Signal Detection on a Patient Cohort: A Disproportionality Analysis of the ANRS CO22 HEPATHER Cohort to Identify Associations between Direct Acting Antivirals and Adverse Events in Patients with Hepatitis C Virus Chronic Infection

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Keywords:	Adverse Drug Event, Cohort Studies, Hepatitis C, Pharmacovigilance

Abstract:	Purpose. Our aim was to explore a signal detection method for early identification of potential adverse drug reactions (ADRs) in a patient cohort. Methods. ANRS CO22 HEPATHER is a French multicentre prospective observational cohort started in 2012. The cohort includes patients with chronic hepatitis C virus (HCV) infection with reports of all adverse events (AEs) occurring in patients exposed to HCV drugs. We applied a disproportionality method, which calculated a measure of association, the Bayesian Information Component (IC), for each drug-AE pair. ICs were continuously updated and a positive drug-AE association was detected when the lower limit of an IC 95% Credible Interval (95%CI) exceeded 0. We illustrate how the method could result in timely detection of photosensitivity reaction with simeprevir use.

	Results. By August 28, 2016, 6,600 patients with HCV infection had been treated or were undergoing current HCV treatment, and 3,464 experienced at least one AE for a total of 12,720 reported AEs. We detected 52 positive drug-AE associations, including 44 that were known ADRs based on the summary of product characteristics. The association between simeprevir and photosensitivity reaction was detected on June 4, 2014. At this date, 68 patients had received simeprevir and 6 photosensitivity reaction (4 during simeprevir treatment) had been reported, for an estimated IC of 1.90 95%CI [0.20; 3.61]. Conclusions. The disproportionality method can help with early detection of potential ADRs in patient cohorts. Detected associations need to be confirmed by a review of clinical data.

Signal detection on a patient cohort: a disproportionality analysis of the ANRS CO22 HEPATHER cohort to identify associations between direct acting antivirals and adverse events in patients with Hepatitis C virus chronic infection

Detection of adverse event in a patient cohort

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KEY WORDS — Adverse Drug Event; Cohort Studies; Hepatitis C; Pharmacovigilance

KEY POINTS

- Safety information from cohort studies can be used to detect adverse drug reactions.
- We applied a quantitative signal detection method for identifying potential adverse drug reactions in a cohort of patients with chronic hepatitis C exposed to new antiviral drugs.
- The disproportionality method relied on the calculation of a Bayesian Information Component, and resulted in timely detection of both known and unknown associations between drugs and adverse events.
- As with any signal detection method, a clinical review of the signal is required to confirm or eliminate the relevance of the detected association.

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ABSTRACT

Purpose. Our aim was to explore a signal detection method for early identification of potential adverse drug reactions (ADRs) in a patient cohort.

Methods. ANRS CO22 HEPATHER is a French multicentre prospective observational cohort started in 2012. The cohort includes patients with chronic hepatitis C virus (HCV) infection with reports of all adverse events (AEs) occurring in patients exposed to HCV drugs. We applied a disproportionality method, which calculated a measure of association, the Bayesian Information Component (IC), for each drug-AE pair. ICs were continuously updated and a positive drug-AE association was detected when the lower limit of an IC 95% Credible Interval (95%CI) exceeded 0. We illustrate how the method could result in timely detection of photosensitivity reaction with simeprevir use.

Results. By August 28, 2016, 6,600 patients with HCV infection had been treated or were undergoing current HCV treatment, and 3,464 experienced at least one AE for a total of 12,720 reported AEs. We detected 52 positive drug-AE associations, including 44 that were known ADRs based on the summary of product characteristics. The association between simeprevir and photosensitivity reaction was detected on June 4, 2014. At this date, 68 patients had received simeprevir and 6 photosensitivity reaction (4 during simeprevir treatment) had been reported, for an estimated IC of 1.90 95%CI [0.20; 3.61].

Conclusions. The disproportionality method can help with early detection of potential ADRs in patient cohorts. Detected associations need to be confirmed by a review of clinical data.

INTRODUCTION

Detection of potential adverse drug reactions (ADRs)[1] is a major concern. Although the gold standard for identifying and quantifying frequent ADRs is clinical trials,[2] the sample sizes of trials are usually too small to detect ADRs when the frequencies of adverse events (AEs) following treatment are rare. To address this issue, spontaneous pharmacovigilance reporting systems have been set up to record incidental serious or unexpected AEs, and numerous analytical methods have been developed to link these events with current or past medication intake.[3–6] Analyses of healthcare databases with thousands of patients exposed to a drug, eventually compared to thousands of unexposed patients, also allow the identification of associations between a drug and an AE, i.e., "a signal". Among various signal detection methods, disproportionality (DP) methods[3] are commonly applied to spontaneous reporting systems[7–9] or healthcare databases.[10,11] However, in some of these systems, and particularly in healthcare databases, the timeliness of data collection is a strong limitation when one wants rapid identification of a signal for a drug recently released on the market. In observational patient cohort studies, a large amount of pharmacovigilance data is also collected. Our main objective was to explore a signal detection method for early identification of potential ADRs in a patient cohort. We illustrate the potentials of the method for detecting associations between antiviral drugs and AEs in patients with chronic hepatitis C virus (HCV) infection included in the prospective ANRS CO22 HEPATHER cohort study.

METHODS

Patients

The ANRS CO22 HEPATHER cohort ("Therapeutic options for hepatitis B and C: a French cohort") is a national multicentre prospective observational cohort study of patients with viral hepatitis B or C (this study is registered with ClinicalTrials.gov, number NCT01953458).[12] The cohort was set up in August 2012 with the main objectives to quantify the clinical efficacy and safety of new hepatitis treatments in real life. Written informed consent was obtained from each patient before enrolment. The protocol was conducted in accordance with the Declaration of Helsinki and French law for biomedical research and was approved by the "CPP Ile de France 3" Ethics Committee (Paris, France) and the French National Agency for Medicines and Health Products Safety (ANSM). HCV-positive patients were defined as patients with positive HCV-RNA or positive anti-HCV antibodies. Main exclusion criteria were HIV coinfection and being on HCV-treatment at inclusion. Enrolment of patients started on August 6, 2012 in two centres and was progressively extended to 32 centres by September 2014 to reach 14,599 patients with past or active HCV infection by August 28, 2016. During the inclusion visit, detailed demographics, clinical (including history of past treatments) and biological data were collected using a dedicated electronic case-report form. Follow-up visits occurred once a year for every patient and the planned duration of follow-up is at least eight years. In some but not all patients, HCV treatment with antivirals was initiated during regular patient visits. The choice of the antiviral combination was left to the physician's discretion but followed the national guidelines.[13] When an antiviral treatment was initiated, a specific schedule was implemented with additional visits 6 months after the last antiviral intake. Date of beginning and end of treatment, any dose modification, as well as all AEs regardless of their intensity occurring from first treatment intake until one month after the end of treatment were to be reported. AEs were described in terms of date of onset and resolution, intensity (using the ANRS grading scale),[14] and causality assessment; all events were coded centrally by a trained research assistant using the Medical Dictionary for Regulatory Activities (MedDRA, v17.0).

