

REVIEW ARTICLE

## Barriers to care and treatment for patients with chronic viral hepatitis in Europe: a systematic review

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### Keywords

barriers – hepatitis B – hepatitis C – treatment

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Received 29 January 2014

Accepted 17 April 2014

DOI:10.1111/liv.12565

### Abstract

**Background & Aims:** Despite the availability of effective therapies for hepatitis B (HBV) and C virus (HCV), only a minority of these patients receive treatment. We systematically reviewed published data on barriers to management for chronic HBV/HCV patients in Europe. **Methods:** Literature search to identify studies including adult patients with chronic HBV/HCV infection from European countries and data on barriers to treatment. **Results:** Twenty-five studies including 6253 chronic HBV and 19 014 HCV patients were identified, of which only two were from Eastern Europe. The mean rate of no treatment in HBV patients was 42% being higher in North-Western European countries than Italy (56% vs. 39%,  $P < 0.001$ ). Immigrants represented the most common barrier to HBV treatment. The mean rate of no treatment in HCV RNA-positive patients was 57%, being highest in Romania (89%), intermediate in France (79%) and lower though still high in other European countries (52%,  $P < 0.001$ ). The predominant barriers to HCV treatment were lack of financial resources in Romania and direct/indirect limitations of interferon-alfa and/or parenteral drug and alcohol abuse in other countries. The mean rate of no treatment was highest in HCV RNA-positive parenteral drug users (72%) and intermediate in those with HCV–HIV co-infection (64%). **Conclusions:** A substantial proportion of diagnosed chronic HBV and the majority of diagnosed HCV patients remain untreated. The rates and most importantly the reasons of barriers to treatment in chronic HBV/HCV patients vary widely among European countries supporting the need for country-specific national strategies, resource allocation and implementation of global management policies.

Hepatitis B (HBV) and C viruses (HCV) are leading causes of chronic liver disease worldwide and responsible for 1.2–1.5 million deaths annually (1, 2). In particular in Europe, according to the estimations of the European Region of the World Health Organization, there are approximately 14 and 9 million people chronically infected with HBV and HCV and around 36 000 and 86 000 related deaths each year, respectively, with the number of deaths reported to be increasing (3).

Over the last 15 years, the efficacy of the therapeutic options for chronic HBV and HCV infections has dramatically improved. Practically all chronic HBV infection can now achieve at least on-therapy virological remission which is associated with improved liver histology and often even reversion of pre-existing histological cirrhosis, reduction in need for liver transplantation and eventually improved survival (4, 5). In patients with chronic HCV infection, sustained virological response,

which is equivalent to viral eradication and has been shown to improve survival (6, 7), can be currently achieved in the majority of cases without contraindication for interferon-alfa-based therapies (8, 9), while emerging and future treatment options are expected to further improve the sustained virological response rates to over 90–95% extending the treatment indications and offering chances for cure in all chronic HCV patients (10, 11).

Despite the availability of effective therapies, however, the morbidity and mortality from both chronic hepatitis B and C are increasing (12, 13), as only a small proportion of such patients actually receive treatment (14–16). Barriers to care and treatment can arise at multiple levels, which often differ widely among countries, even within Europe (3, 14–16).

The aim of this systematic review was to collect all the published data on the barriers to appropriate

management for patients with chronic HBV or HCV infection in the European countries.

### Search strategy and selection criteria

We searched PubMed from January 2000 to March 2013 using the search terms 'hepatitis' AND 'barriers'. In addition, we manually searched the reference lists of all relevant review articles and of the retrieved original articles for additional studies. Studies were analysed if they were published as full articles, included adult patients with chronic hepatitis B (including co-infection with hepatitis D) and/or chronic hepatitis C virus infection (including co-infection with HIV), provided data on barriers to care and treatment and reported data for European countries.

### Search methods, data collection and analysis

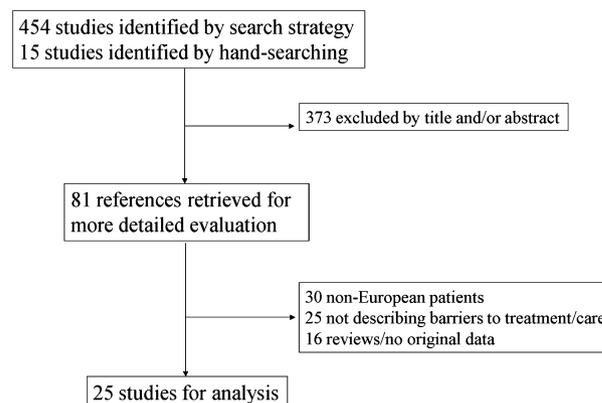
The references were independently searched by two researchers (ET, SH) for identification of relevant studies. Likewise, data were independently extracted by the same researchers and entered into an Excel file created for this purpose. Selected articles and extracted data were compared for concordance and any discrepancies were discussed and if needed arbitrated by a third reviewer (GP). The following data were extracted: country of study's origin, year of publication, study design, primary study question, patients' number, aetiology of liver disease, detailed patients' epidemiological, socio-economic, laboratory and virological characteristics, and detailed data on antiviral treatment with particular attention to reasons of no treatment.

