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Changes in the Profile and Care of HIV-HCV Seropositive Patients in Two Cross-Sectional Surveys in France (2006 and 2013)

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Abstract

Aim: To analyze HCV care and treatment in HIV-HCV coinfected patients and their evolution between 2006 and 2013, in France.

Patients and methods: HIV-HCV consecutive seropositive patients were prospectively included in two cross-sectional studies from April 3 to 10, 2006 (n=416) and from April 8 to 15, 2013 (n=342). A standard data collection form was used.

Results: Patients in 2013 compared to those in 2006 had undetectable HIV viral load and negative HCV viremia more often (82% vs. 69%, and 48% vs. 27%, respectively), with more frequent co-infection by HCV genotype 1 and 4. Liver biopsy was done less frequently (5% vs. 35%). Non-invasive liver damage assessment was done more frequently (42% vs. 22%), using serum biomarkers (37% vs. 67%) or liver-stiffness methods (69% vs. 11%). A sustained virological response to HCV treatment was more frequent (50% vs. 30%). In both surveys, patients who had received HCV treatment compared to those who had never been treated were more often of European origin, had better control of their HIV infection, had more frequent liver damage assessments and were less frequently infected by a genotype 4.

Conclusion: In comparison to 2006, more co-infected patients in 2013 had better control of their HIV infection, had liver damage assessment, received HCV treatment and more frequently had a sustained virological response. New anti-HCV combinations with greater efficacy and less toxicity should soon modify the present picture.

Keywords: HCV; HIV; HIV-HCV co-infection; Treatment

Introduction

About 30% of human immunodeficiency virus (HIV)-infected patients in France are also infected with hepatitis C virus (HCV), representing close to 30,000 patients [1-8]. Since the widespread use of highly active antiretroviral therapy (ART) began, AIDS mortality has progressively decreased, while chronic liver disease, linked primarily to HCV, has emerged as one of the leading causes of morbidity and mortality in HIV-positive patients [2,5,7-10]. The combination of pegylated interferon and ribavirin produces sustained virological

responses (SVR) in 27-44% of co-infected patients [11-14]. In early 2010, the HCV treatment "revolution" started using a combination of pegylated interferon, ribavirin and direct antiviral agents, i.e. first generation protease inhibitors, that increased SVR rates up to 75% in HCV genotype 1 mono-infection [15,16] and 74% in co-infection [17], with a poor tolerance. And more recently, short, well-tolerated oral regimens, without interferon, have been effective in nearly 100% of patients in curing HCV infection [18,19].

HCV treatment, however, has only been given to a small number of HIV-HCV co-infected patients [20,21]. In a previous study in 2006, 42% of 393 HIV-HCV co-infected patients had never received HCV treatment [21]. Following the First European Consensus Conference on the treatment of chronic hepatitis B and C in HIV-infected patients in 2005, new recommendations have been given to optimize the care of HIV-HCV co-infected patients [22].

The aim of the present study was to analyse the profile and care of HIV-HCV co-infected patients in France in 2013 and to compare the results with those obtained in the 2006 survey.

Patients and Methods

The same methodology was used in the two surveys, and details have been published elsewhere [21]. Physicians involved in the management of HIV-infected patients were recruited from 50 specialized centres from all of metropolitan France participating in the GERMIVIC study group. Each physician was asked to prospectively fill out a standardized data collection form for all HIV-HCV co-infected patients seen between April 3 and 10, 2006 (2006 survey) and between April 8 and 15, 2013 (2013 survey). The form included socio-demographic data of the patient and physician, the HIV and HCV virological status, information regarding the pre-therapeutic workup of HCV infection, liver damage assessment (biopsy or non-invasive tests), the type of HCV treatment and its follow-up, and the use of erythropoietin or antidepressants. This form had been pre-tested by five physician specialists managing HIV-HCV co-infected patients in order to optimize the type and means of data collection.

Results

Fifty-eight and 34 physicians following HIV-HCV co-infected patients participated in the 2006 and 2013 studies, respectively. These physicians were from departments of infectious disease (50% vs. 56%), internal medicine (44% vs. 40%), or hepatogastroenterology (6% vs. 4%).

