MARIJUANA SMOKING IMPACTS PULMONARY DISEASE IN HIV-INFECTED MEN

Abstract ID: 2106
Poster #: 747

David R. Lorenz[1] and Dana H. Gabuzda[1,2]
[1]Cancer Immunology & Virology, Dana-Farber Cancer Institute; Harvard Medical School, Boston MA

ABSTRACT

Background: Marijuana smoking is prevalent among HIV+ individuals, but its effects on pulmonary disease in the general population and people living with HIV remain unclear. This longitudinal prospective study examined the relationship between marijuana smoking, tobacco smoking, and pulmonary disease in HIV+ and HIV- men in the Multicenter AIDS Cohort Study.

Methods: 2704 subjects (n=1352 HIV+ and n=1352 HIV-, matched by baseline age and race) with follow-up between 1996-2014 and ≥1 year self-reported marijuana and tobacco smoking exposure data from biannual study visits were included (age ≥30, ART use at baseline for HIV+ subjects). Infectious (influenza or viral pneumonia, bacterial pneumonia, other pneumonia, *Pneumocystis* pneumonia, and tuberculosis) and non-infectious (chronic bronchitis, COPD, emphysema, lung cancer, pulmonary hypertension, and other non-infectious) events were assessed from self-report and ICD-9 codes. Cox regression was used to estimate the association between marijuana smoking and first incident infectious and non-infectious pulmonary diagnosis in models adjusted for tobacco smoking, age, race, education, years of follow-up, calendar period, CD4 count, and ART use.

Results: Median baseline age of participants was 44 years (IQR: 39-50); 70% were white, 83% had education >12 years, median baseline CD4 of HIV+ subjects was 422 cells/µl. 27% of HIV+ subjects reported ≥1 year of daily or weekly marijuana smoking, compared with 18% of HIV- subjects (p<0.001). During 29,370 person-years of follow-up, 436 HIV+ subjects had one or more infectious pulmonary diagnosis (32%, median follow-up 9.5 years), compared with 268 HIV- subjects (20%, median follow-up 11.5 years) (p<0.001), while non-infectious pulmonary diagnoses occurred at slightly higher frequency among HIV+ vs. HIV- subjects (21%, n=278 vs. 17%, n=232; p=0.03). Daily or weekly marijuana smoking in the prior 6 months was associated with higher adjusted hazard ratio (HR) for both infectious (HR 1.32, 95% CI 1.03-1.71) and non-infectious (HR 1.45, 95% CI 1.04-2.01) pulmonary diagnoses in HIV+ subjects, independent of tobacco smoking and other risk factors. Two-year prior average marijuana smoking was associated with increased risk for both infectious and non- infectious pulmonary diagnoses in HIV+ subjects when modeled as a continuous variable (HR 1.07, 95% CI 1.04-1.10, and HR 1.08, 95% CI 1.02-1.13, respectively, per 10 days use/month increase). There was no significant association between marijuana smoking and infectious or non-infectious events in HIV- participants.

Conclusion: Frequent marijuana smoking is a risk factor for infectious and non-infectious pulmonary disease in HIV-infected men, independent of tobacco smoking and other risk factors.

METHODS

Study design and population:
This is a nested longitudinal study in the Multicenter AIDS Cohort Study (MACS), an ongoing prospective study of men who have sex with men (MSM). Established in 1984, the MACS has enrolled 7342 HIV-infected and HIV-uninfected MSM at four urban study sites (Los Angeles, Chicago, Baltimore, and Pittsburgh). Behavioral, clinical, and laboratory data were collected at semiannual visits; Institutional Review Boards at each study site approved the research, and all participants provided written informed consent. Eligible participants for this study were 2704 subjects from the MACS public data set (P25 release), age ≥30 with follow-up between 1996-2014, ≥1 year of self-reported marijuana smoking and tobacco smoking exposure data, and combination ART (cART) use reported at baseline for HIV+ subjects. Subjects reporting daily or weekly heroin or cocaine use for ≥1 year during follow-up were excluded. 1352 HIV+ subjects were propensity score-matched to 1352 HIV- subjects by baseline age and race using the R MatchIt package.

Exposure variables:
Marijuana and tobacco smoking were the primary exposure variables of interest. Subjects reporting daily or weekly use for ≥1 year during follow-up were classified as marijuana smokers. Recent marijuana smoking was evaluated as a time-varying continuous variable (mean days of use/month in the prior 2 years) by calculating a moving average using the following weights: daily use, 20 days/month, weekly use, 4.36 days/ month, monthly use, 1 day/month, less than monthly, 0.33 days/month, never, 0 days/ month. Subjects reporting any tobacco smoking during follow-up were classified as smokers; never vs. former smoking status was summarized using MACS study entry and pre-1996 visit data. Recent tobacco smoking was evaluated as a time-varying continuous variable by calculating mean packs/day in the prior 2 years.

