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Effect of Cigarette Smoking on CD4 count and Viral load among HIV patients attending treatment at Nebraska Medicine

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Abstract

Background

Smoking is known to have a negative impact on both morbidity and mortality in people living with HIV (PLHIV). However, there is inconsistent information about the role of smoking on markers of HIV disease progression (CD4 count and HIV viral load). This study examined the effects of cigarette smoking on markers of HIV disease progression among PLHIV at Nebraska Medicine.

Methods

A retrospective cohort study was conducted utilizing electronic health information of 604 PLHIV who attended treatment at Nebraska Medicine between 2012 and 2020. Multiple linear regression was used to model the effects of smoking on the mean change in CD4 count between the first two visits while adjusting for other covariates. Also, multiple logistic regression was used to model the effects of smoking on viral load suppression status (having <200 copies/ml at both visits or at the second visit versus having >=200 copies/ml at both visits or at the second visit).Other covariates were age at the first visit, sex, and race.

Results

The prevalence of current cigarette smoking was 40.7%. In the analysis of patients regardless of the Antiretroviral Therapy status(ART), older patients had less gain in CD4 count compared to younger patients (-1.16, 95%CI=-2.24,-0.067, p=0.03). However, older patients were more likely to be virally suppressed compared to younger patients (OR=1.02, 95% CI=1.003, 1.044, p=0.03). In the analysis of patients who were on ART, never-smokers had better gain in CD4 count compared to current smokers (OR=162.688, 95%CI=1.47, 243.88, p=0.0001). Also, females had less gain in CD4 count compared to males (-97.39, 95%=-188.29,-6.48, p=0.036).

Conclusion

The findings of lesser CD4 count recovery among current smokers compared to never-smokers indicate the need to implement Public health programs targeting smoking prevention and cessation among PLHIV.

SPECIFIC AIMS

The objective of this study was to examine the association of cigarette smoking with the HIV disease progression.

This study had two specific aims as listed below.

Specific aim 1: The study examined the association between cigarettes smoking and the mean change in CD4 counts between the first and the second hospital visit in people living with HIV.

Specific aim 2: The study examined the association between cigarettes smoking and viral load status (suppressed v/s not suppressed) during the first and second hospital visit in people living with HIV.

The **study hypotheses** were: 1) cigarette smoking is associated with a lower CD4 count.

2) Cigarette smoking is associated with a higher HIV viral load.

This study is of significance because the results help to characterize the distribution of cigarette smoking among HIV patients who are attending treatment at Nebraska Medicine, and also help in explaining the effects of cigarettes smoking on disease progression in people living with HIV.

Background

There is great progress in the prevention and control of Human Immunodeficiency Virus (HIV) infections. HIV infection affects the health of a person by gradually destroying white blood cells with CD4 receptors with subsequent development of Acquired Immunodeficiency Syndrome (AIDS) [4]. Since the onset of the HIV epidemic in the early 1980s, the disease has claimed the life of more than 32 million people [7]. The first breakthrough in the fight against the HIV/ AIDS epidemic came in 1987 when azidothymidine (AZT) was approved in the treatment of AIDS [5]. However, a major significant point was reached in 1996 when a combination of triple therapy was shown to be effective in attaining viral suppression and preventing resistance of HIV [5]. Since then, the introduction of new superior medications and the implementation of evidence-based management and prevention programs has led to a decrease in both the number of new HIV infections and the number of AIDS-related deaths. Currently, people living with HIV have a longer life span compared to previously.

Worldwide, there are approximately 37.9 million people who were living with HIV in 2018, and approximately 770 thousand people died from HIV/AIDS in the same year. Furthermore, the number of new HIV infections was 1.8 million in the same year [7]. The greater burden of the HIV disease is in sub-Saharan Africa, where 70% of the HIV patients are residing [6].

In the USA, the estimated number of people living with HIV was 1.1 million in 2018. The number of new HIV infections was 37,832 in the same year [1]. There is a decrease in the number of new HIV infections in the USA: the number decreased by 7.9% from 41,800 to 38,800 in five years (2011-2015) [19]. However, the distribution of HIV infections is not -uniform in the USA; it varies according to geographical location, gender, transmission category, and race. The South of

the USA leads with a number of new HIV infections, and the Midwest has the least number of new infections [8,19].