During the weeks the studies were carried out, 416 and 342 HIV-HCV co-infected patients were included in 2006 and 2013, respectively (Table 1); they were mainly of male gender and of European origin, with a mean age of 43.6 vs. 49.2 years. Most patients had been infected via drug use injection, although there was an increase of transmission via heterosexual (10% vs. 15%) and homosexual activity (6% vs. 13%). The therapeutic management of HIV was already good in 2006 and it appeared to be even better in 2013, as evidenced by high rates of undetectable HIV viral load and CD4 levels >350/ml. Most patients received ART for their HIV infection (97% vs. 94%), i.e. boosted protease inhibitor based (63% vs. 54%), non-nucleoside based (18% vs. 27%), or other regimen (19% vs. 19%). An excessive alcohol consumption (i.e. >30gr/d) was noted in 145/412 (35%) vs. 32/321 (10%) patients in the 2006 and 2013 survey, respectively. The rate of active IV drug users was 70/410 (17%) vs. 48/319 (15%).

	2006 survey					2013 survey					P*
	Patients treated for HCV infection		Patients NOT treated for HCV infection			Patients treated for HCV infection		Patients NOT treated for HCV infection			
	Number	%	Number	%	Total (%)	Number	%	Number	%	Total (%)	
					416					342	
Age mean, years	43.6		43.3		43.6	49.5		48.9		49.2	<0.001
Gender											
Male	163	74	109	67	272 (71)	140	70	81	66	221 (68)	0.46
Female	58	26	53	33	111 (29)	63	30	42	34	105 (32)	0.27
Geographic origin											
Europe	188	85	122	75	310 (81)	139	81	79	77	218 (80)	0.52
Non Europe	33		41		74 (19)	33	19	23	23	56 (20)	0.11
Mode of infection transmission											
Injection drug use	179	79	131	80	310 (77)	141	63	84	60	225 (62)	0.28
Heterosexual activity	22	10	18	11	40 (10)	27	12	26	19	53 (15)	0.83
Homosexual activity	19	8	7	4	26 (6)	30	13	16	12	46 (13)	0.60
Transfusion	5	2	3	2	8 (2)	15	7	4	3	19 (5)	0.63

Hemophilia	5	2	-	-	5 (1)	8	4	3	2	11 (3)	0.51
Unknown	5	2	10	6	15 (4)	3	1	6	4	9 (2)	1.00
HIV viral load											
Undetectable	170	76	96	60	266 (69)	177	86	96	75	273 (82)	0.86
$<10^5$ copies/ml	36	16	34	21	70 (18)	23	11	25	20	48 (14)	0.85
10^5 -10^6 copies/ml	15	7	26	16	41 (11)	5	2	7	5	12 (4)	0.75
$>10^6$ copies/ml	2	1	5	3	7 (2)	1	1	0	0	1 (-)	0.38
CD4/ml											
<200	16	7	33	20	49 (13)	18	8	19	15	37 (11)	0.18
200-349	69	31	46	28	115 (30)	37	18	27	21	64 (19)	0.87
350-500	70	32	40	25	110 (29)	39	19	25	19	64 (19)	0.77
>500	66	30	44	27	110 (28)	116	55	58	45	174 (51)	0.26

Table 1: Main demographic and HIV characteristics of HIV-HCV co-infected patients, in those who had received HCV treatment and those who had never been treated in the 2006 and 2013 surveys. *P corresponds to the comparison between 2006 and 2013 surveys.

