ARE HIV/HCV CO-INFECTED PATIENTS MORE LIKELY TO EXPERIENCE MULTIPLE LINES OF ANTIRETROVIRAL THERAPY (ART) THAN HIV MONO-INFECTED PATIENTS?

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Background

New antiretroviral drugs show a favorable liver safety profile and are currently recommended by guidelines for HIV/ HCV co-infection.

The impact of cART on liver fibrosis is debated. Some data suggested that cART itself may accelerate the progression of HCV-related liver disease (Rancinan C et al, AIDS, 2002). Other studies supported the beneficial role of cART in slowing HCV progression (Benhamou Y et al, Hepatology, 2001; Moshen AH et al, Gut, 2003) and in reducing mortality among HIV/HCV co-infected patients (Qurishi N et al, Lancet, 2003).

It is unclear whether HCV status would lead to more or less frequent ART use over time for fear of hepatoxicity or poor adherence.

Despite a common perception that HIV-HCV co-infected patients seem to be exposed to more lines of antiretroviral therapy due to hepatotoxicity and/or poor adherence, confirmatory data are strongly needed.

Aims

We aimed to asses whether HIV-HCV co-infected patients are subjected to higher frequency of ART changes as compared to HIV mono-infected patients for a given time in care.

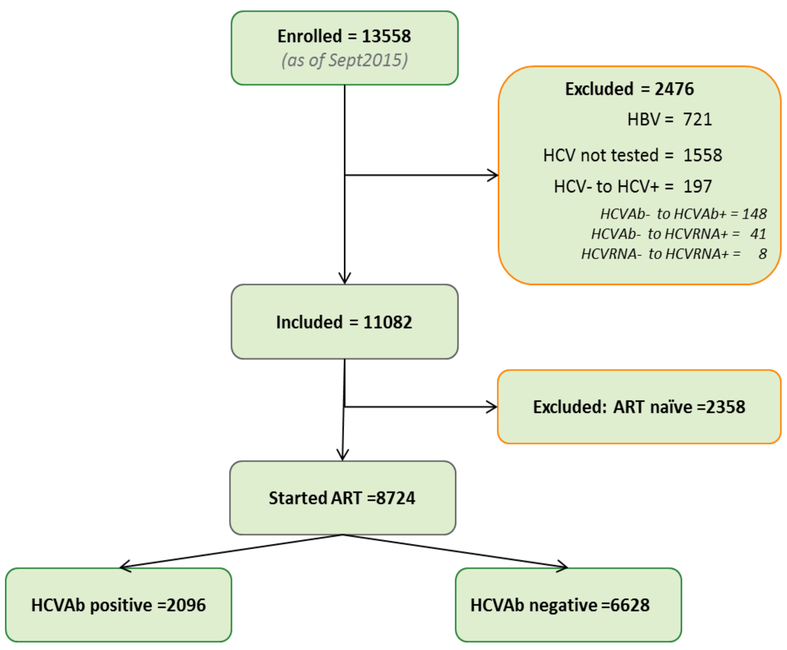
Methods

We selected patients enrolled in ICONA Foundation Study Cohort who started cART and were ever tested for HCVAb at least once over follow-up. Patients were defined to be HCV infected if they tested postive for anti-HCV (HCVAb+). Patients HBV co-infected, seronverted for HCV or ART naive were were excluded from the analysis [Figure 1].

Total ART lines exposed to were calculated first counting all changes regardless of reason of changing; then in other pre-defined separate analyses counting only switches that occurred for a specific reasons as reported by the clinician including; treatment failure (virological or immunological), toxicity/intolerance, treatment simplification and Other/unknown.

