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### Article

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# Hepatitis C Virus Infection Epidemiology among People Who Inject Drugs in Europe: A Systematic Review of Data for Scaling Up Treatment and Prevention

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## Abstract

**Background:** People who inject drugs (PWID) are a key population affected by hepatitis C virus (HCV). Treatment options are improving and may enhance prevention; however access for PWID may be poor. The availability in the literature of information on seven main topic areas (incidence, chronicity, genotypes, HIV co-infection, diagnosis and treatment uptake, and burden of disease) to guide HCV treatment and prevention scale-up for PWID in the 27 countries of the European Union is systematically reviewed.

**Methods and Findings:** We searched MEDLINE, EMBASE and Cochrane Library for publications between 1 January 2000 and 31 December 2012, with a search strategy of general keywords regarding viral hepatitis, substance abuse and geographic scope, as well as topic-specific keywords. Additional articles were found through structured email consultations with a large European expert network. Data availability was highly variable and important limitations existed in comparability and representativeness. Nine of 27 countries had data on HCV incidence among PWID, which was often high (2.7–66/100 person-years, median 13, Interquartile range (IQR) 8.7–28). Most common HCV genotypes were G1 and G3; however, G4 may be increasing, while the proportion of traditionally ‘difficult to treat’ genotypes (G1+G4) showed large variation (median 53, IQR 43–62). Twelve countries reported on HCV chronicity (median 72, IQR 64–81) and 22 on HIV prevalence in HCV-infected PWID (median 3.9%, IQR 0.2–28). Undiagnosed infection, assessed in five countries, was high (median 49%, IQR 38–64), while of those diagnosed, the proportion entering treatment was low (median 9.5%, IQR 3.5–15). Burden of disease, where assessed, was high and will rise in the next decade.

**Conclusion:** Key data on HCV epidemiology, care and disease burden among PWID in Europe are sparse but suggest many undiagnosed infections and poor treatment uptake. Stronger efforts are needed to improve data availability to guide an increase in HCV treatment among PWID.

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## Introduction

Chronic infection with the hepatitis C virus (HCV) affects about 160 million people worldwide [1,2]. In developed countries,

iatrogenic transmission of this blood-borne virus has been substantially reduced and people who inject drugs (PWID), or those who have done so in the past, are now the main group affected [3–6].

HCV infection is a serious public health problem as chronically infected individuals are at risk for long-term sequelae, including liver cirrhosis and hepatocellular carcinoma [7]. Indeed, in Europe, HCV is a leading cause of cirrhosis and primary liver cancer [8]. Since 2001, effective treatment with pegylated interferon and ribavirin has been available. In recent years, there have been advances in treatment with the development of direct acting antiviral (DAA) therapy [9]. PWID in many countries still have limited access to HCV treatment, despite multiple studies providing evidence that this population can be successfully treated [10–17] only 1–6% of HCV-infected current and former PWID in the United States, Canada, and Australia were treated [14–16,18–20]. The low uptake of treatment among PWID is due to both physician and patient-associated factors. Firstly, physicians' concerns about adherence, other co-morbidities including HIV co-infection, treatment side-effects and the potential for re-infection may lead to treatment being withheld [5,10,21,22]. Secondly, poverty, psychiatric co-morbidities, poor social support and stigma are common among PWID and may result in HCV treatment not being viewed as a priority for them [23–25]. Other barriers may relate to educational level, problems with accessing diagnostic tests (e.g. in non-urban regions or when access to primary care is difficult), and entering specialist referral pathways [26,27].

Treatment is likely to have a synergistic impact on HCV prevention efforts. Modelling studies suggest that antiviral treatment could play an important, and cost-effective, role in preventing HCV in PWID by reducing the number at risk of transmitting HCV [28–31].

In Europe, many countries have implemented harm reduction programmes [32,33] as well as health insurance systems to cover treatment costs of PWID (several including DAA). Therefore, access to HCV treatment should be feasible [34,35] and recent European clinical guidelines state it must be considered for PWID [36]. Although national treatment guidelines have varied substantially and have often been highly restrictive with regard to PWID [37,38], the experience in some European countries has shown that it is possible to expand HCV diagnosis, prevention and treatment of PWID [6,34,39–42]. Key data elements to inform HCV treatment scale-up for PWID cover epidemiological data on the prevalence, dynamics and characteristics of the epidemic, estimates of future burden of disease and associated healthcare needs [39,43–47].

To assess data availability for informing a potential future scale up of HCV treatment (including 'treatment for prevention') among PWID in Europe, we performed a systematic review of the literature published between 2000–2012, covering the epidemiology of HCV infection, treatment uptake and estimates of the future burden of disease among PWID in European countries (the EU 27) to complement existing routinely collated data (for example on antibody prevalence and harm reduction service provision as collected by EMCDDA – see Table S2 in Web-appendix S1) [4,44,48,49]. Most of these data might be equally important to informing overall HCV prevention policies. (Further detail on the rationale and importance of these data for HCV treatment and prevention policies is given in Table 1 and Discussion, while Table 2 summarises what this study adds to current knowledge.)

Our overall research question was: 'What data is available in European Union countries to inform a potential scale-up of HCV treatment (for prevention) among PWID?' This was operationalised into five specific questions, covering seven topic areas, all limited to HCV infection among PWID in Europe:

- 1) What is the incidence of infection?
- 2) What proportion of infections become chronic?
- 3) What are infection characteristics, in terms of genotypes and HIV co-infection?
- 4) What proportions of infected are undiagnosed and, of those diagnosed, enter antiviral treatment?
- 5) What estimates exist of the future burden of disease?

## Methods

Seven separate systematic reviews of the literature were performed, covering HCV incidence, chronicity rates, genotype distribution, HIV co-infection, undiagnosed chronic hepatitis C (CHC) cases, HCV treatment uptake, and burden of disease. Study references were identified through searches of MEDLINE, EMBASE and the Cochrane Library databases for articles published in any language between 1 January 2000 and 31 December 2012. A standard search strategy was agreed (Web-appendix S1) with general keywords regarding viral hepatitis, substance abuse and geographic scope (Table 3), as well as seven search strings with topic area-specific keywords. Additional articles were found through structured email consultations with a large European expert network (on substance use and infectious diseases, including viral hepatitis (see Acknowledgments)) covering each of the 27 countries (Table 4). The protocol was consistent with the PRISMA criteria [58]. Search results per topic area were screened for relevance independently by two researchers on the basis of title and abstract and results compared, retaining articles in case of doubt. Duplicates between the three databases were removed. The remaining articles were retrieved and evaluated independently by two researchers on the basis of the full article text using agreed selection criteria across all seven topic areas. Studies were included for the 27 EU member states. Non-English articles were evaluated with the help of native speakers, country experts and online translation services (Google Translate and BabelFish) and if necessary and possible by contacting the authors. Additional inclusion criteria were reporting data collected since 1990 (except for Burden of disease, due to the long-term perspective of modelling projections). Quality criteria for inclusion (Web-appendix S1) were to have a clearly defined study population of PWID only (having ever injected drugs) or data provided for PWID separately, consistency and clarity of the data reported and an unselected sample of PWID with regard to gender or HBV/HIV co-infection (except for Burden of disease, where due to the small number of studies found, two studies based on HIV co-infected samples were included). Sample sizes below  $n = 10$  were excluded except if they provided the only data for a country on a topic area. For articles excluded in this phase the reasons for this were noted. Data were extracted from the remaining articles into tables for each of the topic areas (Tables S3–S10 in Web-appendix S2) and the reference lists were checked for further studies. Multiple publications for one study were consolidated and treated as one entry, in order to maximise information available per study. Data were presented untransformed (Incidence, Burden of disease) or, where possible, pooled weighted prevalences (median, average, range in %) were calculated per country (Chronicity, Genotypes, Co-infection, Diagnosis, Treatment entry) and study type/setting (Incidence, Chronicity, Diagnosis, Treatment entry). Data availability per country was crudely assessed by the number of (out of seven) topic areas where data were available (Table 4). For Genotypes the sum of the proportions of 'difficult to treat' genotypes (1 and 4) [36,59,60] is presented (Table 4). For Co-infection the correlation