Patients had been diagnosed with HCV infection for an average of 9.6 vs. 15.5 years. Patients in 2006 compared to those in 2013 had a positive HCV viremia more often [243/333 (73%) vs. 165/317 (52%)]. The distribution of HCV genotypes has changed from 2006 to 2013, i.e. genotype 1 from 50% to 59% and genotype 4 from 15% to 17% (Table 2). The pre-therapeutic HCV workup including a liver damage assessment by biopsy or non-invasive tests was done in about two-thirds of patients in both surveys. However, the rate of "liver biopsy only" has strikingly decreased from 35% to 5% while the use of "non-invasive tests only" increased from 22% to 42%. Non-invasive liver tests had been done using serum biomarkers in 124/185 (67%) vs. 107/291 (37%), elastometry in 20/185 (11%) vs. 199/298 (69%), or both in 41/185 (22%) vs. 73/291 (25%) patients in the 2006 and 2013 survey, respectively. The follow up of cirrhotic patients (99 vs. 76 patients) included liver ultrasound exam in 83/99 (84%) vs. 66/76 (87%), and upper digestive tract endoscopy in 83/99 (84%) vs. 29/76 (38%) in the 2006 and 2013 survey, respectively. Only 8% and 14% patients had been sent for evaluation to a liver transplant unit.

	2006 survey					**2013 survey**					
	Patients treated for HCV infection		**Patients NOT treated for HCV infection**		**Total (%)**	**Patients treated for HCV infection**		**Patients NOT treated for HCV infection**		**Total (%)**	**P***
	Number	**%**	**Number**	**%**		**Number**	**%**	**Number**	**%**		
HCV RNA copies/ml											
Positive	141	-	102	-	243	94	-	71	-	165	0.84
<800,000	64	-	53	-	117	37	-	30	-	67	1
>800,000	77	-	49	-	126	55	-	37	-	92	0.89
Negative	64	-	26	-	90	104	-	48	-	152	0.77
Not done/missing	17	-	33	-	40	12	-	11	-	23	0.2
HCV genotype											
Genotype 1	105	49	66	50	171 (50)	116	60	44	56	160 (59)	0.036
Genotype 2	22	10	7	5	29 (8)	6	3	1	1	7 (3)	1
Genotype 3	61	29	32	24	93 (27)	35	18	19	24	54 (20)	1
Genotype 4	25	12	27	20	52 (15)	34	18	15	19	49 (17)	0.043
Genotype 5	0	0	0	0	0 (0)	1	1	0	0	1 (1)	.

Genotype 6	0	0	0	0	0 (0)	0	0	0	0	0	.
Liver damage assessment											
Liver biopsy and/or non invasive markers	213	100	112	100	325 (78)	175	100	78	100	253 (74)	0.37
Liver biopsy only	106	47	41	25	147 (35)	14	8	4	5	18 (5)	0.78
Non invasive markers only	40	18	53	32	93 (22)	87	50	57	73	144 (42)	0.011
Both	67	30	18	11	85 (20)	73	42	16	21	89 (26)	0.7
None	14	6	52	32	66 (16)	21	12	30	38	51 (15)	0.025

Table 2: Main characteristics of HCV infection in HIV-HCV co-infected patients, in those who had received HCV treatment and those who had never been treated in the 2006 and 2013 surveys.*P corresponds to the comparison between 2006 and 2013 surveys.

The analysis of HCV treatment showed patients, who had been previously treated or were receiving ongoing treatment represent 58% vs. 62% of the study populations in the 2006 and 2013 surveys, respectively (Table 3). There was no correlation between the rate of treated patients and HCV genotype distribution in both surveys. A sustained virological response to HCV treatment increased from 30% to 50%; an absence of virological response was noted in 44% vs. 31%, and a relapse or virological breakthrough in 26% vs. 19%, respectively. In both surveys, most treated patients received a combination of pegylated interferon plus ribavirin while in the 2013 survey 12% of patients received a triple combination of pegylated interferon plus ribavirin plus protease inhibitor. Use of anti-depressant drug and erythropoietin decreased from the 2006 to 2013 survey.

Survey	**2006**		**2013**		**P**
	N=416	**%**	**N=342**	**%**	
Modalities of HCV treatment					
Never treated	164	42	130	38	0.71
Previously treated or ongoing treatment	227	58	210	62	0.07
Unknown	25	-	2	-	< 0.001
Modalities of the last HCV treatment					
Peg-IFN plus ribavirin	167	80	161	88	0.056
Peg-IFN plus ribavirin plus boceprevir	-	-	11	6	.
Peg-IFN plus ribavirin plus telaprevir	-	-	12	6	.
Virological response to HCV treatment					
Sustained virological response	50	30	80	50	< 0.001
Non virological response	73	44	49	31	0.016
Virological relapse/breakthrough	44	26	30	19	0.11
Missing	-	-	34	-	.
Anti-depressant use	77	20	8	2	< 0.001
Erythropoietin use	27	7	16	5	0.34

Table 3: Modalities and virological results of HCV treatment in HIV-HCV co-infected patients in the 2006 and 2013 surveys.