In 2018, the number of new infections increased in people aged 25-30 years. However, the number of new infections decreased in all other age groups, except people aged above 55 years where it remained stable [19]. Furthermore, the number of new HIV infections decreased in females while it remained stable in males. The number of new HIV infections remained stable in homosexuals, a group with the largest share of HIV infections since the onset of the epidemic [19,32]. In Nebraska, the average number of new annual infections was 95 in a period of ten years from 2006 to 2015. Moreover, 82% of new HIV infections were concentrated in Sarpy, Douglas, and Lancaster counties [9].

Despite being successful in reducing morbidity and mortality in people living with HIV, Antiretroviral Therapy (ARTs) has been established as a major way to decrease the number of HIV infections [20]. The medications(ARVs) suppress viral replication and hence decreased the risk of transmitting HIV to other people [20]. The majority (92%) of new HIV infections occur in people who are undiagnosed and from people who are not on treatment. However, there is 8% of new infections that occur to those who are on treatment and mostly from those who have not achieved viral suppression [18].

Several factors have been associated with HIV disease progressions such as age at diagnosis, sex of the patient, socioeconomic status, ART adherence, and other comorbidities. However, there are inconsistent pieces of evidence regarding the association of cigarette smoking with markers of HIV disease progression (CD4 count and HIV viral load). Some studies have reported that cigarette smoking is associated with lower CD4 count recovery and less chance of

viral load suppression. In contrast, other studies have found no association between smoking and markers of HIV disease progression(CD4 count and viral load) [21, 24, 28, 29, 30].

This study was conducted to explore the association between cigarette smoking and markers of HIV infection disease progression among a cohort of patients attending treatment at Nebraska Medicine. The result of this study is important to explain the effects of cigarette smoking on HIV infection disease progression and in characterizing the distribution and magnitude of cigarette smoking among HIV positive patients in Nebraska. The results of this study will add knowledge in areas relating to HIV treatment and prevention.

METHODS

Study population and settings

This study utilized the electronic health records of patients who attended treatment at the University of Nebraska Medical Center/Nebraska Medicine (UNMC/NM) between 2012 and 2019. The majority of people (71%) who are attending treatment at UNMC/NM are residing in Douglas and Sarpy Counties[10]. Patient information is routinely collected and stored in a database that was established and is maintained by the Nebraska Public Health Laboratory. The database includes information such as hospital visits, demographic characteristics, clinical characteristics, and other behavioral information. The data are de-identified using a special ID to preserve the patient's confidentiality.

Inclusion and exclusion criteria

This study included patients who were on treatment between January 2012 and February 2020 at Nebraska Medicine, and who had complete information on smoking status, laboratory results(CD4 count, and HIV viral load), and other relevant demographic characteristics (age, race, and sex). Patients who lacked smoking status information at baseline were excluded from the study.

Exposures

The main exposure of interest was cigarette smoking status. Smoking status was categorized as current smokers, former smokers, and never-smokers. Other exposures were age at the first visit, sex (male v/s female), and Race (Whites, African American, and others). Also, information on the use of Antiretroviral Therapy was collected.

Outcomes

The primary outcome was the change in CD4 count between the first and the second visit. Approximately 67% of the patients had a second visit between 3 to 6 months. The secondary outcome was Viral load status (suppressed v/s not suppressed) during the follow-up period. Patients who maintained a viral load of <200 copies at both visits, together with patients who improved during the follow-up period(changing from a viral load of >=200 copies to a viral load of <200 copies) were categorized as a suppressed. In contrast, patients who maintained a viral load of >=200 at both visits, together with patients who deteriorates(changing from a viral load of <200 copies to a viral load of >=200) were assigned as not suppressed. Approximately 93% of the patient had a second visit between 3 and 6 months.

