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A Comparison of Risk of Treatment Limiting Adverse Events in HCV-co-infected vs Non-co-infected Persons with HIV in EuroSIDA

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ABSTRACT

Background: Liver damage associated with hepatitis C (HCV) may adversely affect the likelihood of experiencing discontinuation due to toxicities or patient/physician choice (TOX) in patients taking combination antiretroviral therapy (cART). Little information to address this concern is available from clinical trials as patients with HCV are often excluded.

Aims: To compare incidence rates of discontinuation due to TOX associated with specific drugs in patients with or without HCV.

Patients/Methods: 4703 patients from EuroSIDA under follow-up after December 98 on a specific nucleoside pair (zidovudine/lamivudine, didanosine/stavudine, stavudine/lamivudine, other) with a third drug (abacavir, nelfinavir, indinavir, lopinavir, nevirapine, efavirenz, or other dual PI-containing regimen) and with known HCV serostatus were studied for the incidence of discontinuation of any nucleoside pair or third drug due to TOX. Incidence rate ratios (IRR) were derived from Poisson regression models.

Results: 1310 patients had HCV (278%). During 11638 PYFU there were 1955 discontinuations due to TOX for nucleoside pairs and 2325 for third drugs. The incidence of discontinuation due to TOX was consistently higher in patients with HCV after stratification by nucleoside-pair or third drug. After adjustment for CD4 count, gender, exposure group, time since starting HAART, time on HAART, region, treatment regimen, there were few differences in the rate of discontinuation in those with HCV compared to those without for any nucleoside pairs or third drugs when comparing those with or without HCV, or when comparing nucleoside-pairs or third drugs in patients with or without HCV. Similar results were found when concentrating on discontinuation due to toxicities alone.

Conclusions: Although patients with HCV generally had higher rates of discontinuation due to TOX compared to patients without HCV, there was little evidence to suggest that this was associated with any specific nucleoside-pair or third drug used as part of cART. Our results do not suggest that any specific component of cART is more poorly tolerated in patients with HCV or that the presence of HCV should influence the choice between antiretrovirals used as part of a cART regimen.

INTRODUCTION

Recently, we reported an excess risk of drug-related discontinuations of cART in HCV-infected compared with HCV-uninfected HIV positive individuals (Mocroft et al, 7th International Congress on Drug therapy in HIV infection. Glasgow, November, 2004 (abstract PL14.1)). However, that study was not sufficiently powered to disentangle the contribution from injecting drug use and HCV-infection nor was it able to assess possible differences in contribution from individual drugs/drug classes.

The aims of this study were to describe the reasons for stopping cART regimens according to HCV status and to determine whether the increased incidence of discontinuation of any cART regimen due to toxicities and patient/physician choice (TOX) seen in patients with HCV differed according to cART regimen.

METHODOLOGY

The EuroSIDA study is a prospective, European study of patients with HIV-1 infection in 80 centres across Europe. At recruitment, in addition to demographic and clinical information, a complete antiretroviral history was collected, together with the 8 most recent CD_4 counts and viral load measurements.

Table 1: A total of 4703 patients satisfied the inclusion criteria and are described in this table. At baseline, 3393 patients were HCV negative (72.2%) and 1310 were HCV positive (27.8%).

The incidence of discontinuation due to TOX after stratification by HCV status and by nucleoside pair or third drug was calculated. Poisson regression was used to determine the factors related to discontinuation due to TOX of either the nucleoside pair or the third drug, and was adjusted for factors found previously to be related to discontinuation due to TOX.

RESULTS

Figure 1: Shows the reasons for discontinuation. The most common reason for discontinuation was patient choice. There were significant differences in the reason for discontinuation when comparing those with and without HCV infection (p=0.0002), and remained significant if discontinuations due to patient or physician choice were excluded (p=0.0076).

Table 2: For both nucleoside-pairs and the third drug, the incidence of discontinuation due to TOX was significantly higher among patients with HCV compared to those without. After additional stratification for IDU-transmission category, the incidence of discontinuation due to TOX was similar in patients with and without HCV, while the incidence of discontinuation due to TOX was considerably higher in IDU's compared to non-IDU's in both patients with and without HCV infection.