The rate of patients not treated for their HCV infection has decreased from 164/391 (42%) to 130/340 (38%) patients between 2006 and 2013 (Table 4). The main reasons given have changed: HCV treatment deemed questionable (44% vs. 24%), contraindication to HCV treatment (26% vs. 11%) and patient refusal (21% vs. 14%). In addition, in the more recent survey, 20% of patients were waiting for new HCV drugs. Where HCV treatment deemed questionable, the reasons given where: minimal hepatic lesions for 47% vs. 41%, chronic

excessive alcohol consumption for 29% vs. 7% and active drug use for 6% vs. 26% in the 2006 and 2013 survey, respectively.

Survey	2006		2013		P
	N 164/391	% 42	N 130/340	% 38	
Main reason					
HCV treatment deemed questionable	72	44	27	24	< 0.001
Absence of liver biopsy	30	18	4	4	< 0.001
Contraindication to HCV treatment	43	26	13	11	< 0.001
Physician conviction of non-compliance with HCV treatment	32	20	8	7	0.003
Patient refusal	34	21	16	14	0.20
Waiting for new HCV drugs	-	-	23	20	-

Table 4: Main reasons for the non-treatment of HCV infection in HIV-HCV co-infected patients in the 2006 and 2013 surveys.

In comparison to non-treated patients in both surveys (Table 5), patients who had received HCV treatment were more likely to be of European origin, to have a better control of HIV infection, and to have had a liver damage assessment, whereas they were less frequently infected by a genotype 4. When we compared 2006 and 2013 surveys for these parameters, two main differences appeared in the more recent survey i.e. treated patients had an even better control of HIV infection and had had very rarely had a liver biopsy.

	2006 survey		2013 survey		p	
	Patients treated N=163	Patients NOT treated N=253	Patients treated N=210	Patients NOT treated N=130	P for treated patients	P for non-treated patients
Geographic origin from Europe	85 %	75 %	81%	78%	0.33	0.61
Undetectable HIV viral load	76 %	60 %	86%	75%	0.015	0.003
CD4/ml <200	7 %	20 %	9%	15%	0.44	<0.001
Genotype 4	12 %	20 %	17%	19%	0.24	0.010
Liver biopsy	47 %	25 %	7%	4%	<0.001	<0.001

Table 5: Main differences in HIV-HCV co-infected patient, between those who had received HCV treatment and those who did not in the 2006 and 2013 surveys.

Discussion

The care of HIV-HCV co-infected patients has changed in France. In comparison to 2006, more co-infected patients in 2013 had better control of HIV infection, had liver damage assessment, received HCV treatment (that was less contraindicated) and showed higher sustained virological responses rates.