Statistical analysis

Frequencies and percentages were used to describe the distribution of the categorical variables (sex, race, categorized age-groups, categorized CD4 counts, and categorized HIV viral load). Chi-square tests were used to test for differences in distribution between different categorical variables indexed by smoking status. Non-parametric Kruskal-Wallis tests were used to test for the differences in median ages among the different categories of smoking. The same tests were used to test for differences in median CD4 count and mean Viral load among different categories of smoking. Multiple linear regression was used to model the effects of cigarette smoking on the mean change in CD4 counts between the first visit and the second visit. Age, Sex, Race, and CD4 count at the first visit were used as other predictors. The non-normal distribution of the viral load necessitates categorizing viral load into a binary variable. And then, multiple logistic regression was used to model the effects of cigarette smoking on the viral load status (suppressed versus not suppressed) during the follow-period. Age at the first visit, sex, and race were used as other predictors. Because viral load of zero is illogical, then we assigned a value of half the lowest viral load(10 copies/ml) to the not detectable viral load results. The analysis was conducted using the statistical software SAS v. 9.4 (SAS Inst, Cary, NC).

RESULTS SECTION

Characteristics of the study participants

A total of 604 PLHIV with complete information on smoking, laboratory, and demographic characteristics were included in this study at the baseline. There were 246 (40.7%) current smokers**,** 248 (41.1%) never -smokers, and 110 (18.2%) former smokers. Four hundred and ninety-six (82.12%) of the patients were males, while the remaining 108 (17.88%) were females. Two hundred and seventy-nine (46.19%) of the patients aged between 30 and 50 years, while 171 (28.31%) patients aged below 30 years, and the remaining 154 (25.50%) patients aged above 50 years. Three hundred and eighty-four (65.58%) patients were of the white race, while 163 (26.99%) patients were of African American race, and the remaining 57 (9.44%) patients were of other races.

The median age of the patients at first visit was 39.8 years (Range: 2.4-78). The median differences in age at first visit among smoking categories were statistically significant (p=0.0031). Specifically, former smokers were older (Median=45 years, Range: 13.8-78.4) compared to smokers (Median=39, Range:21-70.8), and never-smokers (Median=37.6, Range: 2.4-76.7). Furthermore, there was a statistically significant association between the age category and the Smoking category (p=0.03). Specifically, there were more current smokers in the age-group 30-<50 years compared to other age categories.

The median CD4 count at the first visit was 446 cells/µl (Range:2-1955), while the median CD4 count during the second visit was 482 cells/µl (Range: 4-2083). At the first visit, there were 264 patients (44.00%) with a CD4 count of >500 cells/mm3, 215 patients (35.83%) with a CD4

count of 200-<500 cells/mm3, and 121 (20.17%) patients with a CD4 count of <200 cells/mm3. Four patients had missing information on CD4 count at first visit. At the second visit, there were 216 patients (47.26%) with a CD4 count of >500 cells/mm3, 166 patients (36.32%) with a CD4 count of 200-<500 cells/mm3, and 75 patients (16.41%) with a CD4 count of <200 cells/mm3. One hundred and forty-seven patients had missing information on CD4 count at the second visit.

The median HIV viral load at the first visit was 1189 copies (Range:10-10,000,000), while the median HIV viral load during the second visit was 19.95 copies (Range: 10-10,000,000). Three hundred and forty-two (55.52%) patients were not virally suppressed during the first visit. In contrast, 428 (85.43%) achieved viral suppression during the second visit. One hundred and three patients had missing information on viral load at the second visit.

Effects of cigarettes smoking on the mean change in CD4 counts and viral load status

Two analyses were conducted in this study. The first analysis included patients regardless of their ART status, and the second analysis(sub-analysis) included patients who were on ART. The results of the first analysis are presented in table 2 and table 3, and the results of the second analysis are presented in table 4 and table 5.

In the unadjusted analysis of 457 patients with complete CD4 count results at both visits, the exposures (sex, race, and smoking status) were not associated with mean change in CD4 count (p-value>0.05). However, age at first visit was marginally associated with the mean change in CD4 count (p=0.054). In the adjusted analysis of 457 patients, the age of the patient at the first visit was significantly associated with the mean change in CD4 counts (-1.16, 95%CI=-2.24,-0.067,

p=0.03). Specifically, the mean difference in CD4 count decreased by 1.16 in a group of patients who were one year older compared to a group of younger patients. The mean difference in CD4 count was not associated with smoking status, gender, and race in the adjusted analysis.