Outcome variables:
Incident infectious and non-infectious pulmonary events were translated from ICD-9 diagnosis, ICD-10 mortality, and ICD-O-3 oncology codes and summarized into pulmonary diagnosis categories. Infectious diagnoses included influenza or viral pneumonia, bacterial pneumonia, other pneumonia, *Pneumocystis* pneumonia and tuberculosis. Non-infectious diagnoses included chronic bronchitis, COPD or emphysema, lung cancer, other non-infectious diagnoses, and other lung disease, not otherwise specified.

Statistical analysis:
Univariate/bivariate tests for cohort characteristics and frequencies of pulmonary diagnoses were conducted using Chi-Squared, Fisher's exact, or Wilcoxon rank-sum tests. Kaplan-Meier curves were used to evaluate differences in pulmonary diagnoses by marijuana and tobacco smoking; differences between groups were assessed by log-rank test. Cox proportional hazards models were used to test the association between marijuana smoking and first incident infectious and non-infectious event in each HIV+ and HIV- cohort. Models were adjusted by time-varying tobacco smoking, and by time-invariant race, education, and baseline calendar year; time-varying current CD4 cell count and cART use were included in models for HIV+ subjects. All Cox models used age as the time variable. Time-varying marijuana and tobacco smoking variables were square-root transformed to stabilize variances. All data and statistical analyses were performed in R (version 3.4).

RESULTS

Table 1. Baseline and updated characteristics of the study cohort.

	HIV+			HIV-		
	Non-Users (n=989)	Marijuana Users[1] (n=363)	p	Non-Users (n=1108)	Marijuana Users[1] (n=244)	p
Age (median [IQR])	43 [38.5, 49]	42 [37.5, 47.5]	0.007	45 [40, 52]	43 [38, 47]	<0.001
Years of follow-up (median [IQR])	9 [4, 13]	10.5 [5.5, 15.5]	0.001	11.5 [7, 13]	11.75 [8, 13]	0.032
Race			0.053			0.333
White	638 (64.5)	249 (68.6)		836 (75.5)	173 (70.9)	
Black	209 (21.1)	80 (22.0)		182 (16.4)	48 (19.7)	
Other	142 (14.4)	34 (9.4)		90 (8.1)	23 (9.4)	
Education ≤ 12 years	222 (22.4)	62 (17.1)	0.038	145 (13.1)	41 (16.8)	0.158
Marijuana smoking - mean days use/yr in follow-up (median [IQR])	0 [0, 1.3]	66.7 [26.1, 231.5]	<0.001	0 [0, 0.9]	67 [24.6, 195.9]	<0.001
Cigarette smoking at baseline			<0.001			<0.001
Never	380 (38.4)	85 (23.4)		380 (43.6)	44 (22.1)	
Former	287 (29.0)	114 (31.4)		251 (28.8)	65 (32.7)	
<1/2 packs/day	118 (11.9)	61 (16.8)		99 (11.4)	29 (14.6)	
1/2+ packs/day	204 (20.6)	103 (28.4)		142 (16.3)	61 (30.7)	
Cigarette smoking, mean packs/day in follow-up			<0.001			<0.001
None	599 (60.6)	150 (41.3)		761 (68.7)	111 (45.5)	
>0 - <1/2	211 (21.3)	120 (33.1)		221 (19.9)	73 (29.9)	
≥1/2	179 (18.1)	93 (25.6)		126 (11.4)	60 (24.6)	
Heavy or binge alcohol use[2]	201 (20.3)	103 (28.4)	0.002	255 (23.0)	91 (37.3)	<0.001
CD4 count (cells/µl) (median [IQR])	432 [260, 603]	396 [238, 592]	0.110	914.5 [724, 1134]	970 [777, 1171]	0.012
CD4 count (cells/µl)			0.159			
350+	571 (62.4)	198 (57.1)		--	--	
200-349	176 (19.2)	82 (23.6)		--	--	
<200	168 (18.4)	67 (19.3)		--	--	
CD4 nadir in follow-up (cells/µl) (median [IQR])	303 [172, 451]	279 [164, 435]	0.155	--	--	
HIV viral load ≥ 400 copies/ml	350 (38.7)	146 (42.3)	0.272	--	--	
ART use at 75% of follow-up visits	886 (89.6)	332 (91.5)	0.358	--	--	
ART use at 95% of follow-up visits	645 (65.2)	229 (63.1)	0.508	--	--	
One or more incident infectious pulmonary diagnoses[3]	289 (29.2)	147 (40.5)	<0.001	213 (19.2)	55 (22.5)	0.277
One or more incident non-infectious pulmonary diagnoses[4]	188 (19)	90 (24.8)	0.024	196 (17.7)	36 (14.8)	0.314

