Is ART use associated with increased risk of ALT elevation in HIV/HCV co-infected patients over and above what is expected in HIV mono-infected: a nested case control study approach

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Introduction

- Antiretroviral therapy (ART) induced toxicity has been frequently reported in HIV/HCV co-infected individuals. However, there is conflicting evidence on whether HIV/HCV co-infection has a synergistic effect on ART-induced toxicity.

- One way to evaluate this hypothesis is to compare the risk of ALT elevation associated with the use of ART in HIV/HCV co-infected vs HIV mono-infected populations.

Objective

- To determine whether use of ART in HIV/HCV co-infected patients is associated with increased hepatoxicity defined as ALT elevations as compared to HIV mono-infected patients.

Methods

- We selected individuals in the ICONA Foundation Study cohort with at least one ALT measurement and known current HCV status. We designed a case-control analysis nested in the cohort.

- Cases were defined as individuals who showed liver enzyme elevation (LEE) >5 x upper limit normal at their last clinical observation; controls were participants who showed normal liver enzyme levels after the same time after enrolment in the cohort.

- Controls were matched by a pre-defined set of potential confounders: age {≤20, 21-25, 26-30 to >65}, CD4 count cells/mmc {≤350, 351 - 500, >501}, HIV-RNA viral load copies/ml {≤1000, 1001 – 5000 to >100,000} and mode of HIV transmission.

- A conditional logistic regression model was used to evaluate the association between ART exposure and risk of LEE in a univariable model adjusted for matching factors and after further controlling for gender, nationality, alcohol use, smoking status and calendar year of enrolment. Interaction between HIV/HCV co-infection status and ART exposure were also formally assessed.

Results

- We included 2061 individuals (1:2 matching) with median calendar year of last clinical visit in 2014 (IQR: 2007 - 2015) [Figure 1].

- Overall, median age was 35 (IQR: 31-40), mode of HIV transmission was reported as follows; PWID (32%), MSM (36%), heterosexual (30%) and other/unknown (3%), median CD4 count 386 (IQR: 188-586) cells/mmc and HIV-RNA viral load log10 copies/ml 4.5 (IQR: 3.8 – 5.1).

- Majority were males (70%). Individuals reporting smoking were less in cases than controls 22% and 26% (p=0.03). Proportion of HIV/HCV co-infected individuals was higher in cases than in controls 39% and 29% respectively (p<0.001). Proportion of ART use was higher in cases than controls 79% and 72% respectively (p<0.001) [Table1].

- In the model without interaction, ART use was associated with an increased risk of LEE [adjusted odds ratio (aOR) 1.87 [95% CI: 1.39-2.53; p<0.001] independently of all factors included [Table 2].

- In the model with the interaction term, the association between co-infection and risk of LEE was 3.76 [95% CI: 1.31 – 10.81] in individuals on ART and 3.17 [95% CI: 2.09 – 4.80] in ART naïve individuals (p=0.69) [Figure 2].

Conclusion

- Our analysis show no evidence that risk of ALT elevation due to HIV/HCV co-infection is exacerbated by the exposure to ART(3-fold increased risk in both strata).

- Further analyses are needed to investigate the possible effect associated with the use of specific drugs/regimens