Signal detection

Signal detection in the Hepather database was performed using a disproportionality analysis method already applied to observational healthcare databases.[10,15–17] This method calculates a measure of association, the Bayesian Information Component (IC), for each drug-AE pair reported in the database. The IC is the logarithm of the ratio of the observed count of drug *i* reported with AE *j* to its expected value under the hypothesis of no association (i.e. independence) between the drug and the AE. Weighting is added to both observed and expected counts to increase stability at very low numbers of AEs.[18] Using this method and under the hypothesis that the IC is normally distributed, the IC and its variance V(IC) are calculated by[16]:

$$IC = log_2 \frac{(c_{ij}+\gamma_{11})(C+\alpha)(C+\beta)}{(c_i+\alpha_1)(c_j+\beta_1)(C+\gamma)}$$

$$V(IC) = \left(\frac{1}{log(2)}\right)^2 \left[\frac{C-c_{ij}+\gamma-\gamma_{11}}{(c_{ij}+\gamma_{11})(1+C+\gamma)} + \frac{C-c_i+\alpha-\alpha_1}{(c_i+\alpha_1)(1+C+\alpha)} + \frac{C-c_j+\beta-\beta_1}{(c_j+\beta_1)(1+C+\beta)}\right]$$ with weights $\alpha_1 = 1$, $\alpha = 2$, $\beta_1 = 1$ $\beta = 2$, $\gamma_{11} = 1$

and $\gamma = \gamma_{11} \frac{(C+\alpha)(C+\beta)}{(c_i+\alpha_1)(c_j+\beta_1)}$

C is the total number of events, c_{ij} is the number of times a specific drug-AE pair is reported, c_i the number of reports of a specific drug in the database and c_j the number of reports of a specific AE in the database. The weights α_1, α, β_1, β and γ_{11} are coefficients in the prior beta distributions for the probability of a drug, an AE, or a drug-AE pair to be listed in the database. Their values were chosen under the *a priori* hypothesis of no association between the drug and the AE.

The IC and V(IC) are updated each time a new unit of a drug-AE pair is reported in the database. Based on the posterior normal probability distribution for IC, 95% credible intervals (95%CI) are calculated as plus or minus two standard deviations from the estimated IC value. A signal is identified when the lower bound of the 95%CI exceeds 0 (positive association) or when the upper bound of the 95%CI is less than 0 (negative association).[16] Positive drug-AE associations are considered to be potential ADRs and candidates for further clinical review or investigation. In a sensitivity analysis, we

explored the impact of other choices for prior coefficients α_1, α, β_1, β, γ_{11} on the total number of positive drug-AE associations.

Application to the HEPATHER cohort

The selection of drug-AE pairs for our analysis required defining the at-risk period of a drug,[10] which was chosen as the time between first to last treatment intake + 30 days. We considered a patient as experiencing a potential ADR when an AE was reported during this at-risk period. In addition, two issues had to be addressed to select drug-AE pairs to include in the analysis: (1) Several drugs might be combined while the signal detection is applied to each drug individually (2) A patient might experience recurrent AEs but the drug-AE pair should not be counted more than once in a patient. Therefore we proceeded as follows (for illustration we assume a combination of two drugs A and B): (1) we generated a drug-AE pair for each drug in the combination (e.g. for a combination of two drugs A and B: A-AE, B-AE); (2) for each drug-AE pair we checked if it was already reported in this patient, and if not, we kept the pair for analysis. Finally, for each drug-AE pair, we built a two dimensional contingency table (table 1).[10]

AEs were analyzed at two different hierarchical levels of coding in the MedDRA terminology, the Preferred Term (PT), a level describing a single medical concept, and the System Organ Classes (SOC), a level grouping AEs by etiology, manifestation site, or purpose. Only pairs with a minimum of 1 AE reported were selected (minimum required value of c_{ij} for the IC calculation with PT and with SOC).[19]

To calculate the positive predictive value (PPV) of our method at both the PT and SOC levels, we built a reference set with all described ADRs reported in the summary of product characteristics (SPC) for each drug considered in our study. We used the SPC available at the date of the 26th of November 2017 on the website of the European Medicines Agency[20] (see appendix 1). Our reference set included 893 known different ADRs at the PT level and 170 at the SOC level. We calculated the PPVs (and 95% binomial confidence intervals) at the SOC and PT levels as the number of positive drug-AE

associations reported as ADRs in the reference set, divided by the total number of detected positive drug-AE associations.

To illustrate the method, we chose known ADRs with hepatitis C drugs that are often given together in combination: simeprevir and sofosbuvir with photosensitivity reaction (PT), an association first reported in 2010,[21,22] and dasabuvir, ombitasvir, paritaprevir and ritonavir with hyperbilirubineamia (PT), an association first reported in 2012.[23,24] We also investigated in detail two positive drug-AE associations which were not reported as known ADRs: ledipasvir with chest pain (PT) and asunaprevir with cardiac disorders (SOC).

All statistical computing and analysis were performed with the R statistical computing open source software (version 3.3.1).[25]

RESULTS

General findings

By August 28, 2016, 6600 patients with chronic HCV infection at entry in the cohort had been treated or were undergoing current HCV treatment, and 3464 patients had experienced at least one AE. In total 13,306 drug-AE pairs were reported, of which 12,720 were reported at least once in different patients (table 2).