**Table 1.** Data items reviewed and their rationale for HCV policy.

1. HCV incidence in PWID: complement available prevalence data by giving an estimate for level of recent infections, a direct measure of (treatment for) prevention effectiveness as well as being important for future burden estimates.
2. Chronicity of infections: allow interpreting antibody prevalence data in terms of current and projected future prevalence of infection and treatment need.
3. Genotypes: predictor of current treatment outcomes, Genotypes 1 and 4 are traditionally hard to treat. New treatments may overcome this problem but are not yet implemented at scale and there are important costs issues.
4. HIV co-infection: predictor of current treatment outcomes and mortality (new treatments may overcome this: see previous point).
5. Undiagnosed proportion: extent of under-diagnosis and linkage to care and treatment.
6. Treatment entry: measure of treatment coverage and accessibility.
7. Burden of disease: projections of future costs to the health care system and wider society, important when considering investment into treatment

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was assessed with HIV prevalence. Overall, a meta-analysis was considered outside the scope of this review, although for one topic (Chronicity) a limited analysis was performed (Web-appendix S3).

## Results

Overall the systematic search retrieved 2,955 references to publications. After removal of duplicates and clearly irrelevant references, we screened 1,552 references on the basis of title and abstract. 528 articles were retrieved and obtained in full text, of which 144 were included in the quantitative synthesis. The step-wise description of selection and inclusion of studies is depicted in a flowchart in Figure 1. Followed below are detailed study questions, main findings and results for each of the seven topic areas reviewed.

### Incidence

**Study questions.** What is the incidence of HCV infection among PWID in Europe and how has this been measured? How does incidence vary between countries?

**Main findings.** Data are sparse across Europe and are not easily comparable. The data suggests that incidence is highly variable in the populations studied (Figure 2).

**Studies included.** Studies were included that had directly measured incidence of hepatitis C infection in PWID, by using one of the following approaches: 1) a cohort or follow-up study 2) detection of HCV RNA in the absence of anti-HCV in a cross-sectional study 3) assessing anti-HCV avidity in a cross-sectional study. Studies that had indirectly estimated incidence from HCV prevalence data, for example using force of infection calculations, were excluded. 27 studies, from nine countries, reported the incidence of primary HCV infection (Czech Republic, Denmark,

Ireland, Finland, France, Netherlands, Sweden, Spain, UK; Table 4). Four countries had undertaken more than one (Czech Republic, Ireland, Sweden, UK); most studies had been undertaken in UK (n = 16, 59%). Three studies measured re-infection (Germany, Netherlands, UK; Table 4) (Table S3 in Web-appendix S2). [61–89].

**Study design.** Incidence of primary HCV infection had been measured in 17 follow-up studies, and in ten cross-sectional studies (nine used HCV RNA in the absence of anti-HCV and one anti-HCV avidity to estimate HCV incidence).

**Population.** For primary HCV infection, three studies recruited PWID from community settings, 19 through health services (including needle and syringe programmes) and three from both settings. Two were in custodial settings. The re-infection studies were in clinical settings.

**Findings.** The number of PWID at risk of primary infection in studies undertaken outside of custodial settings ranged from 27 (Spain, ‘new PWID’: injecting less than 2 years) [68] to 2,532 (UK, ‘ever PWID’: having ever injected drugs) [82]; (median:168 people; mean 424). The measured incidence of primary HCV infection varied from 2.7–3.2/100PY in one UK study (ever PWID) [82] to 66/100PY in a study from Ireland (ever PWID) [66]. The median incidence was 13/100PY (Interquartile range (IQR) 8.7–28, mean 19/100PY). In the eleven studies only including current/recent PWID the incidence was higher than in the remaining studies (median 26/100PY IQR 9.4–35 vs. median 12/100PY IQR 9.0–16), and ranged from 5.2/100PY years to 42/100PY (both UK) [74,85]. The two studies in custodial settings were small, with only eight (25/100PY, Denmark, ever PWID) [86] and 69 (12/100PY, UK, ever PWID) [76,87] participants. The three small studies of HCV re-infection reported incidences of

**Table 2.** What is known and what this study adds.

1. More specialised reviews have been carried out [43,50–56], but no systematic review has provided a comprehensive overview [57], across multiple topic areas, of available data to inform hepatitis C treatment scale-up (including prevention) among PWID in a large region of the world.
2. Our review found that the majority of available studies published between 2000–2012 focused on HCV prevalence, treatment and on the genotype characterisation of patients with HCV, while very few investigated the burden of disease. In some of the topic areas data was scarce, in particular for recent years (2006–2012).
3. Incidence of HCV infection in PWID in the EU varies greatly, but can be as high as 66/100 person years (PY). Chronicity rates vary both above and under the expected 75% [56]. Genotypes 1 and 3 predominate among PWID, but 4 appears to be increasing, while the proportion of ‘difficult to treat’ genotypes (1+4) shows large variation (17–91%, median 53%). The prevalence of HIV co-infection in HCV-infected PWID varies widely (0–70%, median 3.9%), correlating closely with but generally higher than overall HIV prevalence among PWIDs.
4. Half of the chronically infected PWID were unaware of their infection, and, of those diagnosed, only one in ten entered treatment for Hepatitis C.
5. This study highlights major information gaps regarding epidemiology, diagnosis, treatment entry and burden of disease of hepatitis C infection in PWID in most European Union countries, potentially hampering HCV treatment scale up.

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**Table 3.** Search terms used.

General terms across all topic areas: ("Substance Abuse, Intravenous"[Mesh] OR "IDU" OR "IDUs" OR "PWID" OR "IVDU" OR "IVDUs" OR "intravenous drug" OR "injecting drug" OR "intravenous substance" OR "Injection drug" OR "inject drugs") AND ("Hepatitis C"[Mesh] OR "hepatitis C" OR "HCV") as well as country specific terms.

Additional search strings per topic area: 1) Incidence: "incidence", 2) Chronicity: HCV-RNA[All Fields] OR ("genotype"[MeSH Terms] OR "genotype"[All Fields]) OR persistence[All Fields] OR ("viraemia"[All Fields] OR "viremia"[MeSH Terms] OR "viremia"[All Fields]), 3) Genotype: "genotype"[tiab] OR "subtype"[tiab] OR "molecular epidemiology" [tiab], 4) Co-infection: HIV or "HIV"[Mesh] or "hiv\*", 5) Diagnosis: "test"[tiab] OR "prevalence"[tiab] OR "proportion"[tiab] OR "referral"[tiab] OR "trend"[tiab] OR "screening"[tiab] OR "diagnostics"[tiab] OR "surveillance"[tiab] OR "unidentified"[tiab] OR "diagnosis"[tiab] OR "undiagnosed"[tiab], 6) Treatment: "antiviral"[tiab] OR "treatment"[tiab] OR "therapeutics"[tiab] OR "access to treatment"[tiab], 7) Burden of Disease: Cost-effectiv\* [tiab] OR burden [tiab] OR daly [tiab] OR qaly[tiab] OR morbidity [tiab] OR mortality[tiab] OR "Cost of Illness"[Mesh] OR illness cost\*[tiab] OR incremental cost-effectiveness ratio [tiab] OR Cost-Benefit Analysis [Mesh].