Data are n (%) at baseline unless otherwise indicated; p value, Chi-Squared or Wilcoxon Rank Sum Test.
1 - 1 or more years daily or weekly marijuana smoking in follow-up.
2 - Heaviest use at 1 year or more in follow-up.
3 - Influenza or viral pneumonia, bacterial pneumonia, other pneumonia, *Pneumocystis* pneumonia, tuberculosis.
4 - Chronic bronchitis, COPD or emphysema, lung cancer, pulmonary hypertension, other non-infectious diagnoses, other lung disease (not otherwise specified).

Table 2. Incident pulmonary diagnoses by marijuana and tobacco smoking.

Marijuana and tobacco smoking exposure[1]	HIV+					HIV-				
	Mj- Sm-	Mj- Sm+	Mj+ Sm-	Mj+ Sm+	p	Mj- Sm-	Mj- Sm+	Mj+ Sm-	Mj+ Sm+	p
n subjects	599	390	150	213		761	347	111	133	
No Diagnosis	383 (63.9)	221 (56.7)	74 (49.3)	105 (49.3)	<0.001	552 (72.5)	232 (66.9)	78 (70.3)	86 (64.7)	0.12
Infectious diagnoses										
Influenza or viral pneumonia	76 (12.7)	48 (12.3)	28 (18.7)	37 (17.4)	0.090	91 (12.0)	33 (9.5)	12 (10.8)	23 (17.3)	0.135
Bacterial pneumonia	47 (7.8)	36 (9.2)	17 (11.3)	22 (10.3)	0.450	16 (2.1)	13 (3.7)	3 (2.7)	1 (0.8)	0.225
Other pneumonia	96 (16.0)	81 (20.8)	33 (22.0)	51 (23.9)	0.037	66 (8.7)	44 (12.7)	7 (6.3)	13 (9.8)	0.128
Pneumocystis pneumonia	16 (2.7)	12 (3.1)	3 (2.0)	9 (4.2)	0.267	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	--
Tuberculosis	5 (0.8)	8 (2.1)	5 (3.3)	4 (1.9)	0.095	0 (0.0)	3 (0.9)	2 (1.8)	1 (0.8)	0.007
Any infectious diagnosis	165 (27.5)	124 (31.8)	62 (41.3)	85 (39.9)	0.001	139 (18.3)	74 (21.3)	22 (19.8)	33 (24.8)	0.284
Non-infectious diagnoses										
Chronic bronchitis	84 (14.0)	73 (18.7)	34 (22.7)	47 (22.1)	0.010	101 (13.3)	64 (18.4)	11 (9.9)	16 (12.0)	0.059
COPD or emphysema	5 (0.8)	16 (4.1)	2 (1.3)	5 (2.3)	0.005	8 (1.1)	19 (5.5)	0 (0.0)	8 (6.0)	<0.001
Lung cancer	1 (0.2)	8 (2.1)	0 (0.0)	1 (0.5)	0.008	1 (0.1)	4 (1.2)	2 (1.8)	0 (0.0)	0.018
Pulmonary hypertension	2 (0.3)	2 (0.5)	1 (0.7)	1 (0.5)	0.826	1 (0.1)	1 (0.3)	0 (0.0)	0 (0.0)	0.683
Other non-infectious diagnoses[2]	4 (0.7)	0 (0.0)	0 (0.0)	1 (0.5)	0.353	4 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0.692
Other lung disease, not otherwise specified	10 (1.7)	11 (2.8)	5 (3.3)	2 (0.9)	0.244	14 (1.8)	6 (1.7)	1 (0.9)	2 (1.5)	0.984
Any non-infectious diagnosis	96 (16.0)	92 (23.6)	40 (26.7)	50 (23.5)	0.002	118 (15.5)	78 (22.5)	14 (12.6)	22 (16.5)	0.022

Data are n (%) of subjects with one or more indicated diagnosis. p value, Fisher's exact test.
1- Exposure during follow-up; Mj+, ≥1 years daily or weekly marijuana smoking; Mj-, <1 year daily or weekly marijuana smoking; Sm-, 0 smoking; Sm+, >0 mean packs/day.
2 - Alveolar pneumonopathy, pulmonary fibrosis, or bronchiectasis.

