokers may be one path by which smoking is associated with medication non-adherence and poor disease management and outcomes among the participants in our sample, as the relation between substance use and medication non-adherence is well-established in the literature (e.g., [39]).

It is possible that we did not observe differences in depressive symptoms between smokers and non-smokers due to a ceiling effect; this is likely given that our sample is comprised of individuals who expressed interest in a clinical trial to treat depression. Although smokers

were no more likely to be depressed compared to non-smokers in our sample, it is plausible that smokers are at higher risk for other psychosocial factors that may compromise adaptive management of HIV. For example, one line of empirical evidence identifies anxiety disorders as representing a prominent concern among persons living with HIV. Rates of current anxiety disorders among HIV-positive individuals range widely but have been estimated to be as high as 43% (e.g., [40–42]). Further, anxiety disorders co-occur with smoking at rates that exceed those found in the general non-psychiatric population [43]. Thus, although beyond the scope of this study, anxiety symptoms may play a key role in the initiation and maintenance of smoking behavior among HIV-positive individuals.

There is also some preliminary evidence for a biological disadvantage for smokers. This biological pathway is supported by previous studies that have found that smokers had poorer viral and immunologic response to antiretroviral therapy, a greater risk of virologic rebound, and more frequent immunologic failure compared to non-smokers [19]. More recently, Feldman and colleagues [20] found that the adverse effects of smoking on medication response remained even after controlling for adherence. Thus, it is plausible that smoking may contribute to a biological vulnerability that increases susceptibility to co-morbid medical conditions and dampens the therapeutic effect of HIV medications, independent of the relationship with adherence. Thus, there are likely biological (e.g., immune function) and behavioral (e.g., medication adherence, under-engagement in care, concurrent substance use), and psychosocial (e.g., depression, anxiety) mechanisms underlying the relations between smoking and HIV health.

Implications

Future studies are needed to identify specific pathways by which smoking leads to poorer HIV health outcomes. In addition, there is a need for further research evaluating the effect of smoking cessation on HIV disease management. Our findings underscore the importance of developing efficacious smoking cessation programs for people living with HIV. To date, only four randomized controlled trials examining the efficacy of smoking cessation interventions among HIV-infected adults have been conducted [44–47]. None of these studies found differences in abstinence rates between treatment and control conditions; however, one study found significant reductions in number of cigarettes smoked at follow-up despite no group differences in abstinence rates [47] and another study observed improvements in HIV-related symptom burden among participants who had achieved abstinence [46]. These studies provide some evidence for the feasibility of smoking cessation programs in HIV care settings.

The relations between medication adherence, viral suppression, and engagement in care with smoking suggest that smoking cessation behavioral programs that are integrated into behavioral, skills-based, programs that also address adherence and engagement in care may be particularly relevant for this multiply challenged patient group. Given the modest performance of smoking cessation interventions in HIV patient groups, this innovation may well support larger effect sizes and may impact HIV treatment outcomes. Moreover, given the high correlation between smoking behavior and problematic use of alcohol and substances, smoking cessation interventions specifically designed for people managing HIV

may benefit from sufficient flexibility to address the effect of these other substances on disease management as well. Going forward, the evaluation of these programs is essential to quantifying the effect that these programs have on the global functioning and health of people living with HIV.

HIV-positive individuals are living healthier and longer lives; thus, clinical care must broaden its focus to other modifiable health risk behaviors, such as smoking. More specifically, our findings further support the need for routine screening for smoking in HIV primary care settings. For example, having smoking status prominent in patients' electronic medical records, as well as clinical reminders for screening and referral to cessation programs, may help link individual to care.

There are some limitations of the present study that should be noted. For example, the cross-sectional nature of the data precludes us from drawing conclusions about causal pathway by which smoking leads to poorer HIV disease management. Further, some of our measures are based on self-report which are vulnerable to social desirability biases. There are some limitations to the generalizability of our findings; namely, our findings cannot be generalized to a) people living with HIV who are not engaged in care, or b) people living with HIV who are not seeking participation in a clinical research study. Also, our smoking behavior measure could not identify individuals who were previously smokers—another subgroup that may have helped to clarify the potential benefits of cessation programs. Whereas we can presume that past smokers, captured in the non-smokers group, were still less likely to evidence poor disease management and substance use relative to current smokers, future studies may benefit from parsing out this subgroup.

Conclusion

The present study has highlighted a smoking-related vulnerability for poor HIV disease management among smokers as evidenced by a higher likelihood of detectable viral load, poorer medication adherence, and lower engagement in routine medical care. Our findings suggest that the development of empirically supported, skills-based, behavioral programs that address smoking cessation, adherence, and other indices of engagement in care may well reap the greatest benefit. Further, the co-occurrence of problematic alcohol and substance use among smokers is an important consideration as smoking cessation interventions are designed or adapted for use among people living with HIV. The multiple HIV disease management disadvantages associated with smoking strongly support the continued and expanded screening and referral for smoking cessation treatment in HIV primary care settings.

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Table I

Demographics and sample characteristics

	n	%
Age (M, SD)	47.2	8.3
Gender		
Male	272	73.5
Female	98	26.5
Race		
African American/Black	117	28.5
Caucasian/White	226	55.1
Other	55	13.4
Hispanic/Latino		
Yes	41	11.1
No	329	88.9
Education		
Partial high school or less	72	19.5
High school graduate	88	23.8
Partial college	98	26.6
College graduate	111	30.0
On Disability		
Yes	145	39.3
No	224	60.7
Sexual Orientation		
Exclusively homosexual	115	31.1
Homosexual with some heterosexual experience	71	19.2
Bisexual	29	7.8
Heterosexual with some homosexual experience	33	8.9
Exclusively heterosexual	122	33.0
Current smoker		
Yes	208	57.6
No	153	42.4
Years of smoking (M, SD)	15.1	14.7
Cigarettes per day (M, SD)	7.5	9.2

Table II

Smoking status and HIV health and health behaviors[a]

Dependent Variable	OR	95% CI	p
Detectable viral load	2.85	1.53 – 5.30	0.001
Inpatient healthcare visits (past 4 months)	1.89	0.99 – 3.57	0.05
	β	*t*	
MEMS-assessed adherence (7 day)	−9.01	−2.91	0.004
Outpatient healthcare visits (past 4 months)	−0.13	−2.51	0.01
Importance of health to quality of life	−0.13	−2.37	0.02

[a] All models adjusted for age, education, race/ethnicity, and gender

Table III

Odds Ratios of problematic alcohol and substance use in the past 30 days and smoking status.[a]

	B	SE (B)	p	Exp (B)	95%CI
Alcohol	0.40	0.23	.08	1.49	0.95 – 2.33
Alcohol (to intoxication)	0.88	0.30	.003	2.41	1.35 – 4.30
Marijuana	1.12	0.29	<.001	3.08	1.76 – 5.38
Cocaine	1.05	0.34	.002	2.87	1.48 – 5.58
Heroin	1.56	.78	<.05	4.75	1.01 – 22.30
Other opiates (non-heroin)	0.18	0.26	.50	1.19	0.71 – 2.00
Sedatives	0.16	0.27	.54	1.18	0.70 – 1.99

[a] All models adjusted for age, education, race/ethnicity, and gender