

## The Relevance of Blue Moods and Depression in the Context of Smoking and Natural Quitting Rates in People Living with HIV

María José Miguez-Burbano<sup>1\*</sup>, Mayra E Vargas-Rivera<sup>2</sup>, Yanerys Leon<sup>3</sup>, Clery Quiros<sup>2</sup>, John E Lewis<sup>4</sup>, Luis A Espinoza<sup>5</sup>, Deshratan Asthana<sup>4</sup> and Cassandra A Stanton<sup>6</sup>

<sup>1</sup>Professor, School of Integrated Science and Humanity, College of Arts and Sciences, Florida International University, USA

<sup>2</sup>Project Research Coordinator, School of Integrated Science and Humanity, College of Arts and Sciences, Florida International University, USA

<sup>3</sup>Assistant Professor, School of Integrated Science and Humanity, College of Arts and Sciences, Florida International University, USA

<sup>4</sup>Associate Professor, Department of Psychiatry and Behavioral Sciences, University of Miami School of Medicine, USA

<sup>5</sup>Associate Professor, Department of Medicine, University of Miami School of Medicine, USA

<sup>6</sup>Assistant Professor, Department of Oncology, Director, Schroeder/Lombardi Cancer Control Consortium, Georgetown University Medical Center, USA

### Abstract

**Objective:** Research suggests that smoking-cessation interventions are less successful among people living with HIV (PLWH). The factors influencing the limited success of evidence-based smoking-cessation interventions in this population are not well understood.

**Design:** Longitudinal analyses (of the first 12-months of an ongoing cohort ("FILTERS") sociodemographically matched sample of 160 PLWH and 180 without HIV) comprised of both smokers and non-smokers.

**Methods:** Semi-annual visits include a detailed survey of smoking behaviors (e.g., type of cigarette, amounts) and cessation efforts (i.e., prior attempts to quit, interest in quitting). Additionally, a fasting blood sample was obtained to assess serum cotinine, biochemical, and viroimmune parameters.

**Results:** Compared to seronegatives, PLWH were more likely to be smokers (OR=1.4; 95% CI: 1-2.2; p=0.05). The readiness-to-quit-stages assessment showed that only 45% of the participants in the PLWH group were in the preparation or ready-to-action stages. PLWH were less likely to express interest in quitting than HIV negatives (OR=0.6; 95% CI: 0.4-1; p=0.05). Analyses indicated that PLWH were twice more likely to report stress, depression and anxiety as causes of relapse in prior quitting attempts (OR=1.6; 95% CI: 1.5-2.4; p=0.004). After a natural course of 12 months, subjects receiving antidepressants exhibited larger reductions in number of cigarettes smoked per day (-2.6 CPD, p=0.06), than those without treatment (-0.8 CPD, p=0.2).

**Conclusions:** Our analyses indicated that negative moods impact quitting success rates, particularly among PLWH. Our findings suggest that evaluation and treatment of depression may be a critical component of a smoking cessation program.

### Introduction

Antiretroviral therapy (ART) has decreased HIV-related morbidity and mortality resulting in longer life spans and improved quality of life for people living with HIV (PLWH) [1]. Thus, ART has also transformed HIV into a chronic disease, whereby PLWH now require primary care that goes beyond the exclusive management of HIV-related conditions, including preventive services. Recent research has suggested smokers who are HIV-positive lose more years of life to smoking than to HIV [2,3]. Furthermore, studies suggest that PLWH that are smokers have lower scores for several dimensions of health-related quality of life components such as physical functioning, pain, reduce cognitive functioning than non-smokers [4]. However, research to-date has documented limited success of evidence-based smoking-cessation interventions in this population [5,6]. Evidence-based treatments for smoking cessation in PLWH have been largely developed from traditional social-cognitive [7] and motivational-interviewing approaches [5,8]. Although these approaches allow counseling to be tailored to the individual, the complex psychosocial and medical needs (e.g., concurrent mood and drug disorders) of PLWH who are attempting to quit tobacco many need to be addressed more directly to support sustained cessation in this population. For example, it is estimated that at least half of PLWH suffer alcohol use disorders. In addition, 20% to 37% of PLWH also suffer from depression [9], which among the general population has been associated as an impediment to succeed at smoking cessation attempts [10].

