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Progression of liver disease in HIV/HCV co-infected people according to gender in the Icona Cohort: role of age as potential different exposure to estrogens

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Background

In patients with HCV-related chronic hepatitis (CHC), female gender has been reported as a protective factor of liver fibrosis progression. High levels of estrogens (as observed during pregnancy) have been associated to decreased inflammatory activity in HCV-pos women. Overall, men with CHC are twice as likely as their female counterparts to progress to fibrosis . However, there is some evidence that in post-menopausal women the rate of liver progression increases, suggesting a causative role of estrogens. Specific data in HIV/HCV coinfected population are lacking.

The aim of our study was to evaluate the effect of age (for women proxy of menopausal status), on liver disease progression in a large HIV/HCV population.

Methods

All patients (pts) enrolled in the ICONA Foundation study with at least 1 HCVAb+ test available were included. Predictors of liver fibrosis (FIB-4>3.25) at baseline (first HCVab+ test available) were identified by logistic regression (gender; age, risk factor for HIV HBsAg, HCV genotype, CD4, baseline HIV RNA, years from HIV diagnosis, calendar year of enrollment). The effect of aging was examined by comparing Fib4 trends before and after the age of 50 years in women and men, using a two-piecewise random coefficient model. Patients who underwent HCV treatment were excluded.

Results

Data from 2833 pts were examined: 739 (26%) women, median age 36 y (IQR 33-40), 6 years from HIV diagnosis (IQR 1-11), median CD4/µl 410 (IQR 221-600). Overall, 15.4% showed liver fibrosis at baseline, with a significantly lower proportion in females, when compared to men (18% vs. 27%, p=<.0001) (Table 1).

Table 1. Baseline characteristics according to the presence of liver fibrosis

	Population N=2833 (100%)	FIB4>3.25 N=436 (15.4%)	FIB4=<3.25 N=2397 (84.6%)	p
Female, n(%)	739 (26.1)	80 (18.3)	659 (27.5)	<.0001^
Age, median (IQR)	36 (33-40)	38 (35-42)	36 (32-39)	<.0001*
Caucasian ethnicity, n(%)	2770 (97,8)	429 (98.4)	2341 (97.7)	.34^
IDU, n(%)	2176 (76.8)	369 (84.6)	1807 (75.4)	<.0001^
HbsAg pos, n(%)	158 /2589 (6.1)	46/393 (11.7)	112/2196 (5.1)	<.0001^
HCV genotype G1 or G4, n(%)	543/1059 (51.3)	71/158 (44.9)	472/901(52.4)	.08^
HCV treatment, n(%)	37 (1.3)	9 (2.1)	28 (1.2)	.12^
AIDS at baseline, n(%)	302(10.7)	58 (13.3)	244 (10.2)	.05^
Baseline CD4/mmc , median (IQR)	410 (221-600)	315 (143-504)	427 (245-616)	<.0001*
Baseline CD4/CD8 , median (IQR)	0.43 (0.25-0.67)	0.38 (0.20-0.61	0.44 (0.26-0.67)	.0012*
HIV-RNA, log10 cp/mL, median (IQR)	4.3 (3.4-4.9)	4.4 (3.5-5.1)	4.3 (3.4-4.9)	.005*
Year of enrollment , median (IQR)	1998 (97-00)	1998 (97-00)	1998 (97-01)	.44*
Years from HIV diagnosis, median (IQR)	6 (1-11)	9 (2-12)	6 (1-11)	<.0001*

^ chisquare test
* Wilcoxon test

However, after adjusting for potential confounders, the protective role of female gender on fibrosis was not confirmed (female AOR 0.78, 95%CI 0.58-1.06). Older age (AOR 1.96, 95%CI 1.61-2.4, +10 years), HBsAg+ (AOR 2.35, 95%CI 1.56-3.54), IDU (AOR 1.81, 95%CI 1.24-2.62) and CD4 count (AOR 0.89, 95%CI 0.85-0.94, +100 cells/µl) were predictors of fibrosis at baseline (Table 2)

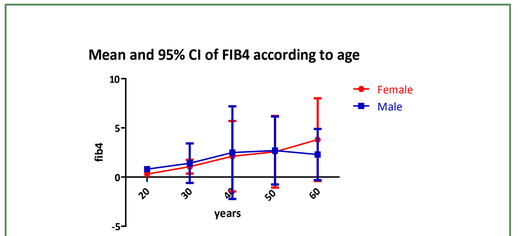
Table 2. Predictive factors of FIB4>3.25 in HCV pos patients: results from logistic regression model

	AOR	95%CI	p
Female	0.78	0.58-1.06	.11
Age, + 10 years	1.96	1.61-2.40	<.0001
HBsAg pos	2.35	1.56-3.54	<.0001
IDU	1.81	1.24-2.62	.001
Calendar year of enrollment, +1 year	0.97	0.95-1.00	.16
Years from HIV diagnosis, +1 year	1.02	0.99-1.04	.08
CD4, +100 cells/mmc	0.89	0.85-0.94	<.0001
HIV-RNA, + 1 log10	1.03	0.91-1.17	.58
HCV genotype 3	1.34	0.95-1.39	.09

In order to study the effect of aging on progression to fibrosis in the HIV/HCV co-infected population, 45498 FIB-4 measurements were analyzed.

Figure 1 shows the mean values of Fib4 according to age by decade in the male and female population.

Figure 1



fib4	Female			Male		
	mean	sd	n	mean	sd	n
20 y	0,3	0,07	17	0,81	0,07	3
30 y	1,06	0,7	217	1,41	2,01	392
40 y	2,12	3,57	783	2,49	4,71	2020
50 y	2,57	3,64	201	2,7	3,46	899
60 y	3,8	4,21	22	2,29	2,6	90

Two different two-piecewise random coefficient models were used to compare Fib4 trends before and after the age of 50 years in women and men.

In women, FIB4 increased by 0.24/10 years before 50 years and by 0.19/10 years after 50 years. The trend did not significantly differ before and after the 50th year of age (estimate -0.05, p=.4488).
Likewise, in the male population, FIB4 increased by 0.15/10 years and 0.18/10 years before and after the 50th year of age respectively,. Again, no change in trend was observed.

Table 3. Analysis of FIB4 trends in female (a) and male (b) according to age group

a)

Effect	estimate	SE	P
Age <50 years	0.15	0.09	<.0001
Age=>50 years	0.18	0.03	<.0001
COMPARE TRENDS	0.03	0.03	.3580

b)

Effect	estimate	SE	P
Age <50 years	0.24	0.04	<.0001
Age=>50 years	0.19	0.05	<.0001
COMPARE TRENDS	-0.05	0.06	.4488

Limitations

- In the ICONA dataset hormonal markers are not routinely collected, so we could not directly measure the real impact of estrogen deprivation on liver damage.
- The small number of FIB4 determinations in the elderly population, especially in women, might have limited the power to detect a difference in the FIb4 trend.

Conclusions

Differently from what reported for HCV mono-infected female population, fibrosis progression in HIV/HCV females seems to be a quite linear phenomenon similar to what observed in the male counterpart. This finding suggests the pathogenic relevance of potential pathways to inflammatory process other than estrogens deprivation in HIV/HCV co-infected women.

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