### Studies flow

Overall, 469 studies were identified, of which 454 were captured by the search strategy and 15 by hand searching. The inclusion criteria were fulfilled in 25 studies (17–41), from which data were extracted and analysed. The studies flow is shown in Figure 1.

### Studies characteristics

Included studies were heterogeneous, with a variety of designs and aims. The vast majority of studies were from Western Europe (22/25 or 88%) (17–24, 27–29, 31–41), of which six were from France (20, 22, 27, 31, 35, 41) and six from Italy (17, 18, 36–39). Two studies were from Eastern Europe (25, 26) and one pan-European (30). There were eight single centre (17, 19, 23–25, 28, 29, 41), 13 multicentre (18, 20–22, 30–35, 37–39), two regional (27, 36) and two nationwide studies (26, 40). Four studies reported the results of surveys (20, 29, 32, 34), of which one was on primary care physicians (32), two on secondary care physicians (20, 34) and one on patients (29). Six studies reported on patients with chronic HBV infection (18, 29, 35, 36, 38, 40) and 19 on



**Fig. 1.** Number of studies identified and eventually included in the systematic review.

patients with chronic HCV infection (17, 19–28, 30–34, 37, 39, 41). Of the 19 studies on patients with chronic HCV infection, six were on parenteral drug users (PDU) (19, 21, 25, 28, 37, 41) and four on HCV–HIV co-infection (17, 20, 24, 30). The main characteristics of the 25 included studies are shown in Table 1.

### Studies on chronic HBV infection

There were six studies including a total of 6253 patients with chronic HBV infection (18, 29, 35, 36, 38, 40). All of them were conducted in Western European countries (three of them in Italy). The mean age of included patients ranged between 40 and 50 years, whereas 65–75% of them were males. All studies reported on the number of treated and untreated patients, but only two studies reported partially on the reasons of no treatment (38, 40). Treatment data of these six studies are summarized in Table 2.

The rates of no treatment ranged from 37 to 66% with a mean rate of 42% (2647/6253). The mean rates of no treatment were significantly higher in the three studies from North-Western European countries [Germany, France, United Kingdom (UK)] (29, 35, 40) than in the three studies from Italy (18, 36, 38) (728/1305 or 56% vs. 1919/4948 or 39%,  $P < 0.001$ ). Unfortunately, information on treatment indications was provided in only two of the six studies (38, 40). In these two studies, treatment was reported to have been initiated in 50% and 100% of patients who had appropriate indications for treatment according to the treating physicians, while unnecessary treatment seem to have been also initiated in a small proportion of patients in both studies.

The information on the reported causes of no treatment varied among the studies. One Italian study including more than 3000 patients reported that immigrant status and alcohol abuse were independently associated with no treatment (18). In another Italian study, 1386 patients with chronic HBV infection were followed up for 6 months at 21 referral centres. During this study

**Table 1.** Main characteristics of the 25 included studies

Study, first author (Ref)	Country	Study design	Type of centre	Study period	Liver disease	Patients, <i>n</i>	Primary study question
Angeli (17)	Italy	Single centre R, C study	Academic	2000–2010	HCV–HIV co-infection	545	To evaluate the rate of recruitment and eligibility to anti-HCV therapy in a cohort of HIV/HCV co-infected patients
Antonucci (18)	Italy	Multicentre R CS study	General Hospitals (24% academic)	2008	HBV	3305	To describe factors associated with the access to antiviral treatment in a cohort of chronic HBV patients
Backmund (19)	Germany	P, CS study	General Hospital	1997–1998	HCV	161	To assess treatment uptake and response in PDU with chronic HCV infection
Cacoub (20)	France	Multicentre CS survey	Tertiary	2004, 2006	HCV–HIV co-infection	416	To analyse the barriers to HCV treatment in HIV–HCV co-infected patients in France in 2006 and to compare the results with those obtained in the 2004 survey
Cullen (21)	Ireland	Multicentre CS study	Primary care	2002	HCV	117	To describe HCV infection care processes among injecting drug users attending general practice
Delarocque-Astagneau (22)	France	Two CS surveys at different timepoints	Public or private laboratories, reference centres	1994, 2004	HCV	3902	To report temporal trends in prevalence, testing, epidemiological and clinical characteristics of patients at first referral from 1994 to 2006 in France in the light of the French national hepatitis C prevention and control programme
Delwaide (23)	Belgium	Single centre CS study	Academic	1996–2003	HCV	299	To investigate the antiviral treatment rate and the reasons for non-treatment in a population of HCV-infected patients
Ena (24)	Spain	Single centre CS study	Regional Hospital	2009	HCV–HIV co-infection	134	To describe the characteristics and assess treatment barriers of HIV-infected patients with hepatitis C virus infection
Gazdag (25)	Hungary	Single centre R, C study	Tertiary	2006–2008	HCV	123	To assess the barriers of access to antiviral treatment of HCV-infected PDU