Country specific terms: Web-appendix S1.

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6.9/100PY following a negative HCV RNA test result (N = 347, UK, ever PWID) [83], 3.4/100PY (N = 11, Netherlands, ever PWID) [88] and 0–4.1/100PY following treatment induced viral clearance (N = 18, Germany, ever PWID) [89].

### Chronicity

**Study questions.** What is the prevalence of chronic HCV infection among anti-HCV positive PWID in Europe? How does chronicity vary by setting, demographics, duration of injecting, and co-infection status?

**Main findings.** Available data on HCV-RNA rates in anti-HCV positive PWID show considerable variation (Table 4, Figure 3).

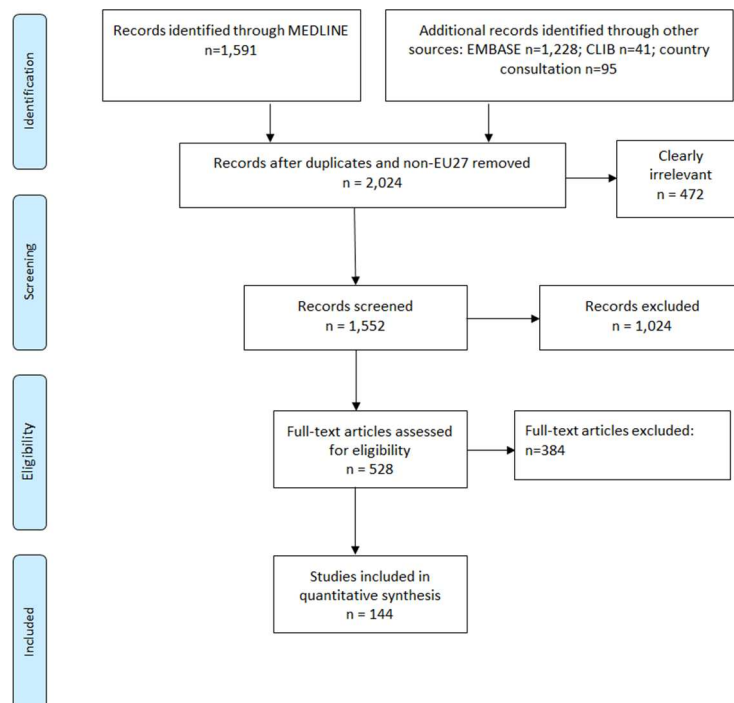
**Studies included.** Twenty-seven studies met the inclusion criteria [81,82,90–116] from fourteen countries (Table 4). These investigated the prevalence of HCV-RNA in 28 populations which included 10,263 anti-HCV positive PWID. Three additional studies were included that investigated the development of chronic infection in 98 PWID acutely infected with HCV [117–119]. (Table S4 in Web-appendix S2).

**Study design.** Nine cohort studies [100,103,105,109,113, 115,117–119], and 21 cross-sectional studies tested HCV-RNA using PCR as a marker for chronic infection [81,82,90–99,101,102,104,106–108,111,112,114,116].

**Population.** PWID were recruited in drug treatment centres, general practices, gastroenterology and hepatology units, infectious diseases and genitourinary medicine clinics, and in the community.

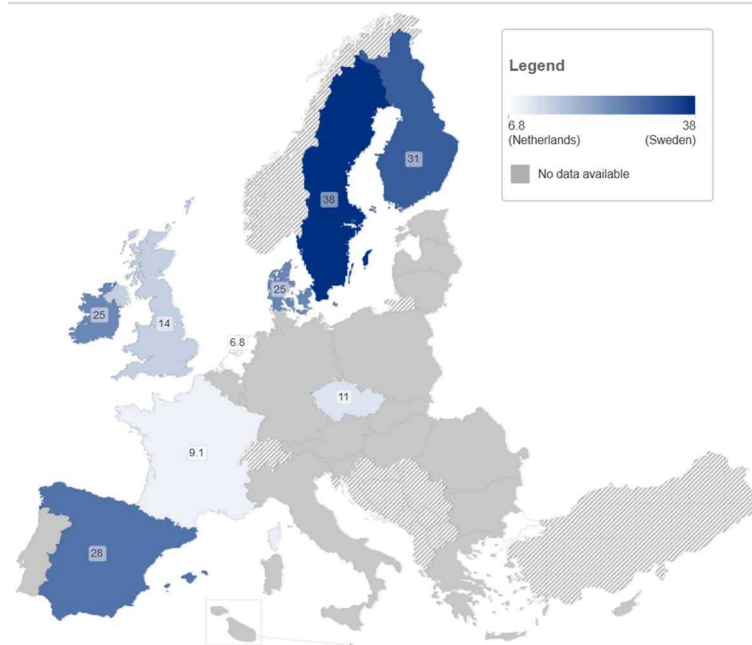
**Findings.** The level of chronic infection in anti-HCV positive PWID ranged between 53% and 97% with a median of 72% (IQR 64–81%). The proportion of acute HCV infections among PWID progressing to chronic infection varied between 0% and 56%.

Based on seven studies with mean age [90,91,96,103, 106,111,115] and four studies with mean duration of injecting drug use of the anti-HCV positive PWID [91,96,111,113] a significant positive linear relation was observed between chronicity rate and both mean age of the population (Regression coefficient = 0.14; 95% CI: 0.00–0.28; P = 0.046) and mean duration of injecting drug use (Regression coefficient = 0.18; 95% CI: 0.02–0.34; P = 0.026). Based on the results of three studies [92,110,116]



**Figure 1. Flow diagram of study selection aggregated over the seven topic areas reviewed.**

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**Figure 2. Incidence of HCV infection in PWID (per 100 person years).**  
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a significant relationship between HIV-co-infection (OR 1.67, 95% CI 1.07–2.60;  $P=0.0025$ ) and chronicity rate was observed. Based on the results of five studies a statistically significant association was found between male gender (OR 1.64, 95% CI 1.06–2.55;  $P=0.016$ ) [90,91,108,110,116] and chronicity rate. Only two studies had examined variation in the prevalence of HCV chronicity by HBV serostatus, and found no association (OR 0.99, 95% CI 0.63–1.57;  $P=0.978$ ) [91,110]. Furthermore, the pooled average chronicity prevalence in the studies conducted in gastroenterology or hepatology units (84%, 95% CI: 74–91) was significantly higher than in the studies conducted in other settings (71%, 95% CI: 67–75) ( $Q$ -value = 5.292;  $df=1$ ;  $P<0.021$ ). Finally, no geographic trends could be detected.

## Genotypes

**Study questions.** What is the genotype distribution in PWID in Europe, and is it changing over time? What is the proportion of traditionally ‘difficult to treat’ genotypes (1 and 4)?

**Main findings.** HCV genotypes 1 and 3, (subtypes 1a and 3a), are the most commonly identified among PWID in Europe. Genotype 4 may be increasing. The proportion of the more ‘difficult to treat’ genotypes (1+4) showed large variation (17–91%, median 53%, IQR 43–62%).