Table 1 — Characteristics of 4703 patients at baseline

			HCV negative at baseline		HCV positive at baseline		P
	All		3393	72.2	1310	27.8	-
Gender		M	2666	78.6	900	68.7	<0.0001
		F	727	21.4	410	31.3	
Risk group		Hom	1870	55.1	101	7.7	<0.0001
		IDU	109	3.2	915	71.9	
		Het	1252	34.9	162	12.4	
		Other	162	7.7	92	7.0	
Race		White	2863	84.4	1284	98.4	<0.0001
		Other	530	15.6	126	9.6	
Region		S/A	899	26.5	533	40.7	<0.0001
		C	1053	31.0	271	20.7	
		N	1018	30.0	246	18.8	
		E	423	12.5	260	19.9	
Hep B		Neg	2253	86.3	979	74.7	<0.0001
Status		Pos	239	7.0	128	9.8	
		Unknown	431	16.7	203	15.5	
AIDS			1048	30.9	362	27.6	0.029
Nuc pair		zid/lam	1460	43.0	453	34.6	<0.0001
		ddi/d4t	404	13.7	167	12.7	
		d4t/lam	1056	34.1	568	43.4	
		Other	333	9.2	122	9.3	
Third Drug		Aba	239	7.0	102	7.8	0.026
		Nel	603	17.8	281	21.5	
		Ind	897	26.4	351	26.8	
		Lop	193	5.7	63	4.8	
		Nev	475	14.0	175	13.4	
		Efa	510	15.0	181	13.3	
		Other dual	476	14.0	177	13.5	
			Median	IQR	Median	IQR	
CD4 1			365	220 – 537	306	181 – 462	<0.0001
VL 1			2.30	1.70 – 3.69	2.60	1.70 – 4.00	<0.0001
Baseline			9/99	1/99 – 1/02	6/99	1/99 – 12/01	0.10
Age			39.6	34.2 – 47.5	37.5	33.5 – 41.5	<0.0001

[1]Measured in the 6 months before baseline; available for 4521 patients (96.1%; 96.4% of HCV negative and 96.0% HCV positive; p = 0.83)
[2]Measured in the 6 months before baseline, available for 4374 patients (93.0%; 93.9% of HCV negative and 90.7% HCV positive; p = 0.0001)

Figure 1 — Reasons for discontinuation due to TOX

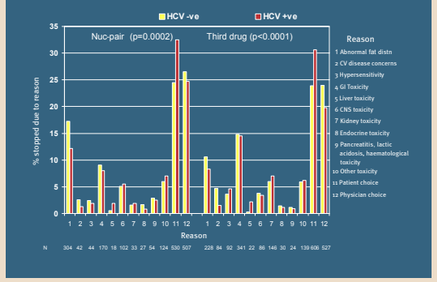


Table 2 — Incidence of discontinuation of nucleoside pair or third drug stratified by HCV status and exposure group

				Incidence		Rate ratio HCV +ve vs -ve within exposure category		
Exposure group	HCV status	Events	PYFU	Rate	95% CI	IRR	95% CI	p
Nucleoside pair								
Overall	Negative	1315	8243.1	16.0	15.1 – 16.8			
	Positive	640	3395.0	18.9	17.4 – 20.3	1.18	1.08 – 1.30	<0.0001
IDU	Negative	48	229.5	20.9	15.0 – 26.8			
	Positive	480	2240.2	19.7	17.9 – 21.4	0.94	0.70 – 1.27	0.69
Non-IDU	Negative	1267	8013.6	15.8	14.9 – 16.7			
	Positive	160	954.8	16.8	14.2 – 19.4	1.05	0.90 – 1.25	0.49
Third drug								
Overall	Negative	1564	8243.1	19.0	18.0 – 19.9			
	Positive	761	3395.0	22.4	20.8 – 24.0	1.18	1.08 – 1.29	<0.0001
IDU	Negative	51	229.5	22.2	16.1 – 28.3			
	Positive	579	2240.2	23.7	21.8 – 25.7	1.07	0.80 – 1.42	0.65
Non-IDU	Negative	1513	8013.6	18.9	17.9 – 19.8			
	Positive	182	954.8	19.1	16.3 – 21.8	1.01	0.87 – 1.18	0.91

Figure 2 — Incidence of discontinuation due to TOX in patients with and without hepatitis C