When the analysis was performed at the PT level, 3550 different drug-AE pairs were reported 1 to 9 times, 423 were reported 10 to 99 times, and 60 were reported more than 100 times (table 3). At the SOC level, 149 different drug-AE pairs were reported 1 to 9 times, 121 pairs 10 to 99 times and 65 more than 100 times. We detected 95 potential drug-PT signals, among which 52 were positive associations, including 44 ADRs reported in the reference set (PPV = 85%, 95% confidence interval [72%; 93%]) (table 4 – see also appendix 2). We detected 49 potential drug-SOC signals among which 26 were positive associations, including 21 ADRs reported in the reference set (PPV = 81%, 95% confidence interval [61%; 93%]). These results were only slightly affected by different choices for the prior coefficients α_1, α, β_1 and β. However the number of positive associations were sensitive to the prior coefficient γ_{11}, related to the prior probability of a specific drug-AE association (see appendix 3).

Illustration with known ADRs caused by HCV drugs

A positive association between simeprevir and photosensitivity reaction (PT), could have been detected on June 4, 2014. At this date 68 patients had received simeprevir, 157 AEs had been reported during the simeprevir at risk period, and a total of 6 photosensitivity reactions (4 during the simeprevir at risk period) were reported, for an estimated IC of 1.9, 95%CI [0.20; 3.61] (figure 1A – see also appendix 2). In contrast, no signal was detected between sofosbuvir and photosensitivity reaction: by August 28, 2016, 6,139 patients had been receiving sofosbuvir and the estimated IC was 0.16, 95%CI [-0.43; 0.74] (figure 1B).

Concerning the drug-PT association dasabuvir-hyperbilirubinaemia, a positive signal was detectable on April 14, 2015. At this date 77 patients had been receiving dasabuvir and the estimated IC was 1.26, 95%CI [0.02; 2.51] (figure 2A). Similarly, a positive signal was detectable on March 12, 2015 for the associations of hyperbilirubinaemia with ombitasvir and paritaprevir (always combined) with an estimated IC of 1.52, 95%CI [0.13; 2.92] and with ritonavir (combined with ombitasvir and paritaprevir but sometimes used as a booster with other drugs) with an estimated IC of 1.42, 95%CI [0.03; 2.80].

Positive HCV drug-AE associations not known as ADRs

Among the eight positive drug-PT associations which were not identified in the safety notices (table A2-1 in appendix 2), the association between ledipasvir (always combined with sofosbuvir as fixed-dose pill) and chest pain (PT) was detectable on July 3, 2015 with an estimated IC of 1.36, 95%CI [0.08; 2.65]. By this date, 1243 patients had received ledipasvir, 1058 AEs had been reported during the ledipasvir at-risk period, and a total of 17 episodes of chest pain (6 during the ledipasvir at-risk period) had been reported. The estimated IC reached 1.19, 95%CI [0.10; 2.29] on August 28, 2016 when 2100 patients had received ledipasvir (figure 3). We performed additional analysis as this positive association between ledipasvir and chest pain could be potentially confounded by the systematic combination of ledipasvir with sofosbuvir, and in some patients with advanced liver disease, to the added use of ribavirin. Chest pain is one reported symptom of anaemia, a frequent AE caused by ribavirin. However, we could not detect associations either between sofosbuvir and chest pain, (estimated IC -0.01, 95%CI [-0.88; 0.86]) or between ribavirin and chest pain (estimated IC -0.04, 95%CI [-1.07; 0.98]). Investigation of the cohort database for these 9 ledipasvir-chest pain reports revealed that one chest pain episode was attributed by the clinician investigator to pulmonary mycobacterial infection and one occurred in a patient with a recent history of colorectal cancer, but we did not identify any other potential specific causes in the other patients. The delay between the first intake of ledipasvir and onset of chest pain was on average 91 days (min: 48 days;

max: 210 days). The other detected positive drug-PT associations which were not known ADR (ranked by order of IC) were simeprevir-sunburn, simeprevir-dyspepsia, ledipasvir-depressed mood, telaprevir-neutropenia, daclatasvir-varices oesophageal, ledipasvir-vertigo and daclatasvir-oedema peripheral.

Five positive drug-SOC associations which were not reported in the safety notices were found (table A2-2 in appendix 2), including an association between asunaprevir and cardiac disorders. The specific AEs reported in patients exposed to asunaprevir were 3 atrial fibrillations and 1 cardiac failure. Although an association of atrial fibrillation with asunaprevir has been suspected but not confirmed[26], all patients who received asunaprevir also received daclatasvir, a drug which is known to be associated with some cardiac events. [12,27,28] In addition, detailed clinical review showed that all patients who experienced asunaprevir-cardiac disorders had a past history of cardiac disorders and were receiving co-medications at the time of the event (including one patient treated with amiodarone). The delay between the first intake of asunaprevir and onset of cardiac event was on average 29 days (min: 0 days; max: 65 days). The other positive drug-SOC associations were peginterferon alpha-2b-surgical and medical procedures, simeprevir-injury poisoning and procedural complications, simeprevir-eye disorders and ledipasvir-vascular disorders.

DISCUSSION

Disproportionality analysis can be applied to patient cohorts for early detection of potential ADRs. With a database of 6600 patients receiving HCV treatment, and 12,720 drug-AE pairs reported in different patients, we could detect 52 potential ADRs when the analysis was performed at the PT level (1.3% of the total drug-PT pairs) and 29 potential ADRs when the analysis was performed at the SOC level (7.8% of the total drug-SOC pairs). Eighty to eighty-five percent of detected potential ADRs were confirmed by a review of safety notices. In addition, the detection could occur early with a limited number of specific drug-AE reports, as illustrated by the positive association between simeprevir and photosensitivity reaction that was based on a total of only 4 reports and was detected just 1 month after market authorization for this drug in France. We found also that the method did not detect a lot of spurious associations, and as an illustration, no association was reported between sofosbuvir and photosensitivity reaction, a drug that is systematically combined with simeprevir but also combined with other antiviral drugs. The coincidental associations of hyperbilirubinemia with dasabuvir and ombitasvir, paritaprevir, ritonavir were expected as these drugs are to be given together; hyperbilirubinemia was almost surely caused by the boosted protease inhibitor Paritaprevir/ritonavir inhibition of the bilirubin transporter OATP1B1 as reported with other NS3 protease inhibitors.[29]

Compared to the analysis at the SOC level, the analysis at the PT level decreased the rate of detected positive association among all reported drug-AE pairs. On the contrary, associations detected at the PT level might be more relevant to investigate as they are related to a more specific characterization of the ADRs.[30,31] However, both analyses are recommended to increase sensitivity and specificity of signal detection.[32]