**Studies included.** 43 studies met the inclusion criteria. Data were available from 20 European countries [81,82,91,92,94–97,102,103,106,108,111–113,115,120–147]. (Table 4, Figure 4 and Table S5 in Web-appendix S2).

**Study design.** Eighteen cohort and twenty-five cross-sectional studies. HCV infection was mainly confirmed by enzyme immunoassays, immunoblot assays and RT-PCR. HCV genotypes/subtypes were determined by reverse hybridization assay and restriction fragment length polymorphisms (RFLPs) assay, sequencing and other PCR-based methods.

**Population.** A total of 6,488 HCV-infected PWID were genotyped or subtyped (range of subjects: 11–865). PWID were: a) enrolled in drug treatment, screening or national survey programs,

b) regularly monitored in drug treatment centres, or c) hospitalised in or referred to specified units.

**Findings.** HCV subtype 1a dominates in Portugal [140], Spain [142,143] and The Netherlands [113,144], while it is also common in the Czech Republic [97] and the UK [81,115,145]. HCV subtype 1b prevails in Bulgaria [95], Czech Republic [122], Estonia [123] and Romania [111].

HCV genotype 2 is relatively uncommon with the exception of Greece [106,132], Lithuania [138], Sweden [112] and the UK [82,145,147]. Genotype 3 predominates in Greece [106,129,130,133,134], Poland [139] and Slovenia [141] and is common in Austria [120], Belgium [91], France [103,125] and Italy [136,137]. Subtype 3a dominates in Belgium [92], Cyprus [96] and France [102,124]. In Ireland, HCV genotypes 1 and 3 are equally distributed (48%) [108].

Levels of genotype 4 are particularly high in Southern European countries (Greece [130,133,134], Italy [136,137], Portugal [140] and Spain [142,143]) compared to Western ones (France [102,125], Belgium [91,92] and The Netherlands [113,144]). The lowest rates of genotype 4 were reported in Lithuania [138], Sweden [112], Czech Republic [97,122], and UK [146,147]. Genetic diversity of genotype 4 suggests that this genotype is emerging among PWID and among the general population (e.g. 4a in Portugal [140] and Germany [127,128], 4d in Portugal [140] and The Netherlands [113] and 4f in Italy [137]). Overall, the proportion of ‘difficult to treat’ genotypes (1+4) varies strongly, from 17% in Lithuania to 76–91% in the Czech Republic (Table 4) with a median of 53% (range 17–91%, IQR 43–62%).

Increasing levels of mixed infections are observed, by either different HCV genotypes (Italy 1b/3a [137], Germany 2a/3b [128] and Sweden 1a/2b, 1b/2a, 1a/4, 1b/2b [112]) or different subtypes of the same genotype (Spain 2a/2c and 4c/4d [143], Belgium 4c/4d [92], The Netherlands 2a/2b [113], and Sweden 2a/2b [112]). This is most likely due to the implementation of newer line probe assays with higher capability in detecting HCV subtypes.

**Table 4.** HCV infection among people who inject drugs in the European Union - availability by country of key data to scale up antiviral treatment (figures that include data since 2006 (inclusive) are shown in **bold** and figures not included in the final analyses are in square brackets []).

	<b>Incidence /100PY of primary infection of HCV in PWID [reinfection]</b>	<b>Chronicity: weighted mean prevalence of HCV RNA (%) among antibody positive PWID (range:number of studies:overall sample size)</b>	<b>Genotype 1 or 4: weighted mean prevalence of the sum of HCV genotypes 1 and 4 among PWID (%) (range:number of studies:overall sample size: G1/G2/G3/G4)@</b>	<b>Co-infection HIV: weighted mean HIV prevalence among HCV antibody positive PWID (%) (range: number of studies: overall sample size)</b>	<b>Diagnosis: weighted mean proportion HCV positive PWID (ab or RNA) who were undiagnosed (%) (range:number of studies:overall sample size)</b>	<b>Treatment entry: weighted mean proportion HCV-infected PWID entering antiviral treatment, (%) (range: number of studies: overall sample size)</b>	<b>Burden of disease from HCV infection in PWID (mortality, liver disease)</b>	<b>Topic areas of this review covered</b>	<b>Written viral hepatitis policy exists#</b>
Austria	NA	83 (NA:1:139) [acute 0.0 (NA:1:3)]	53 (NA:1:75: 48/1.3/40/5.3)	<b>0.7 \$ (NA:1:309)</b>	NA	<b>[int-nonclin 12 (NA:1:141)]</b>	NA	4/7	Yes
Belgium	NA	<b>78 \$ (67–95:3:627)</b>	50 \$ (47–52:2:271:41/1.7/47/9.1)	<b>Multisite 4.9 (2.1–5.9:2:485)</b>	NA	NA	NA	3/7	No
Bulgaria	NA	<b>78 (NA:1:147)</b>	<b>61 (35–65:2:133:61/0.0/38/0.0)</b>	<b>Sofia 3.9 (NA:1:955)</b>	NA	NA	NA	3/7	No
Cyprus	NA	<b>70 (NA:1:20)</b>	<b>43 (NA:1:14: 43/0.0/57/0.0)</b>	<b>0.0 \$ (NA:1:40)</b>	NA	NA	NA	3/7	No
Czech Republic	Multisite 11 \$ (2002–2005), Karvina: 15 (1998–2001)	<b>69 \$ (59–71:2:546)</b>	<b>79 (76–91:2:275:79/0.4/20/0.0)</b>	<b>Multisite 0.0 \$ (0.0–0.0:4:873)</b>	NA	NA	NA	4/7	No&
Denmark	Nyborg prison: 25 (1996–97)	<b>67 \$ (53–68:3:3615)</b>	NA	<b>Nyborg prison 0.0 (0.0–0.0:2:268)</b>	<b>46 \$ (NA:1:9463) (ab or RNA)</b>	NA	<b>Observed mortality \$: MR 12 / 100 (1995–2006)</b>	5/7	Yes
Estonia	NA	NA	63 (NA:1:35: 63/0.0/37/0.0)	62 (NA:1:374)	NA	NA	NA	1/7	No
Finland	Helsinki, Tampere and Turku: 31 (2000–2002)	NA	NA	NA	NA	NA	NA	1/7	No
France	Northeast: 9.1 (1999–2000)	81 \$ (73–85:5:785)	55 (52–60:4:1174:46/2.5/37/9.1)	Multisite 18 (2.4–68:4:1444)	30 \$ (NA:1:91) (ab)	obs-nonclin 18 \$ (1.8–19:3:2453) [obs-clin 25 \$ (8.8–28:3:1421), int-nonclin 29 (17–38:2:387)]	NA	6/7	Yes
Germany	[Re-infection: Munich: 0–4.1 (1997–2000)]	NA	61 (54–65:3:300:63/3.8/31/2.6)	<b>Multisite 7.1 (7.1–7.2:3:681)</b>	NA	<b>obs-nonclin 8.6 \$ (NA:1:301) [int-clin 47 (NA:1:106)]</b>	NA	4/7	No
Greece	NA	NA	<b>36 \$ (32–46:7:1774:24/2.8/61/11)</b>	<b>Multisite 0.8 \$£ (0.0–1.7:12:8,626)</b>	NA	<b>[obs-clin 59 (NA:1:305)]</b>	NA	3/7	Yes&
Hungary	NA	NA	NA	<b>Multisite 0.0 (0.0–0.0:2:396)</b>	NA	<b>obs-nonclin 0.9 (NA:1:234) [obs-clin 29 (NA:1:123)]</b>	NA	2/7	No
Ireland	Dublin: 25 (2001), 66 (1992–1999)	63 (62–81:2:532)	50 (NA:1:299: 49/2.0/49/0.7)	NA	NA	<b>obs-nonclin 10 (NA:1:29)</b> , [obs-nonclin self-ab+ ever-Tx 4.5 (NA:1:22) int-nonclin 7.7 (NA:1:26)]	NA	5/7	No
Italy	NA	97 \$ (1:406) [acute <b>56 (NA:1:71)]</b>	<b>58 (54–61:3:427:45/3.3/38/13)</b>	<b>Multisite 16 (5.2–23:5:3,177)</b>	NA	[int-nonclin 31 (NA:1:169)]	NA	4/7	No