Compared with depression, the role of negative affect during

smoking cessation has been more sparsely examined in the literature. Negative affect is typically characterized as an aversive emotional state and includes feelings of nervousness, sadness, and irritation [11,12]. Since many of these symptoms are relieved by smoking, these individuals have the perception that cigarettes exert a beneficial mood effect, while there are more likely to be the root of the problem [11-14]. However, this relationship has not been observed in all studies [15]. The relationship between smoking, cessation, and depression has not been examined in PLWH, even though such findings may have important implications to inform effective treatment design. Therefore, continued research examined the complex interaction of these factors is warranted. Such information can be used to identify high-risk groups

**\*Corresponding author:** María José Miguez-Burbano, Professor, School of Integrated Science and Humanity, College of Arts and Sciences, Florida International University, Miami, FL, USA, Tel: 305-348-4517; Fax: 305-348-4289; E-mail: [mjmiguez@fiu.edu](mailto:mjmiguez@fiu.edu)

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and correlates of risk, and could potentially aid in the planning of control programs.

Reviews of existing literature suggest that smokers of mentholated cigarettes have lower cessation rates [16,17]. Of concern, reduced responses among users of mentholated cigarettes have been observed with both behavioral interventions, as well as with pharmacological approaches [16,17]. However the causes behind such associations are unknown. Furthermore, these findings have not validated among people living with HIV [16,17]. Nonetheless, such information will be highly relevant given that a sizable proportion of PLWH are consumers of mentholated cigarettes. Information regarding any potential mechanisms associated with reduced odds of cessation among PLWH can aid in the development of more effective interventions.

Given that PLWH are much more likely to smoke and less successful on their quitting efforts, we believed a large scale study to assess the association between comorbid conditions and smoking trajectories was needed.

## Methods

### Participants

The Florida International Liaison for Transdisciplinary and Educational Research on Smoking, "FILTERS", is a single-site ongoing cohort that was developed to examine biological and behavioral mechanisms mediating tobacco related health disparities. These analyses are based on 340 smokers and non-smokers that are currently enrolled in FILTERS and followed for 36 months. This unique cohort includes a racially diverse sample of HIV positive and HIV negative adults (over 18 years), where matched on environmental (zip code) and socio-cultural influences (age, gender, race).

### Exclusion criteria

Adults were excluded if they 1) had a significant history of medical and immunological illnesses (e.g., liver cirrhosis, myopathies, pregnancy, malignancies, congenital or acquired immunosuppressive conditions, recipients of transplants, autoimmune diseases, and those with liver enzymes two standard deviations above normal values); 2) were currently using anti-inflammatory drugs, lipid lowering medications, or hormonal therapy (e.g., transgender fertility treatments); and 3) were injection and/or dependent drug users (DSM IV).

### General procedures

This study was approved by the Florida International University Committee for the Protection of the Rights of Human Subjects. All subjects signed both written informed consent and HIPAA forms. Trained staff members conducted in-person computerized assessment interviews, and collected a 40-ml blood specimen at baseline and during semi-annual visits (4 visits).

### Smoking behavior

We used the Fagerström Test for Nicotine Dependence (FTND, Cronbach's  $\alpha=0.87$ ) to assess the degree of nicotine dependence of our participants [18]. The FTND includes questions about number of cigarettes smoked per day, and latency to first cigarette after awakening. Additionally, we collected information on tobacco consumption history, cessation, second-hand smoke, economics, media and advertising exposure. The tobacco smoking history portion of the questionnaire assesses past and current patterns of cigarette use, age of initiation, number of years smoking and predominant type of

cigarette used. The cessation portion assesses advice to quit smoking (i.e. by family, friends, or health-care provider), interest in quitting, and number of previous attempts, attempt method, and reasons for failing. Participants' nicotine withdrawal symptoms during smoking abstinence (e.g., depressed mood, insomnia, irritability, anxiety, and increased appetite) were assessed retrospectively. Individuals were also asked about weight issues/concerns before and during cessation attempts. Responses were coded as a binary variable (yes/no).

We adopted the National Health Interview Survey (NHIS) guidelines and defined a participant as a) a current smoker if he/she either smoked every day or smoked some days and has smoked at least 100 cigarettes during their lifetime; b) Former smoker if stopped smoking for at least 1 year; c) a non-smoker was defined as someone who has never smoked, or smoked for less than 3 months [19]. Based on these definitions, participants were assigned into one of four groups based on their HIV serostatus (positive/negative) and their smoking status (smoker/non-smoker).