The adjusted analysis of 501 patients showed that age at first visit was significantly associated with viral load suppression status (OR=1.022, 95%CI 1.002, 1.042, p=0.035). Similarly, in the adjusted analysis, the age of the patient at the first visit was significantly associated with viral load suppression status (OR=1.02, 95% CI=1.003, 1.044, p=0.03). Specifically, the odds of having a suppressed viral load status was 2% higher for a group of patients who were one year older compared to a younger group. The analyses of the association of other variables(smoking, gender, and race) and viral load status were not statistically significant (p>0.05).

Effects of cigarettes smoking on the mean change in CD4 counts and viral load status for patients who were on ART

In the unadjusted analysis of the 57 patients who were on ART, the mean change in CD4 count increased by 151.57 cells/mm3 in never smokers compared to current smokers(151.57, 95%CI=69.05, 234.079). Similarly, in the adjusted analysis, the mean change in CD4 count increased by 162.68 cells/mm3 in never smokers compared to current smokers(OR=162.688, 95%CI=1.47, 243.88, p=0.0001).

The unadjusted analysis of the relationship between gender and mean change in CD4 count was not significant(p=0.2). However, the adjusted analysis of the relationship between gender and

mean change in CD4 count was significant (p=0.036).Specifically, the mean change in CD4 count decreased by 97.39 in females compared to males. Other variables (age at the first visit, and race) were not statistically significantly associated with mean CD4 count change. The relationship between all predictors(smoking, age at the first visit, race, and sex) and viral load status was not statistically significant (p>0.05).

DISCUSSION

The prevalence of current cigarette smoking among PLHIV in this study was 40.7%. Several other studies have found a similarly high prevalence of smoking among PLHIV. These studies have documented the prevalence of current cigarette smoking to be above 40% among PLHIV compared to 19% of the general US population [22, 23]. The median age of former smokers was higher compared to the median ages of current smokers and never-smokers. Furthermore, there are more current smokers aged 30-50 years compared to current smokers aged below 30 years and aged above 50 years. For patients of the White race and African American race, there were more current smokers compared to other smoking categories. In contrast, for patients of other races, there were more never-smokers compared to other smoking categories. These findings of the distribution of age category and race according to smoking status highlights the importance of scaling up efforts of cigarettes smoking prevention/cessation programs in HIV patients aged 30-50 years, and HIV patients of White race and African American race.

Current smokers seemed to have a higher median CD4 count at first visit compared to both never-smokers and former smokers. However, this relationship was not statistically significant(p-value=0.101). Other studies have found that HIV positive smokers tend to have higher CD4 count

at baseline compared to HIV positive never-smokers [24]. Furthermore, other studies have found that even in HIV negative individuals, smokers have higher CD4 count compared to non-smokers [25]. There is evidence that smoking promotes immune activation in both HIV positive and HIV negative patients [25]. However, the advantage of having higher CD4 count in smokers is offset by the diminishing normal functioning of those CD4 cells[25]. The analysis of patients who were on ARTs found that compared to smokers, never smokers have better improvement in CD4 count. Other studies have found similar results that never-smokers have better CD4 count recovery compared to smokers when on treatment [21].

In this study, for patients who were on ART, females gained less CD4 cells during the follow-up period compared to males. There is contrasting information about the relationship between sex and CD4 count. One study conducted in South Africa showed that for patients who are on treatment, females have better improvement in CD4 count compared to males [32]. Another study conducted in Uganda showed that there was no difference in CD4 count recovery between males and females [33]. However, one study conducted in Tanzania showed that males have a better CD4 recovery compared to females [34].

Smoking was not associated with viral load status during the follow-up period. Similarly, other studies have found that there is no relationship between smoking and viral load suppression [31]. However, several other studies have found that smokers are less likely to achieve viral suppression compared non-smokers [24,28,29]. Two studies investigated the effect of both smoking frequency and smoking quantity on HIV viral load suppression, one study found that daily smoking is associated with less likely chance of viral suppression, while the second study found that quantity of cigarettes smoking rather than frequency is associated with detectable viral load [29, 30].