There are several limitations in this study. First, we didn't distinguish between AEs reported with a prior knowledge of a potential ADR from those reported without such knowledge. For example, photosensitivity reaction reports with simeprevir might have been driven by prior specific awareness

of this event when using this drug, and the detected signal could be a consequence of over-reporting in simeprevir-treated patients (or of underreporting in patients receiving other treatments). By contrast, prior knowledge of a potential ADR could bias the association towards the null if there was an indication to use other drugs in at-risk patients. As a consequence, the association with the AE could be detected with other unrelated drugs, a bias similar to reverse causality. Confounding by indication and reverse causality also likely explain some striking positive (or negative) drug-AE associations, such as the positive associations between daclatasvir with varices oesophageal or oedema peripheral, as these events are complications of cirrhosis and daclatasvir was preferentially prescribed to patients with cirrhosis at the initial stage of the cohort. These issues of confounding and reverse causality could be addressed with adjustments on patient characteristics or using statistical models for causal inference.[33]

Second, we performed the analysis at the drug level and not at the drug combination level, which prevents detecting associations between AEs and specific drug-drug interactions. However, adapting the method to explore the association of AEs with combinations of drugs would be straightforward.

Third, we did not quantify the sensitivity and specificity of the disproportionality analysis on this cohort databases with a limited number of patients. However, other works performed on simulated data with millions of patients reported adequate performances in terms of sensitivity / specificity for this method.[10,34] We found that detected positive drug-AE associations were only slightly affected by the choice of prior coefficients α_1, α, β_1 and β. However the number of positive associations were sensitive to the prior coefficient γ_{11}, related to the prior probability of a specific drug-AE association. In addition, we showed that the positive predictive values of positive signal detection were over 80% assuming that the positive drug-AE associations that were not reported in our reference set did not correspond to unknown but nevertheless true ADRs.

Fourth, the disproportionality method did not take into account the duration of exposure to the different drugs, as this kind of information is usually not reported in pharmacovigilance database. Other methods dealing with duration of exposure to a drug could be tested for that purpose, such as

the Information Component Temporal Pattern Discovery (ICTPD),[35] the Longitudinal Gamma Poisson Shrinker (LGPS)[36] or the Longitudinal Evaluation of Observational Profiles of Adverse Events Related to Drugs (LEOPARD).[36] Their performances have been tested on real or simulated healthcare or observational databases,[37,38] including millions of patients and reports. How these methods perform for early signal detection on cohorts of thousands of individuals with regularly updated databases remains to be evaluated.

Fifth, variance and 95% credible intervals calculations were performed under the hypothesis of a normal distribution for the IC, and this assumption may not hold true when the number of drug-AE pairs are limited. In this case, other methods based on Monte-Carlo simulations or tabular methods can be used.[18]

A final limitation, common to all signal detection methods, is the impossibility to draw conclusions from a detected association on the causal relationship between exposure to the drug and the AE: any detected signal has to be explored for clinical validation.[11,39–41]

To conclude, the disproportionality method can help with early detection of drug-AE associations using information collected from cohorts of thousands of patients. Other methods that take account of the duration of exposure could also be promising in this context and warrant further explorations.

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The biobank of the cohort is stored by Cell&Co Biorepository, Pont du Château, France and has been managed temporarily by Centre de Ressources Biologiques-HUEP, Hôpital St Antoine, Paris, France.

The Institut national de la santé et de la recherche médicale (INSERM)-ANRS had a role in study design, data collection and approval of the final report. The funders of the study other than INSERM-ANRS had no role in study design, data collection, data analysis, data interpretation, or writing of the report. FC had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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CONFLICT OF INTEREST

SP received honoraria for his participation in advisory boards from Abbvie, Janssen, MSD, BMS, Gilead and Novartis. SFF, NL, CD, AD, IA and FC declare that they have no conflicts of interest.

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Table 1. Two by two contingency table for a drug-AE pair *i-j*

	Drug *i*	Drugs ≠ *i*	total
AE *j*	$a = c_{ij}$	b	c_j
AEs ≠ *j*	c	d	
total	c_i		C

Table 2. Patients characteristics

	HCV past or present
N	14,599
Age (yr). Mean ± SD	60 ± 12
Sex male, %	65% (5378)
Cirrhosis, %	31% (4545)
Hepatitis duration † (yr). Mean ± SD	15 ± 8
Patient given at least one HCV treatment	6600
Patients treated with each drug, %: ‡	
Sofosbuvir	89.9% (5932)
Ribavirin	37.2% (2456)
Daclatasvir	34.2% (2259)
Ledipasvir	31.8% (2096)
Simeprevir	14.7% (969)
Ritonavir	7.6% (499)
Ombitasvir	7.5% (496)
Paritaprevir	7.5% (496)
Pegylated interferon	7.1% (470)
Dasabuvir	5.8% (386)
Telaprevir	1% (64)
Boceprevir	0.4% (25)
Elbasvir	0.3% (18)
Grazoprevir	0.2% (16)
Asunaprevir	0.2% (13)
Patients experiencing AE during the at risk period §	3464
Patients experiencing serious AE during the at risk period §	760
AE during the at risk period §	12,720
Serious AE during the at risk period §	1321

† at inclusion

‡ most frequent combinations of drugs were sofosbuvir/daclatasvir+/-ribavirin (n = 2184), sofosbuvir/ledipasvir+/-ribavirin (n = 2092), sofosbuvir/simeprevir+/-ribavirin (n = 914), sofosbuvir/ribavirin (n = 560), sofosbuvir/pegylated interferon/ribavirin (n = 273), telaprevir/pegylated interferon/ribavirin (n = 46), pegylated interferon/ribavirin (n = 107), boceprevir/pegylated interferon/ribavirin (n = 9), ombitasvir/paritaprevir/ritonavir/dasabuvir+/-ribavirin (n = 382), ombitasvir/paritaprevir/ritonavir +/-ribavirin (n = 115), elbasvir/grazoprevir+/-sofosbuvir (n = 16), others (n = 74)

§ from first treatment intake to D+30 after last treatment intake

Table 3. Distribution of the number of drug-AE pairs reported

	1	2	3 to 9	10 to 99	100 and more	Total
PT	2205	581	764	423	60	4033
SOC	48	17	84	121	65	335