Because self-reported smoking status may not always be reliable, cotinine levels were measured in serum specimens that were collected during interview sessions to validate self-report [20]. Quantification of cotinine was performed using the Cotinine Direct ELISA Kit (Bioquant, San Diego, CA, USA) according to the manufacturer instructions. Results are expressed in nanograms per milliliter.

### Depression

Participants were also tested for mood disorders using the revised Beck Depression Inventory II which yields a coefficient alpha of 0.92 [21]. The BDI-II is a 21-item, 4-point-scale questionnaire used to assess depression severity. A total score of '0-9' is considered normal, '10-18' suggests mild depression, '19-28' indicates moderate depression, and scores above '29' are considered severe depression.

Subjects were queried regarding previous diagnosis of mood disorders particularly depression and if the answer was positive they were asked if they have been prescribed a medication such as Serotonin Reuptake Inhibitors (SSRI) or other types antidepressants and the information was recorded.

### Covariates

Structured questionnaires were used to obtain information related to socioeconomic status, medical history (including antiretroviral treatment) and extent of alcohol and other drug use. Race/ethnicity data were self-reported and categorized as follows; race as Black, Caucasian, American Indian, Black Caribbean, or Asian; and ethnicity as Hispanic or non-Hispanic. The Activity Recall questionnaire was used to assess level of physical activity [22]. Participants were stratified into the following age ranges: a) 18 to 29, b) 30 to 40, and c) 41 and older. Socioeconomic status was determined based in annual income and categorized as earnings a) \$0-\$11,000; b) \$11,001-\$20,000; c) \$20,001-\$49,000; or >d) \$50,000. Educational level was coded 1-16, to account for each year of schooling through college or vocational training. Codes 13-16 corresponded to post-secondary, college education or equivalent vocational training.

We collected blood samples to measure participants' viro-immune (T Lymphocytes phenotypic analysis, using flow cytometry and viral load, using Roche AMPLICOR HIV-1 monitor test) and biochemical profiles (serum albumin levels, liver enzymes, urine function, BUN, creatinine, glucose, and lipid profile). Additionally, we used The Alcohol Use Disorders Identification Test (AUDIT, Cronbach alpha

index: 0.85) [23] and the Alcohol Dependence Scale (ADS; alpha coefficient of 0.92) [24], two standardized and validated brief screening questionnaires, to assess alcohol intake during the previous six months [24]. A “drink” was defined as half of one ounce of alcohol (e.g., one 12 oz. beer, one 5 oz. glass of wine, or one 1.5 oz. shot of distilled spirits). Males who reported more than 14 drinks per week and females who reported more than seven drinks per week were classified as hazardous alcohol users.

### Statistical analysis

Data analyses were performed using SPSS version 18. A normal probability plot was used to examine the distribution of the primary outcomes and the following descriptive statistics to summarize our data and detect outliers: minimum, maximum, median, and mean and standard deviation. Additionally, log transformations were performed for variables that were not normally distributed (e.g., cotinine values). T-tests and chi square analyses were used to compare means and proportions between the three smoking groups, differences in demographic (e.g., race and ethnicity), and clinical characteristics (e.g., HIV, alcohol use), while percentages and frequencies were used to describe categorical variables (e.g., education, smoking). Further, we utilized the Wilcoxon rank sum test for non-parametrically distributed variables.

In a separate model we analyzed significant reductions in number of cigarettes smoked over a one-year follow-up. Participants were dichotomized (“yes/no”) if participant responses indicated they were on an antidepressant versus not on an antidepressant at the time of the baseline or the 12 month visits. A linear regression model was used to examine potential mediators. The model covariates included a) cigarettes per day (continuous), b) menthol, c) age, d) sex, e) race and f) HIV status. The validity of the model assumptions was evaluated using analysis of residuals. P values less than 0.05 (2-tailed) were considered significant.

## Results

### Sociodemographics

Table 1 shows the descriptive characteristics in the total sample by HIV status. No significant differences were found between the groups at baseline in the two measurements of social inequalities, education and income. PLWH were on average slightly older, but otherwise groups were similar.