Figure 1. Patient selection flow diagram
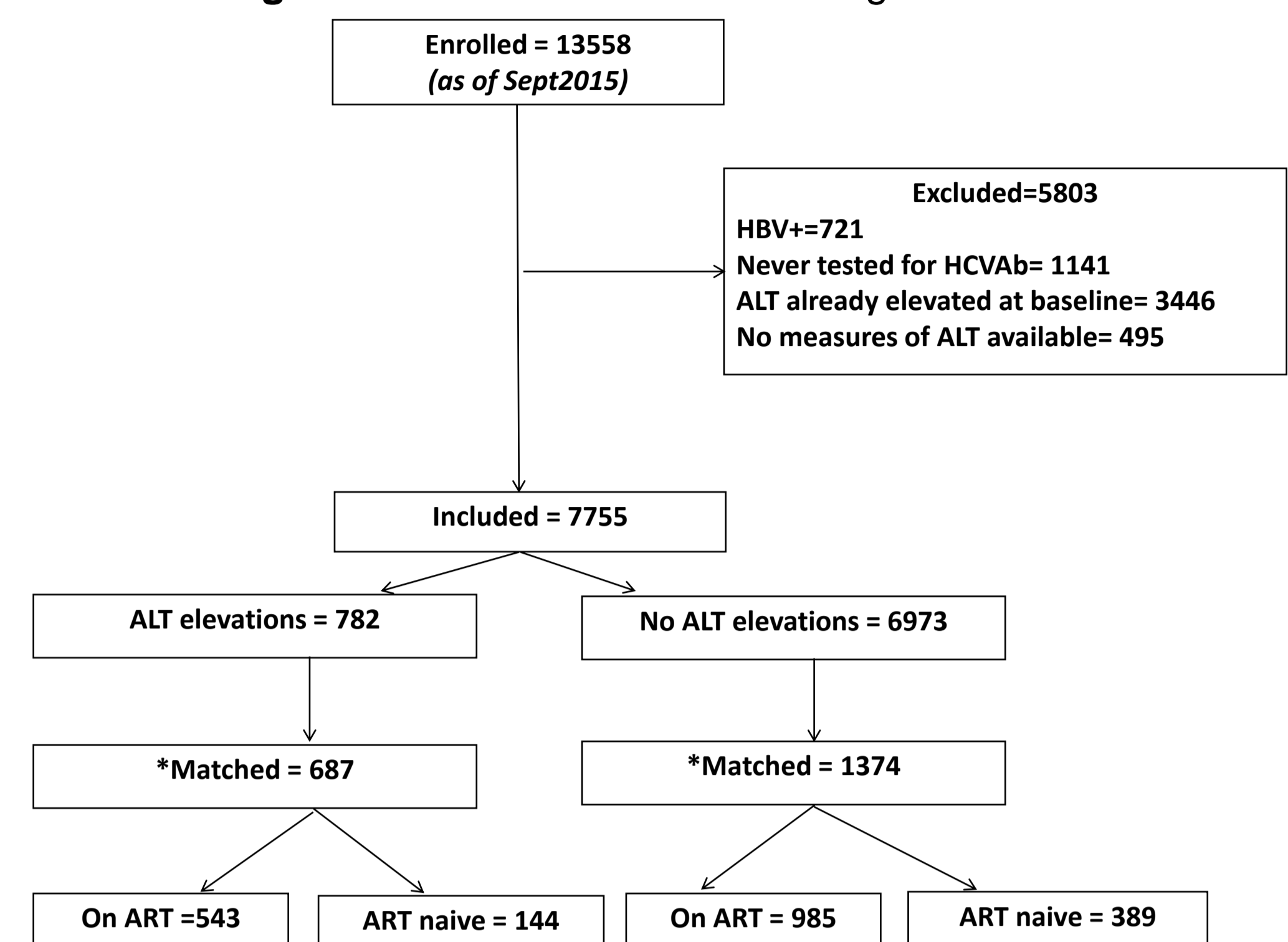
-(Case: Control as 1:2): Matched on age, CD4 cell count HIV-RNA viral load and mode of HIV transmission

Table 1. Patient characteristics stratified by ALT elevation status (cases/controls)

Patient characteristics	Elevated ALT N= 687 (%)	No elevated ALT N= 1374 (%)	Total N= 2061 (%)	p-value
Gender,				
Female	195 (28.4%)	427 (31.1%)	622 (30.2%)	0.209
Nationality				
Italian	614 (89.4%)	1242 (90.4%)	1856 (90.1%)	0.466
Smoking status				0.032
No	152 (22.1%)	335 (24.4%)	487 (23.6%)	
Yes	151 (22.0%)	354 (25.8%)	505 (24.5%)	
Unknown	384 (55.9%)	685 (49.9%)	1069 (51.9%)	
Alcohol consumption				0.174
Abstaining	157 (22.9%)	336 (24.5%)	493 (23.9%)	
Moderate	61 (8.9%)	158 (11.5%)	219 (10.6%)	
Hazardous	18 (2.6%)	29 (2.1%)	47 (2.3%)	
Unknown	451 (65.6%)	851 (61.9%)	1302 (63.2%)	
HCV status (time-dependent)				<.001
HCV negative	418 (60.8%)	971 (70.7%)	1389 (67.4%)	
HCV positive	269 (39.2%)	403 (29.3%)	672 (32.6%)	
ART status (time-dependent)				<.001
ART naive	144 (21.0%)	389 (28.3%)	533 (25.9%)	
On ART	543 (79.0%)	985 (71.7%)	1528 (74.1%)	

Table 2. Unadjusted and adjusted odds ratio from fitting a conditional logistic regression model

	Unadjusted OR(95% CI)	p-value	Adjusted OR(95%CI)	p-value
HCV status(time-dependent)				
HCV negative	1.00		1.00	
HCV positive	2.89 (2.10, 3.97)	<.001	2.95 (2.09, 4.16)	<.001
ART status(time dependent)				
ART naive	1.00		1.00	
on ART	1.82 (1.39, 2.37)	<.001	1.87 (1.39, 2.53)	<.001
Gender				
Male	1.00		1.00	
Female	0.83 (0.66, 1.06)	0.134	0.85 (0.65, 1.10)	0.204
Italian				
No	1.00		1.00	
Yes	0.88 (0.64, 1.21)	0.444	0.83 (0.58, 1.20)	0.323
Smoking				
No	1.00		1.00	
Yes	0.95 (0.72, 1.26)	0.732	0.96 (0.70, 1.32)	0.814
Unknown	1.26 (0.99, 1.60)	0.060	1.17 (0.85, 1.61)	0.325
Alcohol				
Abstain	1.00		1.00	
Moderate	0.82 (0.57, 1.18)	0.280	0.74 (0.48, 1.12)	0.152
Hazardous	1.33 (0.70, 2.52)	0.380	1.18 (0.57, 2.44)	0.650
Unknown	1.15 (0.91, 1.45)	0.233	0.99 (0.73, 1.33)	0.934
Calendar year	0.98 (0.96, 1.00)	0.066	0.99 (0.97, 1.02)	0.540

Figure 2: Adjusted odds ratio from fitting a conditional Logistic regression model