Table 1 (continued)

Study, first author (Ref)	Country	Study design	Type of centre	Study period	Liver disease	Patients, <i>n</i>	Primary study question
Gheorghe (26)	Romania	Nationwide CS survey	–	2002–2007	HCV	177	To analyse the quality/quantity of therapy delivery; to determine the proportion of patients being annually/ever treated; to identify barriers against HCV therapy in Romania
Hatem (27)	France	Regional R, CS study	Laboratories	2001	HCV	1251	To study access to healthcare of HCV patients and identify factors associated with onset of antiviral treatment
Lindenburg (28)	Holland	Observational C study	Academic	2005–2007	HCV	340	To assess HCV screening, treatment uptake and outcomes for all drug users in the Amsterdam Cohort Study at the Public Health Service Amsterdam
Lutgehetmann (29)	Germany	Single centre P survey	Academic	2006–2007	HBV	201	To test knowledge about HBV treatment adherence
Mocroft (30)	All Europe (EuroSIDA)	P, CS study	Multiple	1996–2004	HCV–HIV co-infection	2356	To describe the temporal changes in HCV treatment across Europe in HCV-positive HIV patients from EuroSIDA
Monnet (31)	France	CS population study	General practice and hepatologists	1994–2001	HCV	1938	To compare detection rates in urban and rural areas by geographical access to general practitioner/specialist care; to analyse the influence of urban–rural residency on diagnosis and epidemiological–clinical characteristics
Moussalli (41)	France	Single centre CS study	Primary care	2002–2004	HCV	417	To assess HCV management in PDU after implementation of onsite multidisciplinary team and non-invasive fibrosis assessment
Overbeck (32)	Switzerland	Primary care CS survey	Primary care	2005–2006	HCV	4626	To identify potentially modifiable barriers to anti-HCV treatment

Table 1 (continued)

Study, first author (Ref)	Country	Study design	Type of centre	Study period	Liver disease	Patients, <i>n</i>	Primary study question
Papadopoulos (33)	Greece	R, C study in two tertiary centres	Tertiary	2002–2010	HCV	1146	To examine the overall treatment rate and the reasons for no treatment in chronic HCV patients visiting tertiary liver centres in Greece
Parkes (34)	UK	CS questionnaire survey	Tertiary	2003	HCV		To establish baseline information about current practice and service configuration upon which to plan the future services for patients with chronic hepatitis C
Sene (35)	France	Multicentre P, CS study	Tertiary	2003	HBV	406	To describe the main characteristics of HBV chronic infection in HIV-infected patients compared to HIV-negative patients
Stroffolini (36)	Italy	Multicentre CS survey	Tertiary	2006–2007	HBV	1396	To provide an accurate picture of HBV chronic liver disease in Italy and identify differences from previous studies
Stroffolini (39)	Italy	Multicentre P, CS study	Tertiary	2009	HCV	608	To assess the treatment rate and the causes for non-treatment in HCV RNA-positive subjects referred to various liver units in Southern Italy
Stroffolini (38)	Italy	P, CS study	Tertiary	2010	HBV	247	To evaluate the current practice of HBV therapies in the real world in Southern Italy
Stroffolini (37)	Italy	Multicentre, observational, CS study	Rehabilitation	2009	HCV	543	To assess the prevalence and characteristics of HCV positivity among a representative national sample of drug addicts
Tedder (40)	UK	Nationwide CS study	Tertiary	2007–2009	HBV	698	To characterize persistent HBV infection in patients at referral liver centres and compare clinical practice to the guidelines for best practice available at the time

C, cohort; CS, cross-sectional; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; P, prospective; PDU, parenteral drug users; R, retrospective.