### Stages of change

Results of the stages of change assessment indicated that 45% of participants were either in the preparation or ready to take action stages, whereas the remaining 55% were in the pre-contemplation stage. We conducted further analyses of psychosocial, biological, structural and sociodemographic factors to evaluate any potential differences between current smokers not planning to quit with those ready to quit. The influence of **structural factors** (i.e., employment or financial status, education) was ruled out as significant differences between groups werenot observed. Of concern, PLWH were less likely to express interest in quitting than people living without HIV (PLWOH; OR=0.6; 95% CI: 0.4-1;  $p=0.05$ ). This is not surprising, given that most of the PLWH participants expressed perceptions that were inconsistent with the motivation to quit. For example, many participants expressed no health concerns, but instead alleged benefits to smoking. In fact, in an open-ended question many reported that they smoked to cope with HIV disease (30%) and that smoking helps to increase CD4 cell counts (20%).

Variables	HIV Positives	HIV Negatives	P value
<b>Age</b>	43 ± 6	38 ± 8.5	.001
<b>Men</b>	56%	51%	.3
<b>Women</b>	44%	49%	
<b>Black</b>	51%	52%	.2
<b>Hispanic</b>	42%	36%	
<b>White</b>	7%	12%	
<b>Less than \$11,000</b>	6%	6%	.2
<b>\$11,001-\$20,000</b>	91%	92%	
<b>\$20,001-\$49,000</b>	0%	2%	
<b>&gt;\$50,000</b>	3%	0%	
<b>Marital Status</b>			.5
<b>Married/partner</b>	85%	78%	
<b>Single/divorce/widowed</b>	15%	22%	
<b>Albumin</b>	4.2 ± 0.4	4.1 ± 0.6	.9
<b>Hazardous Alcohol Use</b>	40%	31%	.1
<b>Non Hazardous Use</b>	60%	69%	
<b>Liver Enzymes</b>	D		.6
<b>AST</b>	45 ± 22	36 ± 18	
<b>ALT</b>	41 ± 39	35 ± 19	

Values are means ± SD or percentages

**Table 1:** Baseline socio-demographic information by HIV status.

### Depression and smoking

In addition to having staggering smoking prevalence rates, PLWH were twice more likely to be diagnosed with depression (OR=2; 95% CI: 1.3-3.5,  $p=0.001$ ). BDI scores were similar between smokers and non-smokers (13 ± 10 vs. 12 ± 10). Additional analyses indicated that HIV negative smokers had higher depression scores than those who have never smoked (12 ± 9.6 vs. 9.7 ± 10,  $p=0.4$ ). However, former smokers had a significantly lower mean depression scores than current smokers (5.5 ± 5.1 vs. 12 ± 9.6,  $p=0.05$ ). On the contrary, among PLWH BDI scores were similar among the three groups (15.9 ± 10.7 vs. 14.7 ± 9.9 vs. 12.6 ± 10,  $p>0.05$ ). Depression scores were similar between light and heavy smokers in both PLWH and PLWOH.

Gender analyses were performed and although no significant differences in BDI scores were evident (13 ± 10 vs. 12 ± 10,  $p>0.05$ ), male light-smokers had significantly lower depression scores than male heavy smokers (13 ± 10 vs. 22 ± 10,  $p=0.04$ ). However the relationship was quite the opposite in the females, where the light-smokers group exhibited higher depression scores than heavy-smokers (15.4 ± 11 vs. 8 ± 70,  $p=0.09$ ).

We assessed whether mood disturbance prior to cessation or negative affect during quitting attempts are the driving force influencing smoking changes since this relationship is not clear in the literature [26]. Analyses indicated that as many as 28% of the population was depressed. Of concern, a significantly higher proportion of people living with HIV had depression 34% as compared to 22% among HIV negatives ( $p=0.02$ ). As depicted in Table 2, our data did not indicate differences in smoking rates between depressed and non-depressed individuals. Number of cigarettes smoked per day at baseline or at the one year follow-up ( $p>0.05$ ) was similar between depressed and non-depressed individuals. However, depressed individuals (BDI>19) were more likely to have started smoking at an early age. Despite having comparable FTND scores (4.9 ± 2.7 vs. 4.2 ± 2.1,  $p=0.2$ ), depressed individuals were less likely to express interest in quitting in the next months (OR=0.5; 95% CI: 0.2-1.14;  $p=0.05$ ).