Table 4. IC results by August 28, 2016

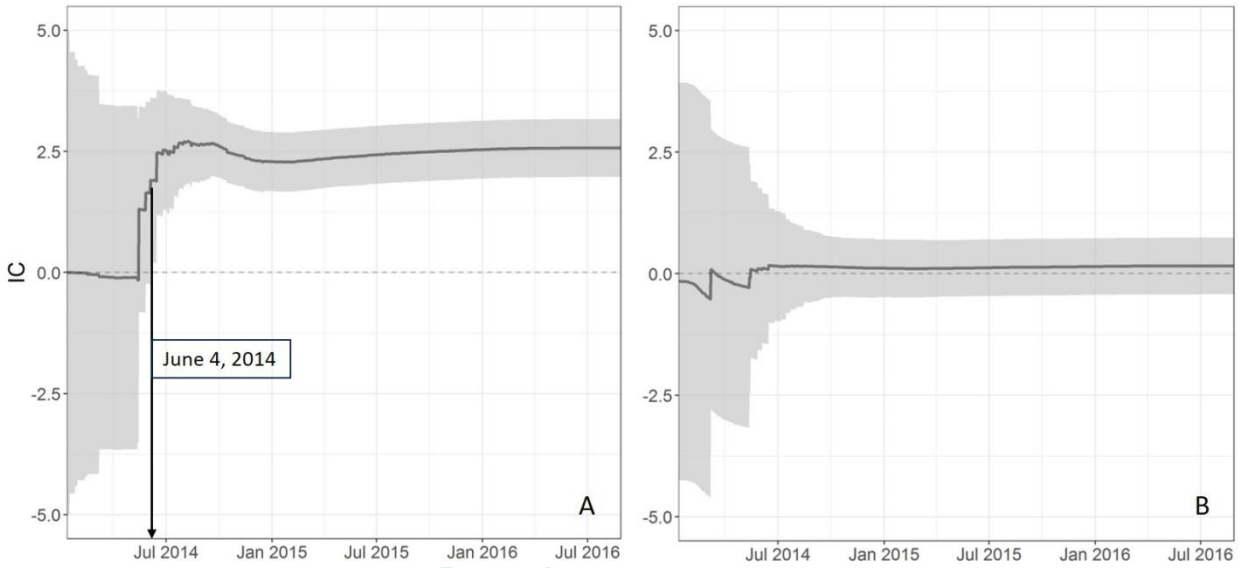
	PT n (%)	SOC n (%)
IC > 0	52 (1.3%)	26 (7.8%)
IC includes 0	3933 (97.6%)	286 (85.4%)
IC < 0	43 (1.1%)	23 (6.9%)

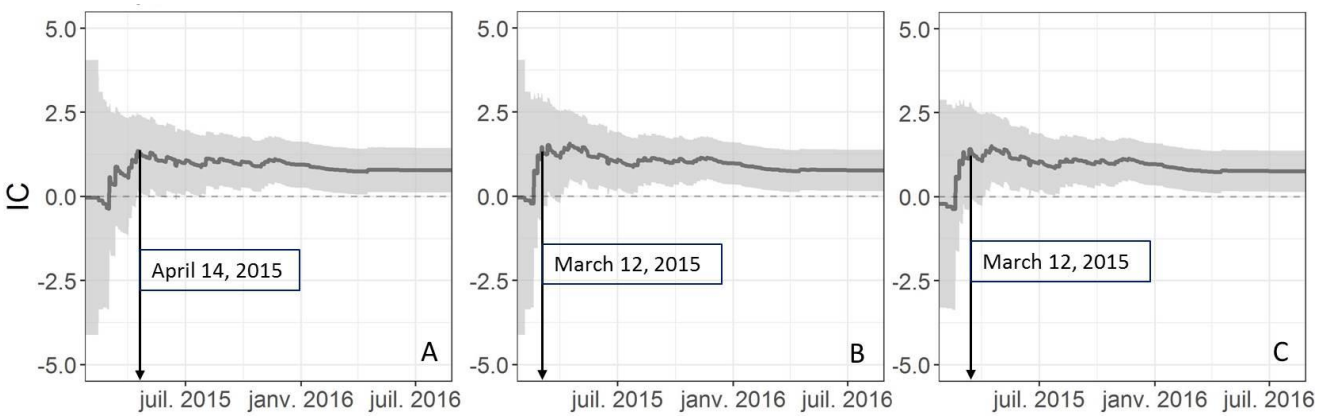
FIGURE LEGENDS

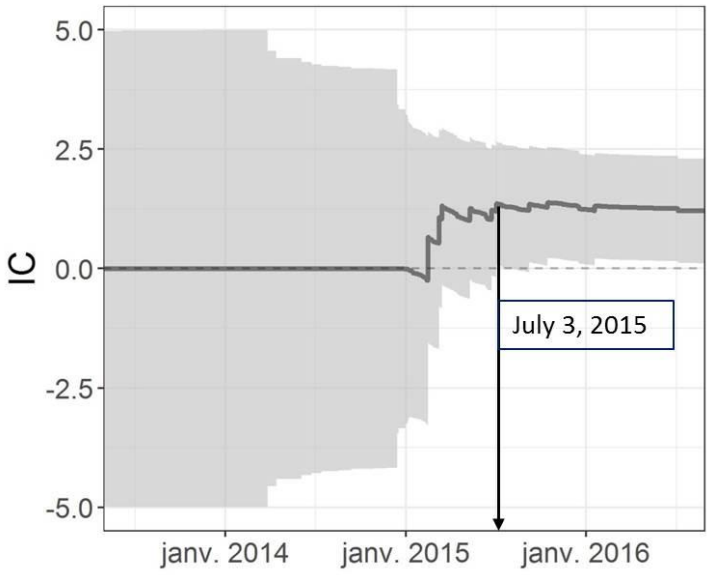
Figure 1. Change in IC between January 10, 2014 and August 28, 2016 for the associations of photosensitivity reaction (PT) with simeprevir (A) and sofosbuvir (B). IC plotted at daily intervals with 95% credible intervals shown.

Figure 2. Change in IC between January 22, 2015 and August 28, 2016 for the associations of hyperbilirubinaemia (PT) with dasabuvir (A), ombitasvir (B), paritaprevir (B) and ritonavir (C). IC plotted at daily intervals with 95% credible intervals shown.

Figure 3. Change in IC between April 29, 2013 and August 28, 2016 for the associations of chest pain (PT) with ledipasvir. IC plotted at daily intervals with 95% credible intervals shown.