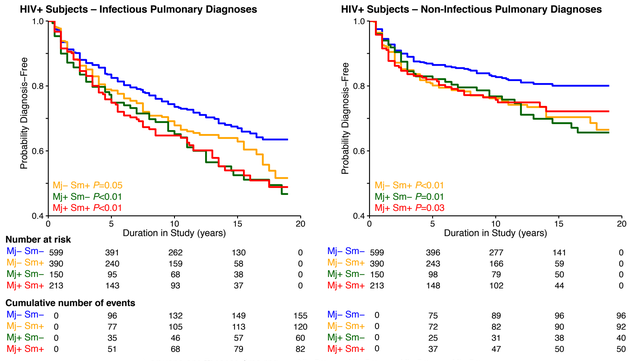


Figure 1. Kaplan-Meier curves of infectious (left panel) and non-infectious (right panel) pulmonary diagnoses in HIV+ subjects. Subjects were stratified by marijuana and tobacco smoking during follow-up as follows: Mj+, ≥1 years daily or weekly marijuana smoking; Mj-, <1 year daily or weekly marijuana smoking; Sm-, 0 tobacco smoking; Sm+, >0 mean tobacco cigarette packs/day. P values denote pair-wise log-rank test vs. Mj- Sm- control group.

Table 3. Marijuana smoking is associated with increased risk of infectious pulmonary diagnoses in HIV-infected individuals.

	HIV+				HIV-			
	Univariate	Model 1	Model 1 - Sensitivity Analysis	Model 2	Univariate	Model 1	Model 2	
	HR (95% CI); p	HR (95% CI); p	HR (95% CI); p	HR (95% CI); p	HR (95% CI); p	HR (95% CI); p	HR (95% CI); p	
Marijuana smoking - current								
Daily or weekly	1.37 (1.07, 1.76); p=0.014	1.32 (1.03, 1.71); p=0.031	1.43 (1.08, 1.89); p=0.012		0.91 (0.62, 1.34); p=0.633	0.82 (0.55, 1.21); p=0.308		
Monthly or less	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)		1.00 (Ref.)	1.00 (Ref.)		
Marijuana smoking - recent (per 10 days use/month increase)	1.08 (0.86, 1.37); p=0.017			1.07 (1.04, 1.10); p=0.037	1.01 (0.7, 1.47); p=0.563		0.94 (0.88, 1.02); p=0.224	
Cigarette smoking - current								
≥ 0 packs/day	1.24 (1, 1.54); p=0.052	1.16 (0.92, 1.45); p=0.203	1.24 (0.97, 1.6); p=0.089		1.55 (1.19, 2.02); p=0.001	1.74 (1.33, 2.28); p<0.0001		
0 packs/day	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)		1.00 (Ref.)	1.00 (Ref.)		
Cigarette smoking - recent (per pack/day increase)	1.05 (0.83, 1.34); p=0.060			1.02 (0.99, 1.05); p=0.298	1.28 (0.96, 1.71); p<0.001		1.44 (1.38, 1.51); p<0.0001	
Baseline calendar year								
2001-2014	0.67 (0.53, 0.83); p<0.001	0.69 (0.54, 0.89); p=0.004	0.65 (0.49, 0.85); p=0.002	0.7 (0.55, 0.90); p=0.006	0.92 (0.71, 1.19); p=0.510	0.97 (0.72, 1.3); p=0.831	0.96 (0.72, 1.3); p=0.814	
1996-2000	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	
CD4 count (cells/uL)								
<200	2.97 (2.28, 3.88); p<0.0001	2.64 (2.01, 3.47); p<0.0001	-	2.66 (2.02, 3.50); p<0.0001	-	-	-	
200-349	1.25 (0.95, 1.66); p=0.116	1.18 (0.89, 1.56); p=0.256	-	1.18 (0.89, 1.56); p=0.252	-	-	-	
350+	1.00 (Ref.)	1.00 (Ref.)	-	1.00 (Ref.)	-	-	-	

Cox Proportional Hazard models of first incident infectious pulmonary diagnosis (influenza or viral pneumonia, bacterial pneumonia, other pneumonia, tuberculosis).
Model 1 compared current time-updated marijuana and cigarette smoking.
Model 1 - Sensitivity Analysis compared current time-updated marijuana and cigarette smoking for a subset of 17,536 person-visits with CD4 count ≥ 200 cells/µl (n=295 events).
Model 2 evaluated recent marijuana and cigarette smoking as continuous variables (mean days of use/month and packs/day, respecively, in the prior 2 years).
All models were adjusted by race, education, and current cART use; age was used as the time variable.

Table 4. Marijuana smoking is associated with increased risk of non-infectious pulmonary diagnoses in HIV-infected individuals.