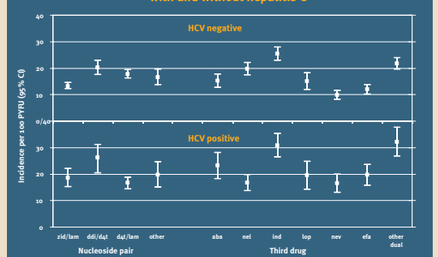
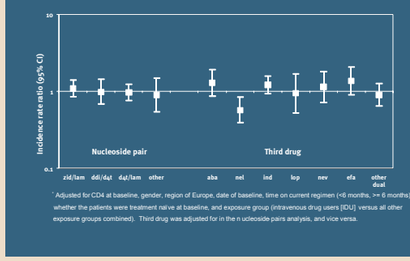
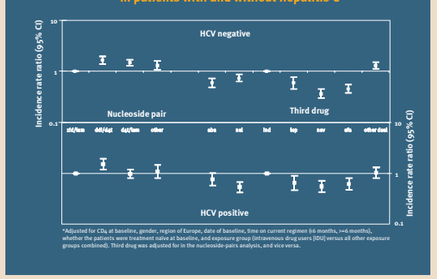


Figure 3 — Adjusted* incidence rate ratio of discontinuation due to TOX in patients with HCV compared to those without HCV



*Adjusted for CD4 at baseline, gender, region of Europe, date of baseline, time on current regimen (<6 months, >= 6 months), whether the patients were treatment naïve at baseline, and exposure group (intravenous drug users [IDU] versus all other exposure groups combined). Third drug was adjusted for in the n ucleoside-pairs analysis, and vice versa.

Figure 4 — Adjusted* incidence rate ratio of discontinuation due to TOX in patients with and without hepatitis C



*Adjusted for CD4 at baseline, gender, region of Europe, date of baseline, time on current regimen (<6 months, >=6 months), whether the patients were treatment naïve at baseline, and exposure group (intravenous drug users [IDU] versus all other exposure groups combined). Third drug was adjusted for in the nucleoside-pairs analysis, and vice versa.

Figure 2: The incidence rates of discontinuation due to TOX in patients with and without HCV, and after stratification by nucleoside pair and third drug. Those drugs with high rates of discontinuation due to TOX in patients with HCV (didanosine/stavudine and indinavir and dual PI-containing regimens) also had high rates of discontinuation due to TOX in patients without HCV.

Figure 3: Shows the adjusted (including IDU-status) IRR of discontinuation due to TOX in patients with HCV compared to those without. After adjustment, there was a comparable incidence of discontinuation due to TOX in patients with HCV compared to those without, regardless of which nucleoside-pair or third drug was used. The exception to this was for nelfinavir, where patients with HCV had a significantly lower incidence of discontinuation due to TOX compared to those without HCV (IRR 0.57; 95% CI 0.39 – 0.84, p = 0.0042). Repeated analyses only focusing on reported treatment-limiting toxicities reveiled highly consistent results.

Figure 4: This figure compares the rate of discontinuation due to TOX using a nucleoside-pair or third drug as reference for HCV negative and HCV positive patients separately. The results of the adjusted models are shown. There was no significant interaction between the effects of HCV status and nucleoside-pairs on the rate of discontinuation due to TOX (p=0.082). This implies that, although there was a variable rate of discontinuation due to TOX in patients with HCV and without HCV, there was no evidence to suggest that the increase differed according to HCV status. Conversely, there was some evidence of an interaction between HCV status and third drug (p=0.020). For both patients with and without HCV, and compared with indinavir, the rate of discontinuation due to TOX was lower , except for other dual PI-containing regimens than lopinavir/ritonavir. The significant interaction is explained by a lower rate of discontinuation of nelfinavir in HCV positive patients compared with HCV negative patients.

SUMMARY

The most common reasons for discontinuation were patient choice, physician choice, abnormal fat distribution and gastrointestinal toxicities. Discontinuation due to abnormal fat distribution was less common in patients with HCV, while discontinuation due to patient choice was more common.

The higher rate of discontinuation due to TOX in HCV positive persons is not explained from their HCV-status but rather by a predominance of IDU's among HCV positive patients.

Our data to NOT suggest that any specific component of cART is more poorly tolerated in HCV positive compared with HCV negative patients.

DISCUSSION

The question of whether there is an increased risk of discontinuation of cART regimens due to toxicities remains extremely important. There are concerns that liver-related toxicities may be a major issue in patients with HCV. However, although the risk of discontinuation due to liver-toxicity is higher in HCV positive patients, liver toxicity as a reason for discontinuation is less than 3%.

It is likely that a significant proportion of patients who discontinued cART due to patient or physician choice were due to tolerability of drugs and associated side-effects. A sensitivity analysis which concentrated on toxicities alone as a reason for discontinuation showed highly consistent results.

CONCLUSION

Our results do not suggest that any specific component of cART is more poorly tolerated in patients with HCV. The presence of HCV should not necessarily influence the choice between ARV's.

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