APPENDIX 1:

Table A1- Source of summary of products characteristics

International non-proprietary name	Trade name	Source	Language	First published	Last updated
Daclatasvir	Daklinza	EMA	English	15/09/2014	15/03/2017
Boceprevir	Victrelis	EMA	English	03/08/2011	21/11/2017
Peginterferon alpha-2a	pegasys	EMA	English	16/11/2009	18/10/2017
Peginterferon alpha 2b	PegIntron	EMA	English	17/09/2009	23/08/2017
Simeprevir	Olysio	EMA	English	04/06/2014	22/08/2017
Asunaprevir		Not available			
Dasabuvir	Exviera	EMA	English	12/02/2015	17/10/2017
Telaprevir	Incivo	EMA	English	03/10/2011	06/10/2016
Ombitasvir/paritaprevir/ ritonavir	Viekirax	EMA	English	09/03/2015	16/10/2017
Ritonavir	Norvir	EMA	English	15/11/2009	27/10/2017
Sofosbuvir	Sovaldi	EMA	English	05/02/2014	18/10/2017
Grazoprevir/elbasvir	Zepatier	EMA	English	28/07/2016	17/05/2017
Ledipasvir/sofosbuvir	Harvoni	EMA	English	04/12/2014	05/09/2017
Ribavirin	Rebetol	EMA	English	22/10/2009	29/03/2017

EMA: European Medicines Agency

APPENDIX 2

Table A2-1 AE-drug positive associations with HCV therapy at the PT level, in decreasing order of IC.

Drug	Event (PT)	Date of detection	Patients treated with drug *i*†	c_i †	c_j †	c_{ij} †	C†	IC‡	ADR reported in the reference set
Simeprevir	Photosensitivity reaction	June 4, 2014	68	157	6	4	3271	2.52 [1.92-3.12]	Yes
Telaprevir	Anal pruritus	June 2, 2014	62	248	4	4	3159	2.11 [0.42-3.81]	Yes
Peginterferon alpha-2a	Neutropenia	March 19, 2014	214	700	82	62	1315	1.85 [1.55-2.15]	Yes
Peginterferon alpha-2a	Influenza like illness	May 15, 2014	280	1148	46	32	2701	1.84 [1.32-2.36]	Yes
Simeprevir	Sunburn	July 11, 2014	225	314	4	4	4539	1.82 [0.28-3.37]	No
Peginterferon alpha-2b	Influenza like illness	June 15, 2014	32	103	49	5	3751	1.78 [0.61-2.95]	Yes
Peginterferon (no more precision)	Neutropenia	June 15, 2014	18	43	174	6	3751	1.71 [0.67-2.74]	Yes
Boceprevir	Anaemia	April 15, 2014	24	62	61	6	1909	1.67 [0.51-2.83]	Yes
Peginterferon (no more precision)	Leukopenia	August 4, 2014	20	51	261	7	5282	1.55 [0.57-2.54]	Yes
Peginterferon alpha-2a	Leukopenia	March 25, 2014	221	747	103	74	1429	1.46 [1.18-1.73]	Yes
Boceprevir	Neutropenia	October 15, 2014	25	64	236	6	7275	1.45 [0.29-2.61]	Yes

Peginterferon alpha-2b	Neutropenia	April 28, 2014	29	80	119	10	2146	1.36 [0.47-2.24]	Yes
Boceprevir	Leukopenia	October 15, 2014	25	64	305	7	7275	1.33 [0.24-2.42]	Yes
Ledipasvir	Chest pain	July 3, 2015	1243	1058	17	6	11,085	1.19 [0.10-2.29]	No
Peginterferon alpha-2a	Thrombocytopenia	June 10, 2014	310	1275	160	79	3438	1.16 [0.84-1.48]	Yes
Telaprevir	Anaemia	June 17, 2014	64	257	89	12	3813	1.13 [0.29-1.97]	Yes
Dasabuvir	Hyperbilirubinaemia	April 14, 2015	77	67	224	5	10,195	1.08 [0.34-1.81]	Yes
Simeprevir	Dyspepsia	November 19, 2014	746	1256	25	10	8055	1.07 [0.14-2.00]	No
Ledipasvir	Depressed mood	November 30, 2015	1743	1570	32	10	12,088	0.97 [0.00-1.93]	No
Telaprevir	Neutropenia	May 15, 2015	65	265	276	13	10,627	0.94 [0.13-1.75]	No
Peginterferon alpha-2b	Leukopenia	December 16, 2014	36	123	331	10	8548	0.93 [0.01-1.85]	Yes
Dasabuvir	Pruritus	March 16, 2015	35	34	247	4	9891	0.92 [0.28-1.56]	Yes
Ombitasvir	Pruritus	June 15, 2015	159	212	271	12	10,938	0.91 [0.35-1.47]	Yes
Paritaprevir	Pruritus	June 15, 2015	159	212	271	12	10,938	0.91 [0.35-1.47]	Yes
Simeprevir	Rash	March 31, 2015	910	1612	67	19	10,046	0.88 [0.19-1.58]	Yes
Peginterferon alpha-2a	Weight decreased	October 15, 2015	415	1790	52	15	11,834	0.87 [0.05-1.69]	Yes

Ombitasvir	Hyperbilirubinaemia	March 12, 2015	41	32	217	4	9732	0.83 [0.21-1.45]	Yes
Paritaprevir	Hyperbilirubinaemia	March 12, 2015	41	32	217	4	9732	0.83 [0.21-1.45]	Yes
Peginterferon alpha-2a	Gamma-glutamyltransferase increased	October 13, 2014	378	1608	127	42	7063	0.82 [0.33-1.31]	Yes
Ritonavir	Pruritus	June 15, 2015	162	218	271	12	10,938	0.82 [0.26-1.37]	Yes
Peginterferon alpha-2a	Decreased appetite	July 15, 2014	335	1443	67	32	4816	0.80 [0.32-1.28]	Yes
Daclatasvir	Varices oesophageal	May 13, 2014	276	466	10	7	2505	0.76 [0.13-1.40]	No
Simeprevir	Hyperbilirubinaemia	June 24, 2014	143	218	94	11	3980	0.76 [0.35-1.17]	Yes
Ritonavir	Hyperbilirubinaemia	March 12, 2015	44	38	217	4	9732	0.74 [0.13-1.35]	Yes
Ledipasvir	Headache	January 13, 2015	82	33	448	6	8870	0.72 [0.48-0.97]	Yes
Simeprevir	Pruritus	March 3, 2014	14	31	31	5	987	0.69 [0.30-1.08]	Yes
Peginterferon alpha-2a	Cough	June 27, 2014	328	1373	32	20	4122	0.68 [0.05-1.31]	Yes
Ritonavir	Asthenia	May 29, 2015	145	168	962	24	10,728	0.66 [0.35-0.97]	Yes
Ledipasvir	Vertigo	April 12, 2015	814	580	93	11	10,164	0.66 [0.08-1.24]	No
Ribavirine	Dyspnoea exertional	October 22, 2014	1239	4169	65	54	7433	0.65 [0.25-1.04]	Yes
Ribavirine	Influenza like illness	October 3, 2014	1189	4009	64	55	6878	0.63 [0.17-1.09]	Yes