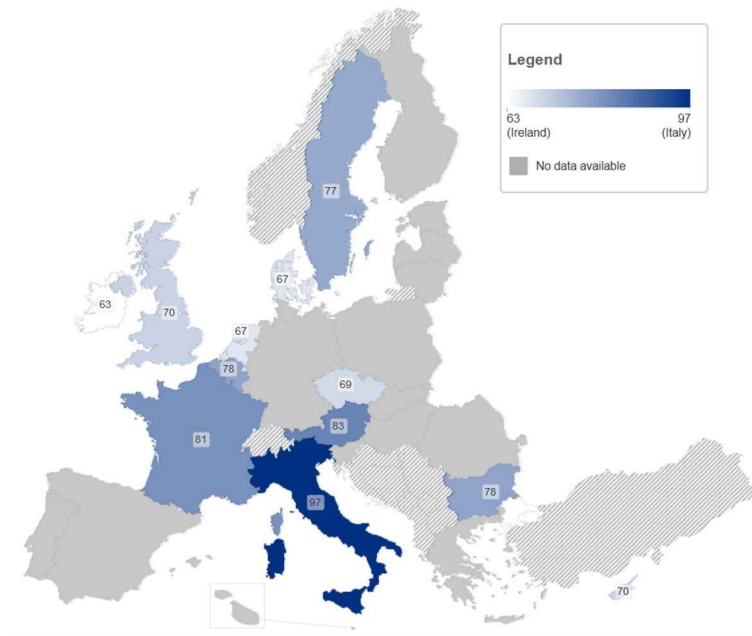


**Table 4.** Cont.

	<b>Incidence /100PY of primary infection of HCV in PWID [reinfection]</b>	<b>Chronicity: weighted mean prevalence of HCV RNA (%) among antibody positive PWID (range:number of studies:overall sample size)</b>	<b>Genotype 1 or 4: weighted mean prevalence of the sum of HCV genotypes 1 and 4 among PWID (%) (range:number of studies:overall sample size: G1/G2/G3/G4)@</b>	<b>Co-infection HIV: weighted mean HIV prevalence among HCV antibody positive PWID (%) (range: number of studies: overall sample size)</b>	<b>Diagnosis: weighted mean proportion HCV positive PWID (ab or RNA) who were undiagnosed (%) (range:number of studies:overall sample size)</b>	<b>Treatment entry: weighted mean proportion HCV-infected PWID entering antiviral treatment, (%) (range: number of studies: overall sample size)</b>	<b>Burden of disease from HCV infection in PWID (mortality, liver disease)</b>	<b>Topic areas of this review covered</b>	<b>Written viral hepatitis policy exists#</b>
Latvia	NA	NA	NA	<b>Multisite 30 (27–35:3:1,080)</b>	NA	<b>[obs-nonclin self-ab+ ever-Tx 4.8 (NA:1:314)]</b>	NA	2/7	No
Lithuania	NA	NA	<b>17 (NA:1:12: 17/8.3/75/0.0)</b>	<b>Vilnius 8.1 (NA:1:400)</b>	NA	NA	NA	2/7	No
Luxembourg	NA	NA		3.0 \$ (NA:1:202)	NA	NA	NA	1/7	No
Malta	NA	NA	NA	NA	NA	NA	NA	0/7	No
Netherlands	Amsterdam: 6.8 (1985–2005) <b>[Re-infection: Amsterdam 3.4 (2005–2010)]</b>	67 (NA:1:106)	66 (62–71:2:128:53/6.0/32/9.0)	Amsterdam 30 (NA:1:952)	NA	<b>[int-nonclin 33 (23–48:2:184)]</b>	<b>Observed mortality: MR 2.3 /100 (1985–2009) Modelled: cirrhosis and HCC: 36% increase in liver disease burden 2011–2025, Amsterdam</b>	5/7	No
Poland	NA	NA	<b>44 (NA:1:23: 35/0.0/57/8.7)</b>	<b>Multisite 31 (4–55:9:1109)</b>	<b>56 (24–65:3:562) (RNA)</b>	NA	NA	3/7	No
Portugal	NA	NA	<b>79 (NA:1:52: 62/0.0/21/17)</b>	Tires 48 (NA:1:45)	NA	NA	NA	2/7	No&
Romania	NA	NA	<b>85 (NA:1:26: 73/0.0/7.7/12)</b>	<b>Bucharest 0.0 £ (NA:1:45)</b>	NA	NA	NA	2/7	Yes&
Slovakia	NA	NA			NA	NA	NA	0/7	No
Slovenia	NA	NA	<b>40 \$ (NA:1:516: 39/1.6/58/1.7)</b>	<b>0.8 \$ (0–1.6:4:1063)</b>	NA	NA	NA	2/7	No&
Spain	Madrid, Barcelona and Seville: 28 (2001–2003)	NA	69 (68–72:2:256:54/2.3/27/16)	<b>Multisite 50 (30–70:10:9,646)</b>	<b>25 (NA:1:545) (ab/RNA NA)</b>	[obs-clin 54 (NA:1:494)]	<b>Observed mortality: MR 2.1–2.4 /100 (1990–2002, 1997–2008)</b>	6/7	No
Sweden	Malmö: 38 (1997–2005), 26 (1990–93)	<b>77 (NA:1:268)</b>	<b>38 (NA:1:206: 36/8.7/34/0.9)</b>	NA	NA	NA	NA	3/7	No
UK	<b>16 studies: 2.7 – 42 (2001–2009) mean 14 [Re-infection: Glasgow, 6.9, (1993–2007)]</b>	<b>70 (60–71:3:2581)</b>	<b>50 (44–58:6:492:49/5.7/42/0.8)</b>	<b>Multisite 2.2 (0–8:11:26,111) \$</b>	<b>59 (49–76:4:1696) (ab or RNA) [58 (NA:1:NA) (RNA)]</b>	[obs-clin 28 (NA:1:179), <b>obs non-clin self-ab+ ever-Tx 37 (NA:1:414), int non-clin 23 (22–25:2:559)]</b>	<b>Modelled: 56% increase of cirrhosis, 64% of moderate liver disease from 2010–2025, Glasgow</b>	7/7	Yes

Data are shown with two significant digits. # Source: The Global Viral Hepatitis Report, WHO 2013. Country response to the question: "In your country, is there a written national strategy or plan that focuses exclusively or primarily on the prevention and control of viral hepatitis?". EMCDDA DRID Group respondents were asked to review and if necessary adjust (indicated by &). ab = antibody, clin = clinical, int = intervention study, nonclin = non-clinical, obs = observational study, NA = not available, RCT = Randomised Controlled Trial, RNA = ribonucleic acid, self = self-reported, Tx = treated, \$ = includes studies with national coverage. £ In 2010 an HIV outbreak occurred among PWID in Greece and Romania, therefore the here presented figures are likely incorrect and co-infection is much higher. @ Genotypes 1 and 4 are harder to treat with conventional treatments, the total here thus gives the proportion of 'hard to treat' cases; "G1/G2/G3/G4" denotes percentages of genotypes 1 to 4 separately; small discrepancies between the sum of genotypes 1 and 4 and separate percentages of genotypes 1 and 4 are due to missing values. For full detail on data see Web-appendix S2.