### Mood disorders associated with withdrawal

In addition to baseline depression measures, we categorized participants based on reports of negative affect (i.e., stress, and anxiety)

Variables	Depression N=112	Non Depression N=288	P value
Age in years	40.8 ± 7.5	38.7 ± 9.2	.001
Men	32%	68%	.7
Women	29%	71%	
Smoking	31%	27%	.5
Age Start Smoking	15.9 ± 4.8	18.1 ± 6.6	.03
Years Smoking	23.4 ± 10.6	21.4 ± 9.7	.2
Cotinine Levels	211 ± 184	225.5 ± 191.4	.5
Number of Cigarettes Baseline	8.8 ± 1.1	8.6 ± 1.3	.4
Number of Cigarettes 12 months	10.0 ± 8.2	10.4 ± 8.0	.7
FTND Scores	4.9 ± 2.7	4.2 ± 2.1	.2
Stress/ Nervousness Withdrawal Symptoms			.08
Yes	63%	37%	
No	48%	52%	

Values are means ± SD or percentages

**Table 2:** Baseline socio-demographic and smoking information by mood status.

as major obstacles to achieve quitting success (yes/no). Despite similar socioeconomic conditions, PLWH were twice as likely to cite negative affect as a cause of relapse (OR=1.6; 95% CI: 1.5-2.4;  $p=0.004$ ) relative to seronegative counterparts. Differences in negative affect between depressed and non-depressed individuals were not statistically significant. Further, our analyses did not identify negative affect across gender as a cause of relapse. Cotinine levels (log -cotinine  $2.1 \pm 0.5$  vs.  $2 \pm 0.4$ ,  $p=0.4$ ), FTND ( $4.4 \pm 2.5$  vs.  $4 \pm 2.4$ ,  $p=0.2$ ) and Beck depression scores ( $15.2 \pm 11$  vs.  $13 \pm 11$ ,  $p=0.1$ ), were very similar between those with and without negative effects.

Because PLWH differed in alcohol use and cotinine levels, we evaluated potential differences in withdrawal symptomology. Participants with a history of Hazardous Alcohol Use (HAU) were less likely to report negative affect during smoking cessation efforts compared to participants without a history of HAU (OR=0.8; 95% CI: 0.7-0.99;  $p=0.02$ ). Our data indicate that PLWH with cotinine levels in the highest quartile were more likely to report more negative affect relative to those with lower cotinine levels (OR=1.5; 95% CI: 1-2.1;  $p=0.02$ ). Notably, that relationship was not significant among HIV seronegatives. As illustrated in table 3, using multivariate analyses we aimed to identify predictors of a negative effect. Only baseline cotinine predicted negative affect. Nonetheless, HIV status, ART and alcohol use still show a tendency.

### Longitudinal analyses

Since prior studies of mood and smoking have relied largely on retrospective self-reports, longitudinal analyses of 12-month follow up data were conducted. It is important to highlight that we did not provide an intervention as part of this study. A noteworthy finding is that larger reductions in the number of cigarettes smoked per day (CPD) were observed at the 12-month follow-up visit for subjects that reported receiving antidepressants at baseline ( $-2.6$  CPD,  $p=0.06$ ) than those without treatment ( $-0.8$  CPD,  $p=0.2$ ).

### Predictors of smoking at the last visit

We compared the total number of drinks per week and number of drinks per occasion in polychotomous ordinal logistic regressions. Of these factors only number of drinks per day was predictive of smoking amount at the 12-month follow up. Additionally, use of mentholated cigarettes was also predictive of smoking status at the 12-month follow-

up. As depicted in table 3 baseline depression was also a significant predictor of cigarette smoking at the last visit. Noteworthy, once alcohol was in the model treatment for depression was no longer significant.

### Discussion

Despite the well-documented health hazards of tobacco for PLWH [27], the interest in quitting is remarkably lower in PLWH compared to their seronegative counterparts. Furthermore, PLWH were less successful at quitting than PLWOH, indicating that smoking cessation treatments tailored to this populations should be a high priority. Results of this study also indicate that high cotinine levels and presence of negative moods during quitting are influential factors in cessation success. Thus, to increase the effectiveness of smoking cessation interventions, tailored treatments should account for these factors.

Results of this study indicate that clinical depression was twice as frequent among PLWH relative to PLWOH. In accord to studies conducted in the general population, and those few among PLWH, we did find a relationship between depression and smoking [26-28]. However, any positive effect of depression treatment on smoking disappeared once hazardous alcohol use is in the model. Thus there is a clear need of additional studies focusing on this intersection.

On the other hand a novel finding of our study is that nicotine withdrawal-induced symptoms of anxiety/depression were more prevalent among PLWH relative to PLWOH. These withdrawal symptoms were associated with unsuccessful cessation attempts, but were not related with severity of nicotine dependence or a history of mood disorders. This finding has important implications for treatment development given that pharmacological smoking cessation treatments have been demonstrated to influence affective trajectories during early cessation periods [29]. These findings suggest that psychotropic medications that have been associated with mood deterioration (e.g., varenicline, bupropion) [30,31] should not be used in PLWH who are attempting to quit smoking.