**Table 2.** Treatment data in six studies of patients with chronic hepatitis B virus infection (the type of treatment was not available for all patients)

Study, first author (Ref)	Patients, <i>n</i>	Age (years)	Immigrants, <i>n</i> (%)	Untreated, <i>n</i> (%)	Patients who underwent liver biopsy, <i>n</i> (%)	No treatment indication, <i>n</i>	PegIFNa, <i>n</i>	Nucleos(t)ide analogues, <i>n</i>
Antonucci (18)	3305	37 (median)	730 (22)	1214 (37)	NA	NA	240	1169 (LAM: 271, Other: 898)
Lutgehetmann (29)	201	42 ± 12	NA	115 (57)	NA	NA	1	49 (LAM: 36)
Sene (35)	406	41 ± 12	NA	151 (37)	169 (42)	NA	82*	324 (LAM: 211, ADV: 54, TDF: 59)
Stroffolini† (38)	247	49 ± 14	NA	153 (62)	NA	108	26	68
Stroffolini (36)	1396	50 ± 13	104 (7)	552 (40)	NA	NA	NA	387
Tedder‡ (40)	698	43 (median)	553 (79)	462 (66)	289 (41)	472	11	225 (LAM: 72, ETV: 15, TDF: 16)

ADV, adefovir; ETV, entecavir; LAM, lamivudine; NA, not available; PegIFNa, pegylated interferon-alfa; TDF, tenofovir.

\*66/82 patients were treated with standard interferon-alfa.

†9/108 patients labelled as inactive carriers received treatment, while 51/103 patients labelled as chronic hepatitis B never receive treatment (38).

‡72 patients (including 12 cirrhotics) did not receive treatment although they had HBV DNA > 2000 IU/ml and ALT > ULN (40).

period, there were 132 incident cases of HBV infection. Although no specific treatment data were provided, immigrants with HBV were younger than Italian patients, were more often incident cases and remained more often untreated (36). The third Italian study assessed the current practice of chronic HBV treatment in Southern Italy in a cohort of 247 patients; nine inactive carriers received unnecessary treatment, while 51 of 103 patients with chronic hepatitis B did not receive treatment (38). A French study compared HIV seropositive vs. seronegative patients with HBV infection; HBV–HIV co-infected patients received antiviral treatment more often and had liver biopsy less frequently compared to HBV mono-infected patients (35). One study from Germany reported the results of a patient survey, in a population that mainly consisted of Eastern European immigrants, of which 50% had only basic education or were illiterate (29); 80% of the patients had language problems and 15% had poor knowledge of HBV infection. Finally, a UK nationwide study of patients from liver referral centres alarmingly reported that only 28% of patients on treatment were on one of the recommended first-line therapies, while testing for HDV, HIV and HCV co-infections was low (40).

### Studies on chronic HCV infection

Data on HCV varied depending on the included patient group(s) (unselected HCV patients, HCV in PDU, HCV–HIV co-infection) and perhaps the country where the study was conducted.

#### HCV in unselected patients

Two French studies including 5840 HCV unselected patients as well as one survey in the UK including 344

consultants with an estimated number of 23 000 managed HCV patients aimed to determine the barriers for HCV diagnosis. In the first French study, HCV detection rates were lower in rural areas and were depended on the distance from the nearest practitioner (31). The second French study analysed trends in prevalence and testing of patients with HCV between 1994 and 2006 (22). Of new referrals in 2001, 41% were diagnosed because of systemic screening. The anti-HCV prevalence and HCV RNA positivity in ages 20–59 years decreased from 1.05 and 81% respectively in 1994 to 0.71% and 57% in 2004, while patients' awareness of their HCV status increased from 24 to 56% during the same period. Finally, the British survey among hepatologists, infectious disease specialists and gastroenterologists on the practice and service configuration in 2006 reported a significant variation between comprehensive service providers, including unit size, eligibility criteria for treatment and drug regimes (34). Key barriers to quality of care identified were staffing capacity, funding of treatment and patient non-attendance.

Six studies specifically reported rates and reasons of no treatment in unselected anti-HCV-positive patients (23, 26, 27, 32, 33, 39) (Table 3). One study was conducted in Belgium (23), one in France (27), one in Switzerland (32), one in Italy (39), one in Greece (33) and one in Romania (26). They included 8355 anti-HCV-positive patients, of whom 4760 (57%) remained untreated. Most of the 8107 anti-HCV-positive patients included in these studies were tested for serum HCV RNA (93% or 7798/8355) and found to have detectable viremia (98% or 7681/7798). Thus, the rate of no treatment in patients with chronic HCV infection defined by detectable serum HCV RNA was also 57% (4373/7681). The rate of no treatment among HCV RNA-positive patients was highest in Romania (89% or 157/177),