doi:10.1371/journal.pone.0103345.t004



**Figure 3. Chronicity of HCV: RNA prevalence (%) among antibody-positive PWID.**  
doi:10.1371/journal.pone.0103345.g003

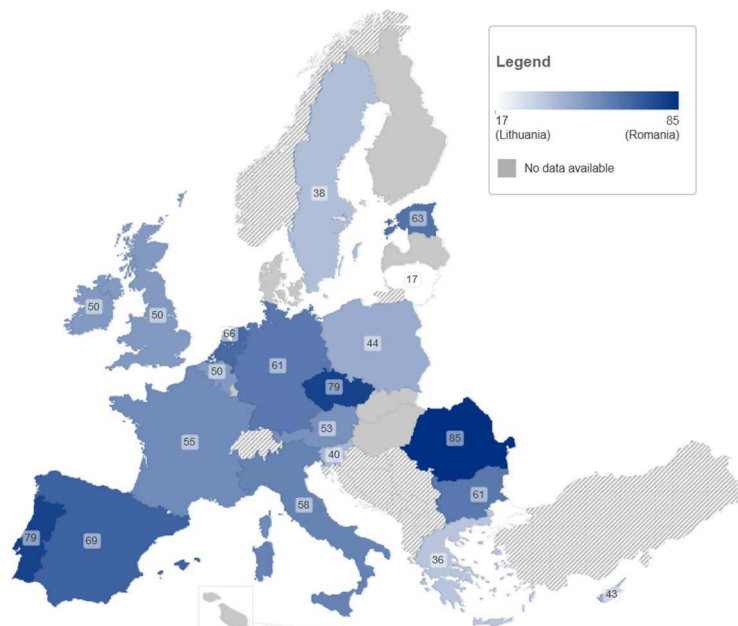
**HIV co-infection**

**Study questions.** What is the prevalence of HIV among PWID with HCV infection (HIV-HCV co-infection prevalence) in Europe?

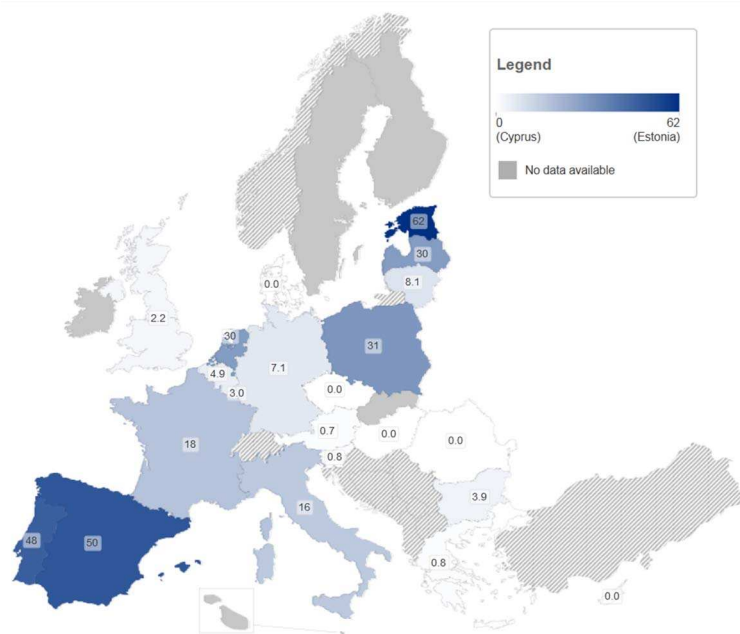
**Main findings.** Available data for 22 countries in Europe suggest considerable variation in the HIV-HCV co-infection prevalence (0–70%, median 3.9, IQR 0.2–28) among PWID (Table 4, Figure 5), with this being correlated (correlation coefficient = 0.98) with the HIV prevalence among PWID, but generally a median of 15% (IQR 0.0–49%) relatively greater.

**Studies included.** Sixty-two studies [22,61,71,82,86,92,96,98,99,103,106,109,111,116,118,122,129,132,134,146,148–189] met the inclusion criteria giving 80 HIV-HCV co-infection estimates. (Table S6 in Web-appendix S2).

**Study design.** Studies either involved diagnostic testing or cross-sectional samples of PWID from a variety of settings involving different sampling methods such as respondent driven sampling, exhaustive sampling and snowball sampling. HCV infection status was not confirmed by RNA status in many studies and so antibody prevalence was used across all studies.



**Figure 4. Proportion (%) of HCV infections among PWID that are genotypes 1 or 4.**  
doi:10.1371/journal.pone.0103345.g004

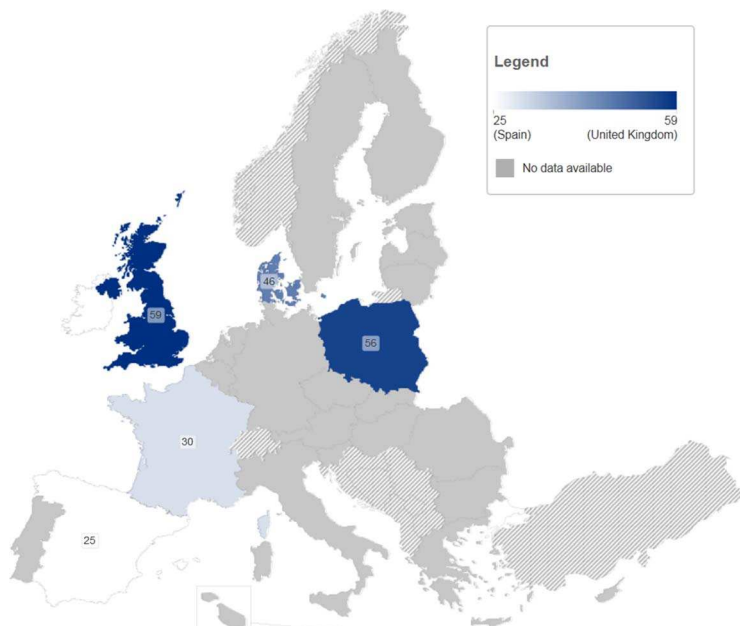


**Figure 5. Proportion (%) of HCV-infected PWID that are co-infected with HIV.**  
doi:10.1371/journal.pone.0103345.g005

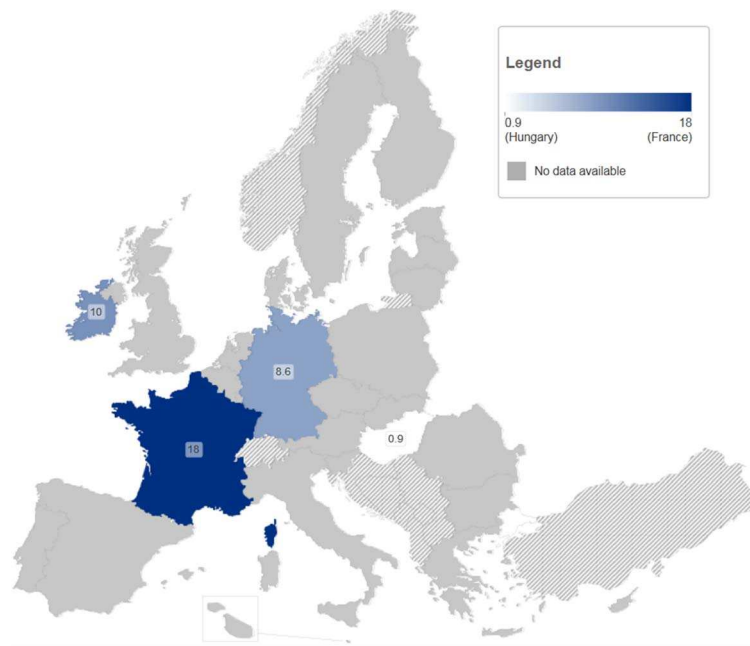
**Population.** PWID were recruited from drug treatment centres, opiate substitution treatment centres, needle and syringe programmes, hospitals, and prisons.