Given that depression and level of dependence were not predictors of increased aversive side effects and increased negative affect observed among PLWH during cessation attempts, we propose two hypotheses to explain these relations. First, given the significantly higher levels of

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	B	Std. Error	Beta		
ART (yes/no)	-0.193	0.116	-0.376	-1.670	0.097
HIV status	0.386	0.226	0.385	1.710	0.089
Continue levels	-0.002	0.001	-0.175	-2.221	0.028
Total drinks	0.000	0.000	-0.134	-1.693	0.092

**Table 3:** Multivariate analyses: Predictors of negative affect during quitting attempts.

Model	Coefficients <sup>a</sup>						
	Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95% Confidence Intervals	
	B	Std. Error	Beta			Lower Bound	Upper bound
Menthol	-1.444	.718	-.152	-2.011	.046	-2.860	-.027
Total drinks per week	-.053	.028	-.147	-1.928	.050	-.108	.001
Baseline BDI score	.177	.084	.226	2.101	.037	.011	.343

<sup>a</sup>Dependent Variable: Number of Cigarettes per day at the 12 month visit

**Table 4:** Predictors of smoking at the last visit.

cotinine observed in PLWH, we propose that dependence could in fact be higher among PLWH. That is, it is possible that the FTND as a sole measure is not sensitive enough to detect smaller changes in smoker behavior and dependence. If correct, our hypothesis could potentially explain the significant relationship observed between withdrawal and cotinine levels and concurrent failure to establish a significant relationship between withdrawal, cotinine levels and FTND scores. A second explanation is that disparities might be related to changes in neurobiological mediators such as Brain Derived Neurotropic Factors (BDNF). Our preliminary analysis indicates that smoking was associated with increased disturbances in BDNF and serotonin among people living with HIV. Given their critical role in cognition and mood disorders future research should examine therapeutic approaches to modify BDNF and its effect on smoking cessation success.

Another unique finding is that although HAU were more likely to continue smoking tobacco, they were also less likely to report negative aversive effects as problematic during their quitting attempts (when they did attempt to quit). It is possible that results reflect a compensatory mechanism in which withdrawal symptoms are compensated with alcohol drinking. It is also likely that by potentiating or inhibiting the function of different nicotine receptors (nAChRs), alcohol may affect nicotine's affinity for these receptors and thus altered the nicotine withdrawn symptoms. Future research should examine the relationship between increased alcohol use and smoking cessation attempts and success.

### Limitations

There are some limitations that warrant discussion. First, non-Hispanic Whites were under represented; therefore limiting the generality of our findings. Nevertheless, the demographic characteristics of this sample are similar to those of the region (i.e., South Florida), and representative of the HIV population in the United States. Another limitation is that our study relied on self-reports of negative affect. Future research should examine direct affect measures across the relevant group comparisons (i.e., PLWH vs. PLWOH, menthol vs. non-menthol smokers, etc.)

### Implications

This study shows that smoking cessation interventions may benefit from comprehensive health models that include direct intervention for mood disorders (e.g., depression). Equally important, while most studies blames socioeconomic disadvantage, less education, social environments and the quality of services for the higher rates of smoking [32,33], this study highlights the relevance of host and biological factors.

### Future research

Findings clearly highlight the relevance of addressing multiple comorbidities. For example, future studies needs to address if by correcting negative moods during smoking cessation attempts with PLWH, interventions will be more effective.

Although the current trend is for interventions to be dually focused in order to address co-occurring disorders (i.e., 12- Step programs, Double Trouble), gaps in knowledge and practice of how to handle multiple comorbidities exist. To address these limitations, an important step will be to establish in clinical trials whether treatments need to be escalated or simultaneous. Under the new Recovery- Oriented Systems of Care model, it is also relevant to evaluate the cost effectiveness of arraying single, dual or triple (tobacco, alcohol and psychology/

psychiatry) supports services for PLWH given their increased risks of these co-occurring disorders.

### Conflict of Interest

The author(s) report(s) no real or perceived vested interests that relate to this article (including relationships with pharmaceutical companies, biomedical device manufacturers, grantors, or other entities whose products or services are related to topics covered in this manuscript) that could be construed as a conflict of interest.

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