The present study shows that between 2006 and 2013, the percentage of co-infected patients who had never received HCV treatment decreased, probably because such treatment was less contraindicated. In a recent Swedish study, 75% of 652 HIV-HCV co-infected patients did not initiate HCV treatment [23]. In a large European analysis of 25 studies including 19,014 HCV patients, the mean rate of no treatment in HCV RNA-positive patients was 57% in the overall population, 64% in HIV-HCV co-infected patients and up to 72% in IV drug users [24]. Provider-level barriers include provider inexperience with antiviral treatment and/or reluctance of providers to refer patients for treatment. The potential difficulties of starting HCV treatment seemed to be reflected by the profile of never-treated patients, notably with HCV treatment being deemed questionable for the patient (excessive alcohol consumption and active drug use), physicians' conviction of poor future compliance (unfavorable socio-economic conditions) or the presence of contraindications to HCV treatment [25,26]. In Europe, the predominant barriers to HCV treatment in co-infected patients are direct or indirect limitations of interferon-alfa and/or parenteral drug and alcohol abuse [23,24,28]. Fifty-three per cent of 200 co-infected patients had an absolute contraindication to interferon therapy, 61% of whom reported heavy drinking [27,28]. Data from the 2005-2010 U.S. National Hospital Ambulatory Medical Care Surveys showed that comorbidities varied across the subgroups with more current tobacco use (40%, 27%, 30%) and depression (32%, 23%, 24%) in the HIV-HCV, HIV and HCV subgroups, respectively [30]. Caring for patients who use illicit drugs presents challenges to the health care team that require patience, experience, and an understanding of the dynamics of substance use and addiction. Nonetheless, programs are successfully integrating hepatitis C care for IV drug users into health-care settings [29]. Patient-level barriers include non-adherence to medical care, refusal of therapy, and social circumstances [31,32]. In order to improve uptake of HCV therapy in persons with HIV-HCV co-infection, it is essential that barriers, both new and ongoing, are addressed through the institution of a therapeutic contract between physicians and patients. This would allow the reduction or termination of chronic alcohol consumption or better management of active drug use, knowing that these addictions no longer constitute an automatic barrier to treatment [21,26,32,33]. In light of newer HCV treatment options, greater efforts to remove the barriers to treatment

that still exist for a great proportion of HIV-HCV co-infected patients should be undertaken. HIV infection per se does not appear as a main barrier to HCV treatment. The immuno-virological control of HIV infection was good in both surveys and even better in the 2013 vs. 2006 survey. Of note, the sub-group of patients who had received HCV treatment had an even better control of HIV infection in both surveys (Table 5).

In both surveys, the wider use of non-invasive markers allowed liver damage to be assessed in more than two third of patients. The use of non-invasive markers of liver fibrosis, either biochemical [34-36] or morphological (liver-stiffness methods) [36-38], allowed the degree of liver involvement in HIV-HCV co-infected patients to be easily assessed. A recent study of 435 liver biopsy pairs from 282 HIV-HCV co-infected patients without cirrhosis showed that fibrosis progression was common and progression was rapid [39]. Liver stiffness method-based prediction can achieve a similar yield as liver biopsy-based models to predict overall mortality in HIV-HCV co-infected patients. Such models can predict better liver decompensations than liver biopsy [40]. Sustained clearance of serum HCV-RNA following a course of antiviral treatment is the major determinant of liver fibrosis regression in HIV-HCV co-infected patients [41]. An observational study of 216 HIV-HCV co-infected patients who received therapy against HCV and had at least three successive transient elastographies during the follow-up showed that the rate of liver fibrosis regression increased during the follow-up after SVR to interferon therapy [42].

The importance of multidisciplinary teams has been underlined for optimizing the management of HCV in co-infected patients [21,26,43]. In both surveys, most treated patients had received the best combination of pegylated interferon and ribavirin. A sustained virological response rate of 50% was noted in the 2013 survey, a figure close to that obtained in other studies in co-infection [44] as well as in HCV mono-infection. Liver transplantation has been approached with caution in HIV-HCV co-infected patients with end-stage liver disease because of concern over the sequelae of immunosuppression and ART-related hepatotoxicity. Such patients, however, should be investigated early in a liver transplant unit where the appropriateness of transplantation will be discussed [45-47]. Several direct-acting antivirals have now entered clinical practice and others have reached advanced stages of clinical development. Treatments such as sofosbuvir have received approval for HIV-HCV co-infected patients [48,49]. The results of trials using direct-acting antivirals in co-infection showed that treatment response rates are similar to those obtained in HCV mono-infection. Moreover, interferon-free options exist for HIV-HCV co-infected patients who may be ineligible or intolerant of interferon [50]. Thus, HIV should no longer be considered as a "special" population, as long as anti-retroviral therapy is given and drug interactions are taken into account [51].

In conclusion, compared to 2006, more co-infected patients in 2013 had better control of their HIV infection, had liver damage assessment, received HCV treatment and more frequently had a sustained virological response. These results underline the importance of continuing efforts to increase the access of co-infected patients to HCV treatment. New anti-HCV combinations with greater efficacy and less toxicity should soon modify the present picture.

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