**Findings.** Many European countries had multiple estimates of HIV and HCV prevalence but few recorded HIV-HCV co-infection prevalence (HIV prevalence among HCV antibody positives). Estimates of HIV-HCV co-infection prevalence were available for 22 countries in Europe with thirteen countries having multiple estimates (Belgium, Czech Republic, Denmark, France, Germany, Greece, Hungary, Italy, Latvia, Poland, Slovenia, Spain and UK). The HIV-HCV co-infection prevalence ranged between

0% and 70% in the different countries (median 3.9, IQR 0.2–28). Co-infection prevalences were low ( $\leq 4\%$ ) in 11 countries (Austria, Bulgaria, Cyprus, Czech Republic, Denmark, Greece, Hungary, Luxembourg, Romania, Slovenia and UK), moderate (4 to 15%) in three countries (Belgium, Germany and Lithuania) and high ( $>15\%$ ) in eight countries (Estonia, France, Latvia, Italy, Netherlands, Poland, Portugal and Spain). As expected the HIV-HCV co-infection prevalence is higher in settings with higher HIV prevalence, with a strong linear correlation existing between each survey's HIV prevalence estimate and the corresponding HIV-HCV co-infection prevalence estimate (correlation coeffi-



**Figure 6. Proportion (%) of HCV positive PWID (antibody or RNA) undiagnosed.**  
doi:10.1371/journal.pone.0103345.g006



**Figure 7. Proportion (%) of HCV-infected PWID entering antiviral treatment in observational studies in non-clinical settings.**  
doi:10.1371/journal.pone.0103345.g007

cient = 0.98), with the HIV-HCV co-infection prevalence being a median of 15% (IQR 0.0–49%) relatively greater than the HIV prevalence. No clear relationship existed between HCV prevalence and the HIV-HCV co-infection prevalence.

### Diagnosis

**Study question.** What percentage of HCV-infected PWID are undiagnosed in Europe?

**Main findings.** Among the studies included, a high proportion of HCV infections in PWID were undiagnosed (median 49%, range 24–76, IQR 38–64) (Table 4, Figure 6).

**Studies included.** Eleven studies reported on the proportion of PWID with undiagnosed hepatitis C infection from five countries in the EU [114,170–172,180,190–195]. (Table 4 and Table S7 in Web-appendix S2).

**Study design.** Ten cross-sectional studies and one retrospective cohort study. All studies were observational and performed in non-clinical settings.

**Population.** Ten studies among PWID in specialised treatment centres and other drug services, one study among PWID attending general practices.

**Findings.** The proportion of infections in PWID that were previously undiagnosed ranged from 24% to 76% with a median of 49% (IQR 38–64%,  $n = 13,561$ ).

### Treatment

**Study question.** What is the proportion entering antiviral treatment among diagnosed cases of chronic HCV infection in PWID?

**Main findings.** In six observational studies with non-clinical recruitment settings, the proportion of PWID diagnosed with chronic HCV infection that started antiviral treatment was generally low, at 1–19% (median 9.5, IQR 3.5–15) (Table 4, Figure 7).

**Studies included.** Twenty-six studies from 11 countries fulfilled the inclusion criteria [22,59,79,103,105,107,114,115,

126,131,146,152,165,188,196–206] (Table 4 and Table S8 in Web-appendix S2).

**Study design.** Eight were retrospective cohort studies; 11 were prospective cohort studies; one a randomised controlled trial; one a semi-experimental intervention study and five were cross-sectional studies. Overall, 16 were observational, whereas 10 were intervention studies (one study included both observational and intervention data).

**Population.** PWID were either patients attending hospitals or specialist services for hepatitis treatment ('clinical' – eight studies), or recruited through PWID specific services, general practice and/or community settings ('non-clinical' – 18 studies).

**Findings.** The proportion of PWID with diagnosed chronic infection entering antiviral treatment was 1–19% (median 9.5, IQR 3.5–15) in six non-clinical observational studies (four countries, total sample size 3,017) [105,107,152,196,199,201]. An increasing proportion is seen by setting and study type with progressively selected study populations, with a median of 23% (IQR 17–31) in nine intervention non-clinical studies, 28% (IQR 24–42) in seven observational clinical studies [22,103,115,131,198,200,204] and 47% in one intervention clinical study [126]. Four studies with non-clinical recruitment settings provided a proportion of antibody positive PWID self-reporting having ever been treated, with a median of 4.7% (3.4–37, IQR 4.3–13,  $n = 868$ ) [79,146,165,202]. Three observational studies with non-clinical recruitment settings provided the proportion of diagnosed PWID referred to a specialist for treatment evaluation (median 57%, range 9.0–59) [79,196,201], as did four intervention studies in non-clinical settings (median 59%, range 21–93, IQR 40–78) [146,197,205,206].

### Burden of disease

**Study questions.** What estimates exist of the future burden of disease among PWID with HCV in Europe?

**Main findings.** The crude mortality rate (CMR) for all-cause mortality ranged from 2.1–12 cases /100PY. Modelling studies

project an increase in the burden of liver disease. HCV treatment could reduce this burden and is cost-effective (Table 4).

**Studies included.** Four observational studies, two modelling studies and one cost-effectiveness study [177,207–211] (Table 4 and Tables S9–S10 in Web-appendix S2).

**Study design.** All cohort studies had a prospective design and one also included retrospective data. Study settings varied from single centre to nationwide.

**Population.** PWID were recruited from HIV centres and through drug treatment centres.

**Findings.** During 33,284 PY of follow-up 895 of 5,340 PWID died. The prevalence of HIV co-infection varied between 16% [209] and 100% [207,208].

All studies reported all-cause CMR, ranging from 2.1 to 12 cases /100PY, (Table S9 in Web-appendix S2). A Danish study [207] found comparable CMR for those with chronic HCV and spontaneous resolvers, whereas a study from The Netherlands [209] observed a two-fold higher CMR for chronically HCV-infected PWID compared to spontaneous resolvers. The Danish study [207] reported a >4 times higher CMR than the other studies. Two studies reported liver-related CMR [207,209], of 0.11 and 3.0/100PY respectively.

Two modelling studies were included, from The Netherlands [210] and the UK [211], (Table S10 in Web-appendix S2). Between 2011 and 2025, the HCV-related liver disease prevalence in The Netherlands was projected to rise by 36% [210]. In Scotland, [211] a 56% increase in cirrhosis and 64% in moderate liver disease between 2010 and 2025 was projected. Both studies showed that HCV treatment could reduce the future liver disease burden.