All analyses were stratified by HCVAb status. ART use was assessed a continuous and categorical variable with cut-offs using quartiles. Summary statistics were presented for description purposes and formal statistical tests were used to compared differences in ART use in both groups. Univariable and multivariable logistic regression models were fitted to assess the association between HCV infection and ART use for all reasons and separately for specific reasons. For multivariable analysis, models were fitted first with only ART use as the covariate secondly with variables (age, CD4 HIV-RNA, mode of HIV transmission, calendar year, follow-up duration, gender, nationality, smoking, alcohol consumption) and finally another model including also previous use of individual drugs.

Figure 1. Patient selection flow diagram



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Results I

Table 1. Patient characteristics stratified by HCVAb status

Characteristics	HCVAb+ N= 2096	HCVAb- N= 6628	Total N= 8724	*p-value
Age, years				
Median (IQR)	37 (33, 42)	38 (31, 46)	38 (32, 45)	<.001
Mode of HIV Transmission, n(%)				
PWID	1590 (75.9%)	193 (2.9%)	1783 (20.4%)	<.001
MSM	135 (6.4%)	2691 (40.6%)	2826 (32.4%)	
Heterosexual contacts	307 (14.6%)	3229 (48.7%)	3536 (40.5%)	
Other/Unknown	64 (3.1%)	515 (7.8%)	579 (6.6%)	
CD4 count , cells/mmc				
≤350	1321 (63.0%)	3652 (55.1%)	4973 (57.0%)	<.001
351-500	434 (20.7%)	1437 (21.7%)	1871 (21.5%)	
>501	285 (13.6%)	1006 (15.2%)	1291 (14.8%)	
Unknown	56 (2.7%)	533 (8.0%)	589 (6.7%)	
CD4 count nadir, cells/mmc				
≤350	1435 (68.5%)	4116 (62.1%)	5551 (63.6%)	<.001
351-500	407 (19.4%)	1461 (22.0%)	1868 (21.4%)	
>501	239 (11.4%)	897 (13.5%)	1136 (13.0%)	
Unknown	15 (0.7%)	154 (2.3%)	169 (1.9%)	
Viral load, log10 copies/mL				
≤1000	137 (6.5%)	291 (4.4%)	428 (4.9%)	<.001
1001 – 5000	166 (7.9%)	429 (6.5%)	595 (6.8%)	
5001- 10,000	119 (5.7%)	355 (5.4%)	474 (5.4%)	
10,001- 100,000	885 (42.2%)	2584 (39.0%)	3469 (39.8%)	
>100,001	700 (33.4%)	2336 (35.2%)	3036 (34.8%)	
Unknown	89 (4.2%)	633 (9.6%)	722 (8.3%)	
Gender, n(%)				
Female	578 (27.6%)	1674 (25.3%)	2252 (25.8%)	0.034
Nationality, n(%)				
Italian	1990 (94.9%)	5484 (82.7%)	7474 (85.7%)	<.001
Smoking, n(%)				
No	245 (11.7%)	2786 (42.0%)	3031 (34.7%)	<.001
Yes	729 (34.8%)	1910 (28.8%)	2639 (30.2%)	
Unknown	1122 (53.5%)	1932 (29.1%)	3054 (35.0%)	
Alcohol consumption, n(%)				
Abstainer	411 (19.6%)	2292 (34.6%)	2703 (31.0%)	<.001
Moderate	232 (11.1%)	1294 (19.5%)	1526 (17.5%)	
+Hazardous	150 (7.2%)	375 (5.7%)	525 (6.0%)	
Unknown	1303 (62.2%)	2667 (40.2%)	3970 (45.5%)	

+Abuse defined as >3 drinks/day for men or >2 drinks/day for women using the National Italian Food and Nutrition drinking guidelines.
***Kruskall Wallis test and chi-squared tests**

Results II

Table 2. Number of changes in ART use stratified by HCVAb status: HCVAb+ were more likely to be exposed to multiple lines of ART than HCVAb mono-infected individuals