Ombitasvir	Asthenia	May 27, 2015	140	160	960	23	10,715	0.62 [0.31-0.93]	Yes
Paritaprevir	Asthenia	May 27, 2015	140	160	960	23	10,715	0.62 [0.31-0.93]	Yes
Peginterferon alpha-2a	Anaemia	August 22, 2014	341	1516	117	44	5858	0.58 [0.13-1.03]	Yes
Ribavirine	Anaemia	August 18, 2014	1064	3617	115	96	5763	0.58 [0.29-0.86]	Yes
Ribavirine	Neutropenia	July 8, 2014	978	3120	195	171	4418	0.57 [0.31-0.83]	Yes
Daclatasvir	Oedema peripheral	November 15, 2014	1454	3487	57	39	7968	0.56 [0.06-1.06]	No
Ribavirine	Dyspnoea	November 22, 2014	1306	4369	103	76	8105	0.51 [0.18-0.84]	Yes
Ribavirine	Leukopenia	July 10, 2014	987	3153	238	202	4512	0.51 [0.29-0.73]	Yes
Ledipasvir	Asthenia	January 21, 2015	168	61	783	11	9065	0.45 [0.25-0.66]	Yes
Ribavirine	Cough	February 15, 2016	2536	6211	107	73	12,499	0.44 [0.01-0.88]	Yes
Daclatasvir	Arthralgia	July 15, 2014	848	1722	49	29	4816	0.43 [0.04-0.81]	Yes

c_i is the number of reports of a specific drug in the database, c_j the number of reports of a specific AE in the database. c_{ii} is the number of times a specific drug-AE association was reported, and C is the total number of events. ADR: adverse drug reaction. † at the date of detection. ‡ at the date of August 28, 2016

Table A2-2 AE-drug positive associations with HCV therapy at the SOC level, in decreasing order of IC.

Drug	Event (SOC)	Date of detection	Patients treated with drug *i*†	c_i†	c_j†	c_{ij}†	C†	IC‡	ADR reported in the reference set
Asunaprevir	Cardiac disorders	August 8, 2014	13	64	36	4	5404	1.78 [0.37-3.19]	No
Boceprevir	Blood and lymphatic system disorders	March 15, 2014	23	62	279	24	1230	1.68 [1.01-2.36]	Yes
Peginterferon (no more precision)	Blood and lymphatic system disorders	May 27, 2014	17	27	578	13	3022	1.46 [0.78-2.15]	Yes
Peginterferon alpha-2a	Endocrine disorders	October 15, 2014	378	1635	8	7	7275	1.36 [0.10-2.63]	Yes
Peginterferon alpha-2a	Blood and lymphatic system disorders	March 5, 2014	185	575	244	166	1029	1.34 [1.18-1.50]	Yes
Peginterferon alpha-2b	Surgical and medical procedures	September 10, 2014	34	116	73	5	6224	1.31 [0.07-2.55]	No
Simeprevir	Injury poisoning and procedural complications	July 11, 2014	225	314	26	6	4539	1.16 [0.56-1.76]	No
Peginterferon alpha 2b	Blood and lymphatic system disorders	February 7, 2014	20	61	156	25	644	1.04 [0.48-1.60]	Yes
Dasabuvir	Hepatobiliary disorders	April 14, 2015	77	67	294	6	10,195	0.97 [0.34-1.60]	Yes
Telaprevir	Skin and subcutaneous tissue disorders	November 29, 2013	43	130	31	18	443	0.80 [0.26-1.33]	Yes
Simeprevir	Skin and subcutaneous tissue disorders	May 15, 2014	43	115	171	15	2701	0.79 [0.56-1.02]	Yes
Ombitasvir	Hepatobiliary disorders	April 7, 2015	79	69	291	6	10,107	0.79 [0.24-1.33]	Yes

Paritaprevir	Hepatobiliary disorders	April 7, 2015	79	69	291	6	10,107	0.79 [0.24-1.33]	Yes
Simeprevir	Hepatobiliary disorders	June 20, 2014	132	204	115	12	3881	0.73 [0.37-1.09]	Yes
Ritonavir	Hepatobiliary disorders	April 8, 2015	84	78	292	7	10,128	0.70 [0.16-1.25]	Yes
Telaprevir	Blood and lymphatic system disorders	December 3, 2014	65	265	1059	47	8305	0.70 [0.24-1.15]	Yes
Simeprevir	Eye disorders	September 18, 2014	468	765	68	15	6537	0.62 [0.04-1.21]	No
Ledipasvir	Vascular disorders	July 7, 2015	1251	1086	145	24	11,127	0.54 [0.01-1.06]	No
Ledipasvir	Nervous system disorders	January 12, 2015	75	28	740	7	8845	0.52 [0.31-0.73]	Yes
Ribavirine	Blood and lymphatic system disorders	May 26, 2014	789	2392	566	510	2976	0.45 [0.33-0.57]	Yes
Ribavirine	Respiratory, thoracic and mediastinal disorders	July 31, 2014	1033	3412	208	168	5231	0.41 [0.22-0.61]	Yes
Ritonavir	General disorders and administration site conditions	May 30, 2015	146	169	1645	38	10,729	0.33 [0.06-0.61]	Yes
Ledipasvir	General disorders and administration site conditions	February 15, 2015	399	210	1409	45	9438	0.32 [0.15-0.49]	Yes
Ombitasvir	General disorders and administration site conditions	May 30, 2015	143	163	1645	37	10,729	0.31 [0.03-0.59]	Yes
Paritaprevir	General disorders and administration site conditions	May 30, 2015	143	163	1645	37	10,729	0.31 [0.03-0.59]	Yes
Daclatasvir	Musculoskeletal and connective tissue disorders	September 16, 2014	1135	2709	326	167	6460	0.28 [0.09-0.48]	Yes

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APPENDIX 3:

We explored the impact of modifying the prior coefficients on the total number of detected positive signals. For drug-AE pairs with a positive signal at both baseline and for other choices of coefficients, we calculated the mean difference of detection times between the scenarios (in days). A negative mean difference indicated an earlier positive signal in the sensitivity analysis than with our baseline non-informative priors.