	HIV+				HIV-			
	Univariate	Model 1	Model 1 - Sensitivity Analysis	Model 2	Univariate	Model 1	Model 2	
	HR (95% CI); p	HR (95% CI); p	HR (95% CI); p	HR (95% CI); p	HR (95% CI); p	HR (95% CI); p	HR (95% CI); p	
Marijuana smoking - current								
Daily or weekly	1.34 (0.99, 1.82); p=0.061	1.45 (1.04, 2.01); p=0.028	1.44 (0.96, 2.15); p=0.079		0.94 (0.63, 1.42); p=0.778	0.78 (0.51, 1.18); p=0.241		
Monthly or less	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)		1.00 (Ref.)	1.00 (Ref.)		
Marijuana smoking - recent (per 10 days use/month increase)	1.06 (0.80, 1.41); p=0.100			1.08 (1.02, 1.13); p=0.093	1.00 (0.67, 1.49); p=0.868		0.90 (0.83, 0.99); p=0.133	
Cigarette smoking - current								
≥ 0 packs/day	1.44 (1.11, 1.86); p=0.006	1.45 (1.11, 1.89); p=0.007	1.42 (1.02, 1.98); p=0.035		1.9 (1.43, 2.52); p<0.0001	2.14 (1.6, 2.86); p<0.0001		
0 packs/day	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)		1.00 (Ref.)	1.00 (Ref.)		
Cigarette smoking - recent (per pack/day increase)	1.50 (1.15, 1.97); p<0.0001			1.40 (1.35, 1.45); p<0.0001	2.43 (1.83, 3.25); p<0.0001		2.03 (1.94, 2.11); p<0.0001	
Baseline calendar year								
2001-2014	0.65 (0.49, 0.85); p=0.002	0.82 (0.58, 1.16); p=0.252	0.76 (0.51, 1.13); p=0.170	0.81 (0.57, 1.14); p=0.221	0.69 (0.51, 0.93); p=0.015	0.7 (0.51, 0.95); p=0.023	0.7 (0.51, 0.95); p=0.022	
1996-2000	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	
CD4 count (cells/uL)								
<200	2.21 (1.56, 3.14); p<0.0001	2.14 (1.5, 3.06); p<0.0001	-	2.12 (1.49, 3.03); p<0.0001	-	-	-	
200-349	1.39 (1, 1.92); p=0.047	1.36 (0.98, 1.88); p=0.067	-	1.34 (0.96, 1.85); p=0.082	-	-	-	
350+	1.00 (Ref.)	1.00 (Ref.)	-	1.00 (Ref.)	-	-	-	

Cox Proportional Hazard models of first incident infectious pulmonary diagnosis (chronic bronchitis, COPD or emphysema, lung cancer, other non-infectious diagnoses, other lung diseases (NOS)).
Model 1 compared current time-updated marijuana and cigarette smoking.
Model 1 - Sensitivity Analysis compared current time-updated marijuana and cigarette smoking for a subset of 18,098 person-visits with CD4 count ≥ 200 cells/µl (n=209 events).
Model 2 evaluated recent marijuana and cigarette smoking as continuous variables (mean days of use/month and packs/day, respecively, in the prior 2 years).
All models were adjusted by race, education, and current cART use; age was used as the time variable.

CONCLUSIONS

- Frequent marijuana smoking was associated with increased risk of infectious and non-infectious pulmonary diagnoses in HIV+ men on ART, independent of tobacco smoking and other factors including CD4 count, cART use, and baseline calendar period.
- Additional risk factors associated with pulmonary diagnoses in HIV+ men on ART included CD4 count < 200 cells/µl and baseline calendar period for infectious diagnoses, and CD4 count < 200 cells/µl and tobacco smoking for non-infectious diagnoses.
- Associations between marijuana or tobacco smoking and risk of infectious or non-infectious pulmonary diagnoses remained significant in sensitivity analyses restricted to visits with CD4 count ≥ 200 cells/µl.
- There was no association between marijuana smoking and risk of either infectious or non-infectious pulmonary diagnoses in HIV-uninfected men with similar demographics.
- These findings suggest that effects of marijuana smoking on respiratory health may be more significant in individuals who already have an increased risk of pulmonary disease, including people living with HIV/AIDS.

This work was supported by NIH grants R01 DA040391 and DA 30985 to D.G. The MACS is funded by NIAID (U01-AI35039,U01-AI35040; U01-AI35041; U01-AI35042; and UM1-AI35043), with additional cofunding from NCI, NIDA, and NIMH at the NIH. MACS data collection is also supported by UL1-TR000424.