This study found that age at first visit, which was a proxy for age at baseline, was associated with viral load suppression status. Older HIV patients were more likely to have a viral suppression status compared to younger patients. Two studies have reported similar relationship between age and HIV viral load suppression: old age at diagnosis is associated with better viral load status [26,27].

There are several limitations to this study which might distort the true relationship between the exposures(smoking, age at first visit, sex, and race) and outcome(mean change in CD4 count, and viral load status). First, the analysis of the larger sample size was done regardless of whether the patient was on medication or not. ARTs have a greater influence on both outcomes, CD4 count, and viral load. The second limitation is that, because of the secondary nature of the data, this study could not get the quantitative measure of the exposure (smoking). The quantitative measure of smoking would be much more informative in assessing the dose-effect response. Also, lack of information on adherence to ART, socio-economic status, and alcohol might distort the relationship of the effects of cigarette smoking on markers of HIV disease progression.

Conclusively, the higher prevalence of cigarette smoking in PLHIV together with a poor CD4 count recovery in smokers compared to never smokers indicate the need to put in place Public Health measures in targeting smoking prevention and cessation in PLHIV.

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Appendices

Table 1: Demographic and clinical characteristics of the sample patients according to smoking categories

Characteristic	All Patients (N=604)	Smokers(N=246)	Former smokers(N=110)	Never smokers(N=248)	P-value
Median Age at First Visit	39.8 (2.4-78)	39 (21-70.8)	45 (13.8-78.4)	37.6 (2.4-76.7)	0.0031*
Age Category					
<30	171 (28.31%)	68 (39.77%)	24(14.04%)	79 (46.20%)	0.03*
30-<50	279 (46.19%)	126 (54.16%)	48 (17.20%)	105 (37.63)	
>=50	154 (25.50%)	52 (33.77%)	38(24.68%)	64 (41.56%)	
Gender					
Male	108	41 (37.96%)	18 (16.67%)	49 (45.37%)	0.6021
Female	496	205 (41.33%)	92(18.55%)	199(40.12%)	
Race					
Black	163 (26.99%)	72 (44.17%)	26 (15.95%)	65 (39.88%)	0.0022*
White	384 (63.58%)	159 (41.41%)	79 (20.57%)	146 (38.02%)	
Other	57 (9.44%)	15 (26.32%)	5 (8.77%)	37 (64.91%)	
CD4 count (cells/µl)					
First visit					
Median CD4 counts	446 (2-1955)	489 (2-1955)	419 (8-1655)	431 (8-1676)	0.1012
CD4 counts category					
Stage 3 (<200)	121 (20.17%)	42 (34.71%)	28 (23.14%)	51 (42.15%)	0.099
Stage 2 (200-<500)	215 (35.83%)	86 (39.63%)	34 (15.67%)	97 (44.70%)	
Stage 1 (>500)	264 (44%)	117 (44.15%)	48 (18.11%)	100 (37.74%)	
Second visit					
Median CD4 count	482 (4-2083)	557.52	537.54	515.47	0.5822
CD4 counts category					
Stage 3 (<200)	75 (16.41%)	29 (38.67%)	14 (18.67%)	32 (42.67%)	0.1665
Stage 2 (200-<500)	166 (36.32%)	63 (37.95%)	35 (21.08%)	68 (40.96%)	
Stage 1 (>500)	216 (47.26%)	97 (44.91%)	33 (15.28%)	86 (39.81%)	
HIV Viral Load(VL)					
First visit					
Median VL	1189 (10-10,000,000)	2041 (10-10,000,000)	245 (10-2511886)	3165 (10-10,000,000)	0.5714
HIV viral loads category					
Suppressed <200	266 (44.04%)	105 (39.47%)	55 (20.68%)	106 (39.85%)	0.7572
Detectable >=200	228(37.75%)	101 (44.30%)	35 (15.35%)	92 (40.35%)	
high Viral load > 100,000	110(18.21%)	37 (33.64%)	23 (20.91%)	50 (45.45%)	
Second visit					
Median VL	19.95 (0-10,000,000)	19.95 (0-389045)	19.95 (0-794328)	19.95 (0-10,000,000)	0.7464
HIV viral loads category					
Suppressed <200	428(85.43%)	173 (40.42%)	72 (16.82%)	183 (42.76%)	0.5892
Detectable >=200	73 (14.57%)	31 (42.47%)	15 (20.55%)	27 (36.9%)	