**Table 3.** Rates and reasons of no treatment in 16 studies of patients with chronic hepatitis C virus (HCV) infection

Study, first author year (Ref)	Anti-HCV (+), n	HCV RNA (+), n	Untreated, n/N	Treatment contraindication	Patient refusal for treatment	Main treatment barriers identified (reasons of no treatment)
<b>HCV in unselected patients</b>						
Delwaide (23)	299	299	176/299	60 (34%)	29 (16%)	Lost to follow-up: 44 (25%), normal ALT: 43 (24%)
Gheorghe (26)	425	177/177	157/177	22 (12%)	12 (8%)	Unaware of diagnosis: 27 (15%), Lost to follow-up: 26 (15%), No referral: 25 (14%), Treatment recommended but not started: 25 (14%), Lack of local funds: 25 (14%)
Hatem (27)	1251	1251	989/1251	160 (16%)	75 (8%)	Normal ALT: 334 (34%), lost to follow-up: 295 (24%), minimal–mild fibrosis: 100 (10%), old age: 32 (3%), active PDU or alcohol abuse: 103 (10%)
Overbeck (32)	4626	4622	2566/4626	233 (9%) (absolute: 49)	295 (11%)	Specialist's advice: 313 (12%), normal ALT: 284 (11%), old age: 125 (5%), lost to follow-up: 48 (2%), minimal–mild fibrosis: 35 (1%), difficult genotype: 18 (1%)
Papadopoulos (33)	1146	798/837	518/1146	30 (6%)	14 (3%)	Lost to follow-up: 435 (84%), HCV RNA negative: 39 (8%)
Stroffolini (39)	608	534	354/608	158 (45%) (absolute: 90)	37 (10%)	Old age (>65 years): 176 (50%), normal ALT: 14%
<b>HCV in PDU</b>						
Backmund (19)	161	106	56/106	0	50 (89%)	Patient's refusal: 50 (89%), HIV–HCV co-infection: 6 (11%)
Cullen (21)	104	29/36	33/36	NA	NA	Hepatology referral discussed: 44 (43%), Referral: 31 (30%), Liver clinic: 24 (23%)
Gazdag (25)	123	111	72/111	23 (32%) (absolute: 3)	0	Mild disease: 22 (31%), ongoing PDU: 19 (26%)
Lindenburg (28)	340	249	192/249	14 (7%)	18 (9%)	HCV–HIV co-infection: 53 (28%)
Moussalli (41)	417	337	250/337	NA	NA	Not reported
Stroffolini (37)	347	237	170/237	NA	NA	Not reported
<b>HCV–HIV co-infection</b>						
Angeli (17)	421	373	322/373	99 (31%)	57 (18%)	PDU, low CD <sub>4</sub> count, higher ALT, HCV genotype 1 or 4, >6 anti-HIV regimens
Cacoub (20)	416	396	162/396	43 (27%)	34 (21%)	Lack of liver biopsy, physicians' conviction of poor compliance, treatment deemed questionable
Ena (24)	134	113	77/113	22 (29%)	18 (23%)	Low education, civil status, no anti-HIV therapy, detectable HIV RNA, lack of funds: 15
Mocroft (30)	2356	NA	2176/2356	NA	NA	CD <sub>4</sub> count, European region (lower in Eastern Europe)

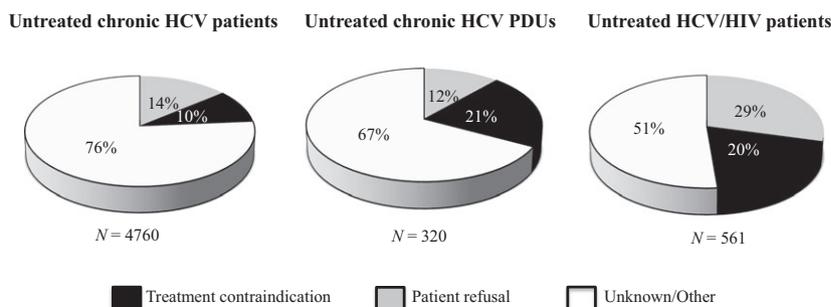
HIV, human immunodeficiency virus; NA, not available; PDU, parenteral drug use.

intermediate in France (79% or 989/1251) and lower though still high in the other four countries (52% or 3227/6253,  $P < 0.001$ ).

The main reasons of no treatment varied widely among the six studies. They included medical contraindications to interferon-alfa-based therapy (6–45%), non-adherence or loss to follow-up (2–84%) and patients' refusal for interferon-alfa-based therapy (3–16%) in all six studies (23, 26, 27, 32, 33, 39), normal ALT (11–34%) in four studies (23, 27, 32, 39), older age (usually >65 years) at a low rate (3–5%) in two (27, 32) and high rate (50%) in one study (39), non-advanced fibrosis at liver biopsy (1–10%) in two studies (27, 32) and active PDU or alcohol abuse (7–10%) in two studies

(27, 32) (Fig. 2). The lack of funds was the main reason for no treatment in Romania, where only 4% of the chronic HCV cases were reported to have received treatment until 2009 (26).

