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Increased Risk of Antiretroviral Drug Discontinuation among Patients with High Hyaluronic Acid, a Marker of Liver Fibrosis

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INTRODUCTION

- Most antiretroviral (ARV) drugs, specifically protease inhibitors (PI) and non-nucleoside reverse transcriptase inhibitors (NNRTI), are metabolised by the hepatic cytochrome P450 enzyme system[1].
- Any hepatic disease such as chronic HCV and resulting liver damage could impair this metabolism leading to increased risk of ARV drug toxicity and discontinuation[2].
- Hyaluronic acid (HA) has been shown to be an accurate non-invasive marker of liver fibrosis with a normal range in a healthy population between 0-75ng/ml and a value above 100ng/ml indicative of significant hepatic fibrosis[3].

AIMS

- To determine whether patients with chronic HCV co-infection were at increased risk of ARV drug discontinuation.
- To determine whether patients with high HA (>100ng/ml) were at increased risk of ARV drug discontinuation.
- To identify ARV drug classes at highest risk of discontinuation and to explore individual ARVs where there are >10 discontinuations.

METHODS

EuroSIDA patients on cART (≥3 ARVs of any class) with known HCVAb status were included. Poisson regression was used to assess the risk of ARV discontinuation allowing for multiple discontinuations in individual patients. Baseline was defined as the date of starting cART or 1/1/1999 (when collection of reasons for treatment discontinuation started), whichever came later. Follow-up accrued until discontinuation of any ARV. HA was measured in all patients HCVAb positive and/or HBsAg positive with stored plasma samples available. In patients with HA measurements available in a 2 year window either side of a measurement was used to create an analysis subpopulation.

RESULTS

At baseline the majority of patients were male (74%), white (89%), infected with HIV via MSM (41%) and HBsAg negative (88%). Among those HCV-RNA+ the most common HIV transmission group was IDU (75%) and the most common HCV genotype was 1 (48%) (**Table 1**). In the subset of HCVAb and/or HBsAg positive patients with HA measured the majority were HCVAb+ / HCV-RNA+ (54%) (**Figure 1**).

Table 1

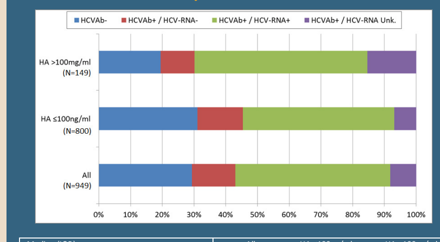
Baseline characteristics by HCV status

Median (IQR) / %		All (N=8953*)	HCVAb- (N=6480)	HCVAb+ / HCV-RNA- (N=323)	HCVAb+ / HCV-RNA+ (N=1007)
Age		40 (35 - 48)	41 (36 - 50)	40 (35 - 46)	39 (34 - 44)
Male		73.9	76.2	65.9	68.2
White		88.7	87.0	92.8	91.8
Region	South	25.0	23.2	29.4	28.5
	West Central	25.3	28.3	23.5	23.6
	North	23.6	27.3	16.4	15.6
	East Central	13.2	12.0	19.8	20.5
	East	9.8	6.1	9.9	9.4
	Argentina	3.1	3.2	0.9	2.4
Transmission group	MSM	40.6	53.2	12.7	7.0
	IDU	22.3	2.8	67.8	75.2
	Heterosexual	29.5	35.9	12.7	10.6
	Other	7.6	8.1	6.8	7.3
HCV genotype	1	-	-	-	48.4
	2	-	-	-	3.0
	3	-	-	-	24.7
	4	-	-	-	13.4
	Unknown	-	-	-	10.5
HBsAg	Negative	87.5	88.6	82.0	86.1
	Positive	6.6	6.4	11.8	5.7
	Unknown	5.9	5.0	6.2	8.0
CD4 cell count	Cells/mm³	333 (207 - 512)	352 (224 - 531)	320 (187 - 469)	303 (183 - 470)
HIV-RNA	Log_{10} copies/ml	2.7 (1.7 - 4.4)	2.6 (1.7 - 4.3)	2.7 (1.7 - 4.4)	2.7 (1.7 - 4.4)
HCV-RNA	Log_{10} IU/ml	-	-	-	5.8 (5.2 - 6.2)

*Includes 1143 patients HCVAb+ with unknown HCV-RNA at baseline.

