Marijuana Use Does Not Accelerate Liver Fibrosis in HCV/HIV Coinfected Women

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BACKGROUND

- Endocannabinoids may play a role in modulating liver fibrosis and expression is influenced by the presence of liver disease
- Cross-sectional analyses suggest daily cannabis (THC) use predicts fibrosis progression in patients with Hepatitis C (HCV)
- A recent study in HCV/HIV co-infected patients without baseline fibrosis showed no association between THC use and fibrosis progression
- The effect of THC over prolonged follow-up, especially in those with baseline fibrosis, is incompletely characterized

AIM

- To establish whether there is an association between THC use and fibrosis progression (as measured by APRI and FIB-4) in HIV/HCV coinfected women
- To investigate the influence of THC and fibrosis progression in patients with mild fibrosis at baseline (APRI >0.5)

METHODS

Study Design: Longitudinal cohort study

Data Source: Women's Interagency HIV Study (WIHS)

-NIH-funded, prospective, multicenter cohort of women with HIV or at risk for acquiring HIV

-Enrollment in two study waves: 1994-95 and 2001-02

Eligible Cohort: (n=790)

-Women with HIV/HCV co-infection at WIHS study entry defined by detectable HCV RNA, HCV antibody, and positive HIV Western blot

-We excluded 120 with APRI >1.5 at WIHS entry

Outcome Measure: Time to significant fibrosis (APRI >1.5)

Covariates:

-HIV and HCV-related factors, metabolic and socio-demographic factors including THC and alcohol use were collected at 6 month intervals.

-Cumulative alcohol and THC use was divided by number of 6 month intervals where data were reported to determine average weekly use.

-To identify and evaluate patients with heavy exposure at some point during study observation, subjects were categorized as >=weekly use if ever reported >=weekly use; <weekly use if subjects reported use but never reported weekly or daily use; and non-users if no use reported

Statistical Analysis:

- Survival analyses performed by Cox proportional hazards models
- Multivariate analyses with backwards elimination (p<0.05)
- Analysis performed using Stata 13.0 and SAS 9.4

Results

Table 1. Selected Cohort Characteristics at WIHS Entry

Variable	THC: none (n=327)	Less than Weekly Use* (n=134)	p value	Greater than Weekly Use* (n=209)	p value
Mean Age (SD)	40 (6.1)	40 (6.8)	0.84	39 (5.8)	**0.02**
Race/Ethnicity					
Caucasian (non-hispanic)	14% (45)	22% (30)	**0.02**	15% (32)	0.62
Hispanic	19% (62)	14% (19)	0.22	22% (46)	0.39
African American (non-hispanic)	66% (216)	62% (83)	0.40	60% (125)	0.14
Median Entry APRI	0.53 (0.37-0.80)	0.49 (0.32-0.73)	0.11	0.49 (0.32-0.73)	0.06
HCV Genotype 1	87% (197)	89% (90)	0.62	87% (138)	0.96
Mean HCV viral load (log IU/ml)	6.1 (1.0)	6.0 (1.1)	0.26	6.2 (0.8)	0.36
Median CD4	314 (150-513)	384 (219-578)	**0.02**	386 (235-570)	**0.001**
HIV viral load (log IU/ml)	4.3 (1.1)	4.0 (1.1)	**0.008**	4.0 (1.2)	**0.005**
ART therapy	28% (92)	20% (27)	0.08	17% (35)	**0.002**
Mean BMI	26.2 (5.4)	26.4 (6.6)	0.78	25.6 (6.1)	0.25
Hypertension	30% (98)	35% (47)	0.28	31% (64)	0.87
Diabetes	15% (48)	16% (22)	0.66	18% (38)	0.30
Cigarette smoking	70% (229)	86% (115)	**<0.001**	88% (183)	**<0.001**
Intravenous drug use	18% (58)	28% (38)	**0.01**	28% (59)	**0.004**
Past THC use	72% (235)	94% (126)	**<0.001**	92% (193)	**<0.001**
Median alcohol use [drinks/wk]	0 (0-2)	1 (0-6)	**0.002**	1 (0-7)	**<0.001**
Heavy alcohol use [>7 drinks/week]	14% (45)	20% (27)	0.09	24% (51)	**0.004**

Data expressed as % (n), mean (SD) or median (IQR) as appropriate
*: Comparisons to THC: none group