Most studies provided additional information on the factors that were associated with the probability of treatment initiation. In the French study that evaluated treatment data up to 2001, male gender, age between 35 and 64 years, geographical area of residence, specialty of treating physician (gastroenterologist > general practitioner > other specialties), elevated ALT and no alcohol consumption were independently associated with initiation of antiviral therapy (27). The Swiss study reported that 17% of primary care practices did not fol-



**Fig. 2.** Mean rates of main barriers to treatment among untreated patients with chronic hepatitis C virus (HCV) infection, parenteral drug users (PDUs) with chronic HCV infection and patients with co-infection of HCV and human immunodeficiency virus (HIV). In studies providing more detailed data, the main 'other' barriers to treatment were normal ALT in 8%, old age in 7%, minimal to mild fibrosis in 3% and active PDU or alcohol abuse in 2% of chronic HCV patients as well as HIV co-infection in 18%, minimal to mild fibrosis in 7% and ongoing PDU in 6% of chronic HCV PDUs.

low the HCV patients in their practice; moreover, in a subsurvey of diagnostic work-up, only 54% of their HCV patients had HCV genotype determined and 77% viral load measured (32). In the Greek study from two tertiary centres in Athens, a substantial proportion (30%) of referred anti-HCV-positive patients were lost to follow-up without completing the initial evaluation process and without being tested for serum HCV RNA (33). PDU, male gender, normal ALT, the treating physician and the period of initial evaluation related to the free availability of virological testing were the factors which independently affected the probability of initial HCV RNA testing, while normal ALT and the treating physician were the main independent factors associated with treatment initiation in HCV RNA-positive patients (33).

#### HCV in PDU

Six studies specifically reported on HCV testing and treatment in a total of 1492 PDU (19, 21, 25, 28, 37, 41) (Table 3). Four were single centre studies from the Netherlands (Amsterdam) (28), France (Paris) (41), Germany (Munich) (19) and Hungary (Budapest) (25) and two multicentre studies from Ireland (21) and Italy (37). The mean patient's age ranged between 32 and 40 years, whereas 65–70% of PDU were males.

The mean rate of no treatment among the anti-HCV-positive PDU was 52% (773/1492) ranging from 32 to 60%. HCV RNA was detected in 1069 (75%) of 1424 PDU tested. Among the HCV RNA-positive cases, the rate of no treatment was 72% (773/1069) being significantly higher than the respective rate in HCV unselected patients (57%,  $P < 0.001$ ).

The main reasons for no treatment as well as their rates varied widely among studies providing relevant data. They included medical contraindications to interferon-alfa-based therapy (7–32%) in two studies (25, 28), patients' refusal for interferon-alfa-based therapy (0%, 9% and 89%) in three studies (19, 25, 28), mild

liver disease (31%) and ongoing PDU (26%) in one study (25) and co-infection with HIV in another study (28%) (28) (Fig. 2). The Irish study reported that a possible hepatology referral was discussed with less than 50% of PDU who found to be anti-HCV positive in primary care (21).

Three studies also evaluated the efficacy of antiviral therapy in PDU using a multidisciplinary team approach in controlled settings and reported encouraging results (19, 28, 41).

#### HCV–HIV co-infected patients

There were four studies including a total of 3327 patients with HCV–HIV co-infection (17, 20, 24, 30) (Table 3). Two were single centre studies from Italy and Spain (17, 24), one was a multicentre study from France (20) and one was a multicentre study from several European countries (30). The mean patients' age ranged between 43 and 47 years and the majority was males (70%).

The mean rate of no treatment among the anti-HCV-positive patients with HIV co-infection was 82% (2737/3327) ranging from 39 to 92%. The rate of no treatment among the anti-HCV positive was significantly higher than the respective rate in HCV unselected patients (57%,  $P < 0.001$ ) or PDU (52%,  $P < 0.001$ ). HCV RNA was detected in 882 (91%) of 971 PDU tested. Among the HCV RNA-positive cases, the rate of no treatment was 64% (561/882) being significantly higher than the respective rate in HCV unselected patients (57%,  $P < 0.001$ ) and significantly lower than the respective rate in PDU (72%,  $P < 0.001$ ).

The rates of medical contraindications to (27–29%) and of patients' refusal for interferon-alfa-based therapy (18–23%) were similar in the three studies which provided such data (17, 20, 24) (Fig. 2). Additional common reasons of no treatment were factors of poor control of HIV infection (low CD<sub>4</sub> count, >6 anti-HIV regimens, no HIV therapy, detectable HIV RNA)

reported in the same three studies (17, 20, 24). Moreover, in the European study from the EuroSIDA cohort, treatment rates were reported to be significantly lower in patients from Eastern compared to Southern European countries (11% vs. 46%) (30).