Figure 1

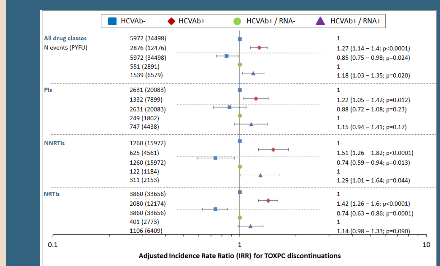
Distribution of patients with HA measured



Median (IQR)		All (N=949)	HA ≤100ng/ml (N=800)	HA >100ng/ml (N=149)
CD4 cell count	Cells/mm³	298 (179 - 440)	308 (192 - 445)	238 (134 - 363)
HIV-RNA	Log_{10} copies/ml	2.6 (1.7 - 4.1)	2.6 (1.7 - 4.1)	2.6 (1.7 - 4.2)
HCV-RNA	Log_{10} IU/ml	5.3 (2.8 - 6.0)	5.3 (2.8 – 5.9)	5.5 (4.3 – 6.1)
All HA measurements	Ng/ml	33.5 (19 – 65.7)	-	-

Figure 2

Models for each drug class of TOXPC according to HCVAb and HCV-RNA



TOXPC: drug discontinuation due to toxicity or patient/physician choice. Models adjusted for: age, gender, HIV transmission group, region of Europe, HCV genotype, baseline date, HIV-RNA, CD4 cell count, HBsAg status

RESULTS (CONTINUED)

A total of 8864 ARV drug discontinuations due to toxicity or patient/physician choice (TOXPC) from 47144 person years follow-up (PYFU) in 8953 patients were included at an incidence of 18.8 (95% CI: 18.4 – 19.2)/100 PYFU.

- HCVAb positivity was associated with increased TOXPC discontinuations for all drug classes and for each individual drug class (**Figure 2**).
- For all drug classes there was a clear gradient of increasing incidence of TOXPC discontinuations from HCVAb- to HCVAb+ aviremic infection to HCVAb+ viremic infection, with the clearest differentiation between groups seen among NNRTIs (**Figure 2**).
- In the subset of 949 patients with HA measured, across all drug classes HA >100 ng/ml was associated with 45% increased incidence of TOXPC discontinuations while the effect of HCV-RNA became non-significant when adjusting for HA level (**Figure 3**).
- HA >100ng/ml was significantly associated with TOXPC discontinuations among the PI and NRTI drug classes, but not among NNRTIs (**Figure 4**).
- In particular, HA >100ng/ml was significantly associated with TOXPC discontinuations of zidovudine and didanosine, while for individual PI drugs the estimates were all in the positive direction though none reached statistical significance due to limited power (**Figure 4**).

CONCLUSIONS

- HCVAb and HCV-RNA positive patients were at increased risk of TOXPC drug discontinuations with the strongest association seen among NNRTIs.
- However, after adjustment for HA the effect of HCVAb and HCV-RNA become non-significant.
- Patients with HA >100ng/ml were at increased risk of TOXPC drug discontinuations among the PI and NRTI drug classes, in particular the older NRTIs zidovudine and didanosine.
- TOXPC discontinuations among the NNRTI drug class were associated with viremic HCV infection but not with impairment of liver function *per se*.
- Increased drug discontinuation due to toxicity among co-infected and fibrotic patients suggests more research is required to better understand drug dosing in these populations.

LIMITATIONS

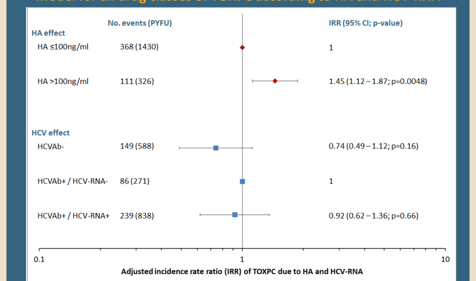
That HA was not found to be associated with NNRTI discontinuation suggests that confounding by indication may be under estimating these effects. Physicians may channel patients with potential liver impairment to other drug classes in anticipation of problems. This may be evidenced by the lower total PYFU seen among the NNRTI drug class in the HA subpopulation (**Figure 4**).

References

[1]den Brinker M, AIDS 2000; [2]McCabe S, Clin Pharmacokinet 2008; [3]Nunes D, J Acquir Immune Defic Syndr 2005;

Figure 3

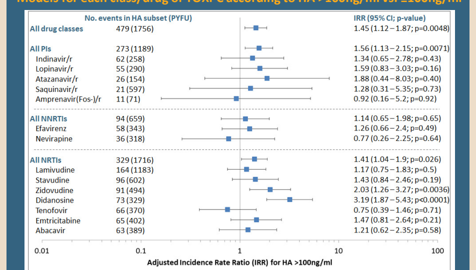
Model for all drug classes of TOXPC according to HA and HCV-RNA



TOXPC: drug discontinuation due to toxicity or patient/physician choice. Model adjusted for: age, gender, HIV transmission group, region of Europe, HCV genotype, baseline date, HIV-RNA, CD4 cell count, HBsAg status

Figure 4

Models for each class/drug of TOXPC according to HA >100ng/ml vs. ≤100ng/ml



TOXPC: toxicity or patient/physician choice. Models adjusted for: age, gender, HIV transmission group, region of Europe, HCV genotype, baseline date, HIV-RNA, CD4 cell count, HBsAg status and HCV-RNA status

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