Time to Significant Fibrosis (APRI >1.5) by THC Use Category

Figure 1. All Participants

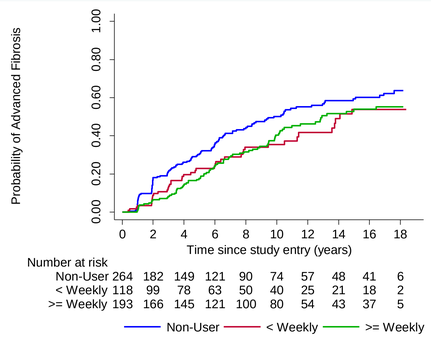


Figure 2. Subgroup with Baseline Fibrosis

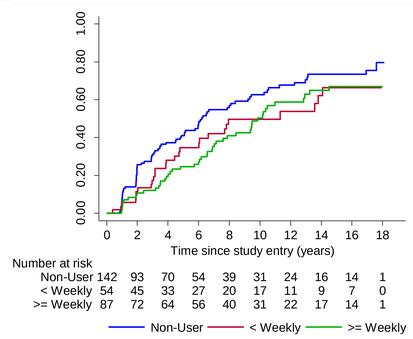


Table 2. In WIHS Follow-up by THC use

	THC: None (n=327)	Less than Weekly Use (n=134)	p value	Greater than Weekly Use (n=209)	p value
Median THC use [Joints/wk]	0 (0-0)	0.03 (0.02-0.10)	**<0.001**	0.9 (0.3-2.5)	**<0.001**
Median Average Cumulative alcohol use [Drinks/wk]	0.2 (0-2.1)	1.4 (0.3-6.0)	**<0.001**	1.6 (0.2-6.2)	**<0.001**
HCV treatment	14% (280)	10% (14)	0.7	13% (27)	0.07
HIV ARV use	61% (200)	71% (95)	**<0.001**	78% (162)	**0.048**
Median Follow up [years]	7.5 (1.5-17.0)	8.9 (3.1-14.1)	0.46	10.7 (6.5-17.4)	**<0.001**
Median Time to APRI >1.5 [years]	3.2 (1.0-8.6)	5.8 (2.0-11.0)	**0.005**	7.4 (3.2-12.4)	**<0.001**
Death	65% (212)	54% (72)	**0.03**	51% (107)	**0.001**

Table 3. Predictors of Fibrosis on Univariate Analyses

Variable	All participants (n=670)		Subgroup with established baseline fibrosis (APRI >0.5) (n=340)	
	HR (95% CI)	p value	HR (95% CI)	p value
Baseline APRI	4.74 (3.27-6.89)	**<0.001**	3.30 (1.85-5.89)	**<0.001**
Baseline Age	1.00 (0.98-1.02)	0.88	0.99 (0.96-1.02)	0.38
Race				
Hispanic	1.08 (0.70-1.62)	0.77	0.77 (0.47-1.27)	0.31
Non-Hispanic Black	0.96 (0.68-1.37)	0.74	0.74 (0.48-1.14)	0.17
Baseline Diabetes	0.86 (0.62-1.18)	0.34	0.94 (0.63-1.39)	0.75
Baseline eGFR	1.00 (0.99-1.003)	0.45	1.00 (0.99-1.003)	0.36
Baseline Hypertension	0.92 (0.69-1.22)	0.56	0.85 (0.60-1.20)	0.35
Baseline BMI	1.00 (0.97-1.02)	0.67	1.00 (0.97-1.03)	0.98
Baseline log10 HCV RNA	1.30 (1.10-1.54)	**0.002**	1.09 (0.91-1.32)	0.35
HCV Genotype1 (vs others)	1.09 (0.71-1.67)	0.70	0.94 (0.56-1.58)	0.81
Baseline log10 HIV viral load	1.14 (1.02-1.29)	**0.03**	1.03 (0.88-1.20)	0.73
HIV HAART (ever)	0.96 (0.65-1.40)	0.82	0.62 (0.38-1.01)	0.05
Cohort Entry (1994/5 vs 2001/2)	0.89 (0.58-1.37)	0.59	0.87 (0.51-1.49)	0.62
Baseline CD4	0.999 (0.999-1.00)	**<0.001**	1.00 (0.999-1.001)	0.74
Baseline IDU	1.08 (0.81-1.45)	0.59	1.11 (0.76-1.63)	0.60
Baseline Other Drug Use	1.21 (0.94-1.56)	0.14	1.39 (1.01-1.92)	**0.04**
Baseline Tobacco Use	1.19 (0.87-1.64)	0.28	1.04 (0.70-1.52)	0.86
Heavy Baseline Alcohol Use (>=14 drinks/week)	1.48 (1.06-2.09)	**0.02**	1.58 (1.02-2.43)	**0.04**
Average drinks per week during the observation period (risk per 1 drink increase in the weekly average)	1.03 (1.02-1.04)	**<0.001**	1.02 (1.01-1.04)	**<0.001**
Risk per 1 joint increase in average THC use per week	0.99 (0.90-1.09)	0.85	2.00 (0.86-1.17)	0.95

Table 4. Predictors of Fibrosis on Multivariate Analyses

Variable	All participants (n=661)		Subgroup with baseline fibrosis (APRI >0.5) (n=333)	
	HR (95% CI)	p value	HR (95% CI)	p value
Baseline APRI	3.54 (2.40-5.22)	**<0.001**	2.73 (1.52-4.92)	**0.001**
Log10 HCV RNA	1.20 (1.02-1.41)	**0.03**	1.07 (0.89-1.30)	0.46
Baseline CD4	0.999 (0.999-1.00)	**0.008**	1.00 (0.999-1.001)	0.73
Average drinks per week during the observation period (risk per 1 drink increase in the weekly average)	1.02 (1.02-1.04)	**<0.001**	1.02 (1.01-1.03)	**0.001**
Risk per 1 joint increase in average weekly THC use	0.99 (0.90-1.09)	0.80	1.00 (0.88-1.14)	0.98

CONCLUSIONS

- In this large cohort of HCV/HIV co-infected women with prospectively collected cumulative alcohol and THC use, THC was not independently associated with liver fibrosis progression
- Women without THC use had worse baseline prognostic factors: higher HIV viral loads, lower CD4 counts. Although more likely to be on ART and lower alcohol and IDU rates, they may represent a "sick-abstaining" group. This may explain the higher rates of liver fibrosis progression observed in uncontrolled time-to-event analyses.
- Unlike other short term or cross sectional studies, long term follow up of THC use in HCV/HIV co-infected women does not appear to be detrimental

Supported by: CASL scholarship
UCSF Liver Center