## Discussion

Despite the increased morbidity and mortality in untreated chronic hepatitis B and C patients and the high efficacy of current antiviral therapies (1–6, 8), only a minority of patients with chronic HBV or HCV infection is considered to be currently treated (3, 14, 15, 42). This was confirmed in our systematic review as approximately 40% (range: 37–66%) of diagnosed chronic HBV and 57% (range: 45–89%) of diagnosed unselected chronic HCV patients were reported to remain untreated. Considering a likely referral bias for most of the studies, the true rate of undertreatment is probably even higher. Studies from USA also report that 50% of diagnosed chronic HBV patients are not usually treated (14, 43), whereas approximately 70% of chronic HCV patients followed in US Academic tertiary centres and up to 95% of chronic HCV patients followed in US primary care settings remain untreated (15).

The undertreatment rates in the total infected patient population are of course much higher than the above rates of no treatment among diagnosed cases, as a large proportion and often the majority of chronic HBV and HCV patients remain undiagnosed (3, 14–16, 42, 44). Thus, the understanding of all barriers to diagnosis and therapy is critical for the improvement of the proportion of treated cases and eventually for the reduction in the negative outcomes of this disease. Unfortunately, there were only three studies (two from France, one from the UK), which provided some data for the barriers to diagnosis exclusively for HCV infection. According to the French studies, the probability of HCV detection was lower for people living in rural areas and far from practitioners (31), while the French national hepatitis C prevention programme initiated in 1999 was found to have a positive impact at the population level through improved prevention, screening and management (22). On the other hand, the findings of the UK survey suggested that all aspects of their healthcare services need to improve if the burden of chronic HCV infection is to be reduced (34).

The rates and factors of no treatment varied widely among European countries. In particular, chronic HBV patients were reported to be treated less frequently in North-Western European countries (Germany, France, UK: 44%) (29, 35, 40) than in Italy (61%) (18, 36, 38), a Southern European country with higher prevalence of and perhaps greater awareness for chronic HBV infection. It should be noted, however, that the characteristics of chronic HBV patients strongly affect the probability of treatment initiation, as anti-HBV therapy should be given only in the patients with appropriate

treatment indications (4, 45). In another recent report (46), the rates of treatment initiation were reported to vary widely among five European countries and, as expected, to be associated with ALT and HBV DNA levels. Therefore, no valid conclusions can be drawn from the comparisons of the treatment rates among all diagnosed patients without knowing the proportion of patients who fulfilled the appropriate treatment indications. In two studies providing such information (38, 40), treatment was reported to have been initiated in 50% and 100% of patients with treatment indications, whereas the respective rate was 67% in a study from the US (14).

There are several reasons of no treatment in patients who fulfil the treatment indications. Immigrants, who are responsible for a substantial proportion of chronic HBV patients in all European countries today (18, 36, 47, 48), may certainly have an impact on this issue. According to two of the studies from Italy, immigrants with access to the national healthcare system and chronic HBV infection had a lower probability of initiating anti-HBV therapy (18, 36). This can be because of poorer information and lower awareness about the risks of chronic hepatitis B among immigrants, several economic issues, such as lack of health insurance and/or fears of missed work obligations, as well as social pressures including language difficulties, lack of social support, social rejection and stigmatization. In one study from Germany, immigrants with access to the national healthcare system and poor compared to those with good German language skills were found to have lower knowledge scores about hepatitis B and lower HBV vaccination rates among their family members (29). Many of the above barriers to treatment can be of course present in any chronic HBV patient everywhere, while barriers to therapy may also arise from the providers, including limited knowledge and awareness among primary care physicians and even difficulties in access and communication with specialists. One of the most critical factors, however, is the overall patient knowledge and awareness about hepatitis B. It is noteworthy that one study from France reported that the usually better informed HBV–HIV co-infected patients received anti-HBV therapy more often than HBV mono-infected patients (35).

The rates of no treatment in diagnosed unselected chronic HCV patients were reported to be highest (89%) in Romania (26). Although there may be several barriers to treatment of chronic HCV infection, lack of financial resources appears to be the predominant barrier in Eastern European countries like Romania (26) where treatment is not reimbursed for the majority of the patients. The cost of treatment was probably a modest barrier in our review, as all available studies evaluated the barriers to treatment in the pegylated interferon and ribavirin era. The importance of cost and funds has recently increased with the introduction of the first-generation protease inhibitors, boceprevir and telaprevir, and is expected to increase further with the anticipated avail-