All switches (N =8724)				
	HCVAb+ N= 2096	HCVAb- N= 6628	Total N= 8724	p-value
N. of ARV lines				
Median (IQR)	2 (1, 4)	2 (1, 3)	2 (1, 3)	<.001
No of ARV lines, n(%)				<.001
1	671 (32.0%)	2756 (41.6%)	3427 (39.3%)	
2-3	713 (34.0%)	2563 (38.7%)	3276 (37.6%)	
>3	712 (34.0%)	1309 (19.7%)	2021 (23.2%)	
Only switches due to virological/immunological failure (N =841)				
	HCVAb+	HCVAb-	Total	p-value
N. of ARV lines				
n	273	568	841	
Median (IQR)	3 (1,4)	2 (1,4)	3 (1,4)	0.335
No of ARV lines, n(%)				<.001
None	1823 (87.0%)	6060 (91.4%)	7883 (90.4%)	
1	76 (3.6%)	148 (2.2%)	224 (2.6%)	
2-3	94 (4.5%)	231 (3.5%)	325 (3.7%)	
>3	103 (4.9%)	189 (2.8%)	292 (3.4%)	
Only switches due to toxicity/ intolerance (N = 1613)				
	HCVAb+	HCVAb-	Total	p-value
N. of ARV lines				
n	509	1104	1613	
Median (IQR)	3 (2,5)	3 (2,4)	3 (2,4)	0.032
No of ARV lines, n(%)				<.001
None	1587 (75.9%)	5524 (83.3%)	7111 (81.5%)	
1	106 (5.1%)	216 (3.3%)	322 (3.7%)	
2-3	208 (9.9%)	559 (8.4%)	767 (8.8%)	
>3	195 (9.3%)	329 (5.0%)	524 (6.0%)	
Only switches due to simplification (N = 1427)				
	HCVAb+	HCVAb-	Total	p-value
N. of ARV lines				
n	272	1155	142	
Median (IQR)	3 (2,5)	2 (2,4)	2 (2,4)	0.043
No of ARV lines, n(%)				<.001
None	1824 (87.1%)	5473 (82.6%)	7297 (83.6%)	
1	17 (0.8%)	126 (1.9%)	143 (1.6%)	
2-3	143 (6.8%)	738 (11.1%)	881 (10.1%)	
>3	112 (5.3%)	291 (4.4%)	403 (4.6%)	
Other/Unknown (n =6489)				
	HCVAb+	HCVAb-	Total	p-value
N. of ARV lines				
n	1547	4942	6489	
Median (IQR)	2 (1,4)	1 (1,3)	1 (1,3)	<.001
No of ARV lines, n(%)				<.001
None	549 (26.2%)	1686 (25.4%)	2235 (25.6%)	
1	640 (30.5%)	2704 (40.8%)	3346 (38.4%)	
2-3	446 (21.3%)	1417 (21.4%)	1863 (21.3%)	
>3	461 (22.0%)	819 (12.4%)	1280 (14.7%)	

***Kruskall Wallis test and chi-squared tests**

Results III

Table 3 - Adjusted logistic regression models for HCV Ab+: HCV Ab co-infection was associated with an increased independent OR of changing ART