Table 2

Mean Difference in CD4 count between the first two visits (N=457)

	Unadjusted analysis		**Adjusted analysis**	
	Mean Difference 95%CI	**P**	**Mean Difference 95%CI**	**P**
Age at First visit	-1.08(-2.17,0.02)	0.054**	-1.16(-2.24, -0.067)	0.03*
Gender				
Female	-0.44(-37.76, 36.88)	0.98	4.3708(-32.87,41.61)	0.82
Male	Ref	-	Ref	-
Race				
Black	18.44(-14.07,50.95)	0.27	12.66(-19.54,44.86)	0.44
other	16.21(-37.24, 69.65)	0.26	8.74(-44.32, 61.81)	0.75
white	Ref	-	Ref	-
Smoking				
Never	28.96(-2.78,60.70)	0.07	22.78(-8.67,54.23)	0.16
Former	18.15(22.55, 58.85)	0.38	17.71(-22.18,57.59)	0.38
Current	Ref	-	Ref	-

*Results are statistically significant at $p<0.05$
**Marginally significant

Table 3

Factors associated with viral load suppression during the follow-up period (N=501)

	Unadjusted analysis		Adjusted analysis	
	OR 95%CI	**P**	**OR 95%CI**	**P**
Age at First visit	1.022 (1.002, 1.042)	0.035*	1.02(1.003, 1.044)	0.03*
Gender				
Female	0.88(0.47, 1.62)	0.67	0.801(0.43, 1.511)	0.5
Male	Ref		Ref	-
Race				
Black	0.83 (0.47,1.47)	0.53	0.91(0.510, 1.61)	0.74
other	0.71(0.32,1.57)	0.4	0.69(0.31,1.57)	0.38
white	Ref		Ref	-
Smoking				
Never	1.21(0.70, 2.12)	0.32	1.32(0.74, 2.34)	0.34
Former	0.86 (0.44,1.69)	0.43	0.80(0.41,1.58)	0.52
Current	Ref		Ref	-

*Results are statistically significant at $p<0.05$

Table 4

Mean Differences in CD4 count between the first two visits (N=57)

	Unadjusted mean difference		**Adjusted mean difference**	
	Mean Difference (95%CI)	**P**	**Mean Difference (95%CI)**	**P**
Age at First visit	0.93(-2.60,4.46)	0.6	0.27(-2.82,3.36)	0.86
Gender				
Female	-61.45(-156.25, 33.35)	0.2	-97.39(-188.29,-6.48)	0.036
Male	Ref	-	Ref	-
Race				
other	21.75(-65.07,108.58)	0.62	18.66(-66.35,103.67)	0.67
white	Ref	-	Ref	-
Smoking				
Never	151.57(69.05,234.0792)	0.0003*	162.68(81.47, 243.88)	0.0001*
Former	54.95(-44.80, 154.70)	0.28	29.02(-75.73, 133.76)	0.59
Current	Ref	-	Ref	-

*Results are statistically significant at $p<0.05$

Table 5

Factors associated with viral load suppression during the follow-up period (N=57)

	Unadjusted OR		Adjusted OR	
	OR (95%CI)	**P**	**OR (95%CI)**	**P**
Age at First visit	1.05 (0.996,1.095)	0.07	1.035 (0.99,1.09)	0.17
Gender				
Female	0.70 (0.19,2.51)	0.58	0.66(0.15, 2.99)	0.59
Male	Ref	-	Ref	-
Race				
other	0.612 (0.19,1.99)	0.41	1.08 (0.26, 4.53)	0.92
white	Ref	-	Ref	-
Smoking				
Never	0.88(0.23,3.44)	0.86	0.98(0.223, 4.28)	0.98
Former	0.25(0.05,1.16)	0.08	0.27(0.05,1.52)	0.14
Current	Ref	-	Ref	-