At the PT level of analysis, 45 of 52 positive associations detected with our baseline choice for prior coefficients were also detected using other coefficient combinations. The highest absolute mean difference between detection times was 35.54 days. At the SOC level, 22 of 26 positive associations detected with our baseline choice for prior coefficients were also detected using all 30 combinations, and the highest absolute mean difference was 22.12 days (table A3-1 & 2). Overall this sensitivity analysis shows that our results were slightly affected by different choices for the prior coefficients α_1, α, β_1 and β. However the number of positive associations were sensitive to the prior coefficient γ_{11}, related to the prior probability of a specific drug-AE association.

Table A3-1 Sensitivity analysis at the PT level with 30 different combinations of coefficients.

Combination$_i$	**α_1**	**α**	**β_1**	**β**	**γ_{11}**	**positive signals by August 28, 2016 (N)**	**Mean relative detection time (baseline reference: combination 11), days**
1	1	2	1	2	0.5	62	-17.52
2	0	1	1	2	0.5	69	-24.00
3	1	1	1	2	0.5	62	-17.46
4	1	2	0	1	0.5	63	-21.31
5	1	2	1	1	0.5	62	-17.46
6	0	1	0	1	0.5	70	-28.37
7	0	1	1	1	0.5	69	-23.96
8	1	1	0	1	0.5	63	-21.31
9	1	1	1	1	0.5	61	-17.46
10	2	4	2	4	0.5	56	-6.27
11†	**1**	**2**	**1**	**2**	**1**	**52**	**0**
12	0	1	1	2	1	53	-11.79
13	1	1	1	2	1	52	0.02
14	1	2	0	1	1	53	-0.35
15	1	2	1	1	1	52	0.02
16	0	1	0	1	1	53	-12.13
17	0	1	1	1	1	53	-11.77
18	1	1	0	1	1	53	-0.33
19	1	1	1	1	1	52	0.10
20	2	4	2	4	1	50	4.54
21	1	2	1	2	2	46	26.29
22	0	1	1	2	2	48	20.92
23	1	1	1	2	2	46	26.38
24	1	2	0	1	2	47	31.06

25	1	2	1	1	2	46	26.38
26	0	1	0	1	2	49	19.73
27	0	1	1	1	2	48	20.96
28	1	1	0	1	2	47	31.06
29	1	1	1	1	2	46	26.48
30	2	4	2	4	2	45	35.54

†Baseline

Table A3-2 Sensitivity analysis at the SOC level with 30 different combinations of coefficients.

Combination$_i$	**α_1**	**α**	**β_1**	**β**	**γ_{11}**	**positive signals by August 28, 2016 (N)**	**Mean relative detection time (baseline reference: combination 11), days**
1	1	2	1	2	0.5	26	-14.77
2	0	1	1	2	0.5	26	-20.50
3	1	1	1	2	0.5	26	-14.77
4	1	2	0	1	0.5	26	-15.46
5	1	2	1	1	0.5	26	-14.77
6	0	1	0	1	0.5	26	-22.12
7	0	1	1	1	0.5	26	-20.50
8	1	1	0	1	0.5	26	-15.42
9	1	1	1	1	0.5	26	-14.77
10	2	4	2	4	0.5	26	-9.23
11†	**1**	**2**	**1**	**2**	**1**	**26**	**0**
12	0	1	1	2	1	26	-2.12
13	1	1	1	2	1	26	0.00
14	1	2	0	1	1	26	-1.38
15	1	2	1	1	1	26	0.00
16	0	1	0	1	1	26	-8.15
17	0	1	1	1	1	26	-2.12
18	1	1	0	1	1	26	-1.38
19	1	1	1	1	1	26	0.00
20	2	4	2	4	1	26	2.65
21	1	2	1	2	2	22	2.26
22	0	1	1	2	2	23	8.96
23	1	1	1	2	2	22	2.35
24	1	2	0	1	2	22	1.39
25	1	2	1	1	2	22	2.35
26	0	1	0	1	2	23	8.13
27	0	1	1	1	2	23	8.96
28	1	1	0	1	2	22	1.39
29	1	1	1	1	2	22	2.35
30	2	4	2	4	2	22	3.61

†Baseline

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The Editors of *Pharmacoepidemiology and Drug Safety* recognize that most studies in pharmacoepidemiology cost money and thus pose a potential conflict of interest. As a conflict of interest may affect the assessment or judgment of an author, we ask that **all** authors (not just the Corresponding Author) complete the following form.

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1. Some or all of the data that were used in this study were provided by a company with a vested interest in the product being studied. No

2. The sponsor of this project had the right of commenting but the authors retained the right to accept or reject comments or suggestions. No

3. The sponsor of this project had the right of final editing and/or approval of the manuscript submitted. No

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Corresponding author and Co-authors:
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4. I, my spouse, or one of my dependent children is an employee of a company whose product is being studied. No

5. I, my spouse, or one of my dependent children has significant equity interest (>USD 10,000) in the company that owns the product being studied. No

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- been paid as a consultant (or in a similar capacity) by a company with a vested interest in the product being studied, on issues related to the product being studied; No
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7. A company whose product is being studied has provided funding to support the work on this project. No

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8. Manuscript title (first six words are sufficient)

Signal detection on a patient cohort: a disproportionality analysis of the ANRS CO22 HEPATHER cohort to identify associations between direct acting antivirals and adverse events in patients with HCV chronic infection

9. Author's full name (a separate form must be submitted for each author)

Imane AMRI

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Oral presentations, boards, invitatinons for national and international meetings, sub investigator for therapeutic trials: BMS, Gilead, MSD, Roche, Janssen and Abbvie.

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SP received honoraria for his participation in advisory boards from Abbvie, Janssen, MSD, BMS, Gilead and Novartis

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the ANRS CO22 HEPATHER cohort study is sponsored by ANRS - the French Agency on AIDS and Viral Hepatitis - a public agency. ANRS has received fundings from BMS, Gilead, Abbvie, Janssen, MSD to support this cohort study (but not specifically in relation with this paper).

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