All switches (N=8724)						
	Unadjusted ORs (95% CI)	p-value	**Adjusted OR(95%CI)	**p-value	***Adjusted OR(95%CI)	***p-value
No. of ARV lines						
per additional	1.14 (1.12, 1.16)	<.001	1.0 (0.96, 1.05)	0.807	1.02 (0.95, 1.10)	0.536
1	1.0		1.0		1.0	
2-3	1.14 (1.02, 1.29)	0.027	0.977 (0.80, 1.20)	0.820	1.171 (0.93, 1.47)	0.176
>3	2.234 (1.97, 2.53)	<0.001	1.144 (0.87, 1.50)	0.333	1.622 (1.13, 2.32)	0.008
Only switches due to treatment failure (N =841)						
	Unadjusted ORs (95% CI)	p-value	**Adjusted OR(95%CI)	**p-value	***Adjusted OR(95%CI)	***p-value
per additional	1.09 (1.05, 1.13)	<.001	0.975 (0.92, 1.04)	0.400	0.928 (0.87, 0.99)	0.034
None	1.0		1.0		1.0	
1	1.708 (1.29, 2.26)	<.001	0.750 (0.47, 1.20)	0.233	0.800 (0.49, 1.31)	0.375
2-3	1.353 (1.06, 1.73)	0.016	0.824 (0.54, 1.25)	0.362	0.777 (0.50, 1.20)	0.254
>3	1.812 (1.42, 2.32)	<.001	0.881 (0.58, 1.34)	0.552	0.699 (0.44, 1.12)	0.139
Only switches due to simplification (N = 1427)						
	Unadjusted ORs (95% CI)	p-value	**Adjusted OR(95%CI)	**p-value	***Adjusted OR(95%CI)	***p-value
per additional	0.977 (0.94, 1.01)	0.190	0.947 (0.89, 1.00)	0.0617	0.949 (0.90, 1.01)	0.081
None	1.0		1.0		1.0	
1	0.405 (0.24, 0.67)	<.001	0.282 (0.13, 0.63)	0.002	0.312 (0.14, 0.69)	0.004
2-3	0.581 (0.48, 0.70)	<.001	0.888 (0.66, 1.20)	0.444	0.938 (0.68, 1.29)	0.691
>3	1.155 (0.92, 1.45)	0.208	0.839 (0.57, 1.23)	0.368	0.879 (0.59, 1.31)	0.528
Only switches due to toxicity/ intolerance (N = 1613)						
	Unadjusted ORs (95% CI)	p-value	**Adjusted OR(95%CI)	**p-value	***Adjusted OR(95%CI)	***p-value
per additional	1.11 (1.08, 1.14)	<.001	1.01 (0.96, 1.05)	0.835	0.993 (0.94, 1.05)	0.779
None	1.0		1.0		1.0	
1	1.708 (1.35, 2.17)	<.001	1.121 (0.74, 1.69)	0.586	1.220 (0.80, 1.86)	0.354
2-3	1.295 (1.09, 1.53)	0.003	1.096 (0.83, 1.45)	0.522	1.080 (0.81, 1.43)	0.602
>3	2.063 (1.71, 2.48)	<.001	0.918 (0.65, 1.29)	0.623	0.896 (0.61, 1.31)	0.572
Other/Unknown (N =6489)						
	Unadjusted ORs (95% CI)	p-value	**Adjusted OR(95%CI)	**p-value	***Adjusted OR(95%CI)	***p-value
per additional	1.11 (1.08, 1.13)	<.001	1.01 (0.97, 1.05)	0.497	1.01 (0.97, 1.06)	0.587
None	1.0		1.0		1.0	
1	0.726 (0.64, 0.83)	0.001	0.971 (0.76, 1.23)	0.808	0.801 (0.61, 1.05)	0.105
2-3	0.967 (0.84, 1.12)	0.643	0.903 (0.71, 1.15)	0.415	0.889 (0.69, 1.15)	0.361
>3	1.729 (1.49, 2.01)	<.001	1.138 (0.88, 1.47)	0.329	1.211 (0.91, 1.61)	0.187

**** Adjusted only factors used in matching age, cd4, HIV-RNA, mode of HIV transmission, gender, nationality, smoking, alcohol consumption and calendar year, follow-up duration**
***** Adjusted for age, CD4+, HIV-RNA, mode of HIV transmission, gender, nationality, smoking, alcohol consumption, calendar year, follow-up duration and previous use of individual drugs.**

Conclusions

- Overall, HCVAb+ individuals are more likely to be exposed to multiple lines of antiretroviral therapy than HIV mono-infected while in care, especially when comparing people who used at least three ART lines.
- The higher probability of changing ART in HCVAb+ versus HCVAb-negative patients seems driven by reasons that are not captured by the investigation of viro-immunological failure, toxicity and simplification as reported by the physician.

ICONA Foundation Study Group