ability of newer, safer and more effective, but at the same time more expensive direct antiviral agents (DAAs) during the next years. In contrast to Romania, the reasons of no treatment in non-Eastern European countries did not usually include the lack of funds in the pegylated interferon-alfa and ribavirin era, but they are related to direct or indirect limitations of interferon-alfa-based regimens and/or non-hepatic comorbidities including PDU and alcohol abuse in the majority of patients. Limitations to interferon-alfa-based regimens are directly responsible for no treatment in patients with medical contraindications (6–45%) (23, 26, 27, 32, 33, 39), refusing therapy with such regimens (3–16%) (23, 26, 27, 32, 33, 39), of older age (3–50%) (27, 32, 39), but also for a proportion of patient who do not adhere or are lost during follow-up (2–84%) (23, 26, 27, 32, 33, 39) or remain untreated because of normal ALT (11–34%) (23, 27, 32, 39) and/or non-advanced fibrosis at liver biopsy (1–10%) (27, 32). The wide range of the medical contraindication rates should be most probably because of different inclusion and exclusion criteria and eventually different patient characteristics among the included studies. In another recent large study, approximately 17% of HCV patients in the general US population were reported to have at least one contraindication to pegylated interferon-alfa and ribavirin therapy (49).

Active PDU and sometimes alcohol abuse were reported to be the main reasons for no treatment in 7–10% of diagnosed unselected chronic HCV cases in one study from France and one from Switzerland (27, 32). However, the mean rate of no treatment in HCV RNA-positive PDU was significantly higher than that in unselected patient populations and PDU represented the group with the higher rates of non-compliance to follow-up at any stage of management (33). Given that PDU represent a significant and increasing proportion of chronic HCV patients in all European countries (47, 50), their management is becoming extremely relevant not only for decreasing the future burden of disease but also for limiting the continuing spread of HCV infection (51, 52). The treatment rates in PDU are expected to improve in the forthcoming interferon-free era with the availability of oral DAAs that will be much better tolerated, without major adverse events, much easier to apply and will require less strict patient's follow-up (10, 11, 53).

The treatment rates in HCV–HIV co-infected patients seem to be between those in unselected chronic HCV patients and PDU. Given that the main reasons of no treatment in this setting are medical contraindications to (27–29%) and patients' refusal for interferon-alfa-based therapy (18–23%) (17, 20, 24), the treatment rates are also expected to improve with the availability of new DAAs without important interactions with anti-HIV agents (10, 11).

Time of study recruitment is another factor that might potentially influence diagnosis and treatment rates in patients with chronic viral hepatitis. We attempted to discern different rates of diagnosis and

treatment between studies based on their recruitment period, however because of the large heterogeneity no such patterns were clearly visible. However, there was a clear increase in diagnosis (22) and treatment rates over time (17, 20, 30, 33) within studies that extended over a prolonged period or evaluated at different time points.

Our review has several limitations, which are inherent to these types of systematic reviews. The included studies are rather heterogenous, populations-based studies are missing and therefore the extent of referral bias is not clear and additional relevant studies might have been excluded if they were written in the respective local language and/or published in local journal not included in the PubMed database. However, most of these limitations probably result in underestimation than overestimation of the no treatment rates in both chronic HBV and HCV patients.

In conclusion, although the rates and reasons of barriers to treatment in patients with chronic viral hepatitis vary widely among European countries, it is evident that a substantial proportion of diagnosed chronic HBV patients and the majority of diagnosed chronic HCV patients remain untreated. As a large proportion of such patients remain undiagnosed because of the uniform lack of screening strategies in most European countries, the overall proportion of treated patients is remarkably low. The systematic review and awareness of the multiple barriers to appropriate management including diagnosis, evaluation and delivery of therapy in patients with chronic hepatitis B and C are necessary for the wider implementation of therapy and eventually for the better global management of these progressive chronic liver diseases. Given the high efficacy of antiviral treatment for both chronic hepatitis B and C, public health and state authorities should recognize the importance of chronic viral hepatitis epidemic, develop country-specific national strategies and allocate enough resources for the implementation of prevention, effective screening and global management policies.

### Acknowledgements

The project was financially supported by the Hepatitis B & C Public Policy Association and non-financially endorsed by the European Association for the Study of Liver and the European Liver Patient Association.

*Conflict of interest:* George Papatheodoridis has served as advisor and/or lecturer for Abbvie, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, Glaxo-Smith Klein, Janssen, Merck, Novartis, Roche and has received research grants from Abbvie, Bristol-Myers Squibb, Gilead, Janssen, Roche.

Emmanuel Tsochatzis has nothing to declare.

Svenja Hardtke has nothing to declare.

Heiner Wedemeyer has received honoraria for consulting or speaking from Abbott, Abbvie, Achillon, Bristol-Myers Squibb, Gilead, Glaxo-Smith Klein, Roche,

Roche Diagnostics, Merck, Novartis, Siemens, Transgene and has received research grants from Bristol-Myers Squibb, Merck, Novartis, Roche.

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