One cost-effectiveness analysis from the UK, based on a dynamic model of HCV transmission and disease progression [28], found that in a steady state epidemic with HCV prevalence among PWID of 20% or 40%, HCV treatment of PWIDs was more cost-effective than treating non/ex-PWIDs with an incremental cost-effectiveness ratio of 599 and 2,920 euro, respectively, per quality adjusted life year as compared to no treatment.

## Discussion

Our study suggests that availability of key data for informing the scale-up of HCV treatment for PWID in Europe is highly variable, but diagnosis and treatment uptake remain low. To our knowledge, this is the first attempt to provide a comprehensive and comparative review of data for HCV treatment scale-up among PWID in a large number of countries.

While most countries have information on the genotype distribution and HIV-HCV co-infection prevalence in PWID (22/27 countries), only six countries have estimates for five or more of the seven topic areas reviewed here (Denmark, France, Ireland, The Netherlands, Spain and UK). In addition, available data are often based on selected subpopulations (e.g. clinical) and local studies, which might not be representative for all PWID living in a country, while in some of the topic areas recent data (collected since 2006) are scarce. Our review reveals serious gaps in data availability and comparability, suggesting that many countries in Europe may not yet have invested sufficiently in studies or surveillance systems to guide HCV treatment and prevention policies for PWID. Moreover, although we did not systematically evaluate the quality of data, we observed large differences in methods and definitions, likely affecting comparability across data sources [212]. Importantly, the limited data suggest that overall there are poor levels of diagnosis and treatment uptake among HCV-infected PWID.

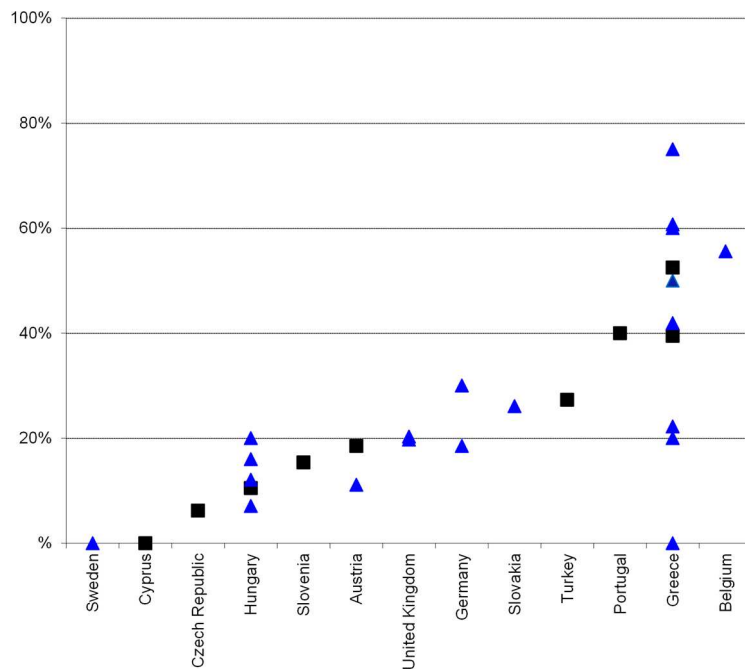
Although diagnosis is a pre-condition for treatment entry and under-diagnosis an important reason for non-treatment [34], we found information on the undiagnosed fraction in PWID in only five countries (19%). The proportion undiagnosed was over 50% in five of the 11 studies (overall median 49%, range 24–76%), while methods were not always clear or comparable.

More countries (11/27, 41%) had data on antiviral treatment access among PWID (note: among those diagnosed). However, only four countries had studies in non-clinical settings that were non-interventional (i.e. did not specifically attempt to enhance treatment access). Among the studies in these countries, the median proportion of diagnosed PWID who had actually started treatment was 9.5% (range 1–19%). Interestingly, the proportion entering treatment increased with the level of selection of the study population (with a median of 23% in nine non-clinical intervention studies, 28% in seven clinical observational studies and 47% in one clinical intervention study) suggesting that potentially higher treatment rates may be achieved with specific interventions. However, even in the most selected intervention studies a large proportion of diagnosed PWID remained untreated.

The median proportion of antibody-positive PWID who self-reported lifetime treatment uptake for HCV in four non-clinical studies (4.7%), although within a large range (3.4–37%), was roughly similar to that in two studies in the US, which found a lifetime uptake of 4.8% among RNA-positive PWID [20] and of 6% among antibody positive PWID [15]. An Australian study found a self-reported life-time treatment uptake of 10% and an increasing trend in the annual treatment uptake (0.5% in 1999–2% in 2011) among HCV antibody-positive PWID [19]. A recent study in UK used a novel method based on laboratory data to estimate HCV treatment uptake and outcomes, however was unable to obtain information by risk group [213].

Referral of chronically infected PWID from non-specialist to specialist care was found to be incomplete, explaining part of the low treatment access. However, this was reported by only three of the observational studies in non-clinical settings (median 57%, range 9–59) and was found to be similar in four (non-clinical) intervention studies (59%, range 21–93). The limited treatment uptake may finally also be due to the absence of national treatment policies for PWID (Table 4) and/or a decision to wait for the new potent direct-acting antiviral agents (DAA).

Treatment outcomes are determined by patient characteristics, which traditionally include HIV co-infection and HCV genotype [22,36,214]. Although in principle both may soon be less relevant [36,214,215], it remains to be seen if the much higher costs of treatment for the unfavourable genotypes and DAA may hamper their scale-up for PWID in many countries [30,216]. Data on these two topic areas were more abundant with 20 countries (74%) having information on genotype distributions and 22 on HIV co-infection in PWID. The data suggest important variation in genotypes across countries in Europe, with large variation in the proportion of ‘difficult to treat’ genotypes among PWID (sum of percentages of genotypes 1 and 4), ranging from 17% in Lithuania to 76–91% in the Czech Republic (median 53%). Genotypes 1 and 3, especially subtypes 1a and 3a, are common and have demonstrated exponential growth during the 20<sup>th</sup> century [217]. Genotype 4 has been spreading in Western Europe since the 1960s [217]. It appears to be genetically diversifying and increasing in particular among PWID in Europe [46,113,128,137,140,144,218–220]. Countries with predominance of genotypes 1 and high or increasing levels of genotype 4 face more difficulties in treating PWID with peginterferon and ribavirin. High levels of HIV co-infection (over 4%) were found in 11 countries, with levels over



**Figure 8. HCV antibody prevalence (%) among PWID injecting <2 years in the EU, 2006–2011.** Note Figure 8: Source EMCDDA, 2013. (<http://www.emcdda.europa.eu/stats13/#inf:displayTables>); black squares are data with national coverage, blue triangles are data with sub-national (local, regional) coverage. doi:10.1371/journal.pone.0103345.g008

15% being found in eight of these (Estonia, France, Italy, Latvia, The Netherlands, Poland and Portugal, Spain).

Future treatment needs among PWID, especially for ‘treatment as prevention’, will not only depend on the current prevalence of chronic infection, but importantly on the incidence of new infections and re-infection. Incidence estimates of new infections in PWID based on direct methods were located for only nine countries (33%) and suggested wide variation in infection rates (2.7–66/100PY overall and 5.2–42/100PY among current and recent PWID) whereas just three countries have reported re-infection rates (0–6.9/100PY), although these are likely to be underestimates of the real re-infection rate [53,221]. The countries at highest (Sweden) and lowest (Netherlands) incidence appear to confirm a previous, prevalence-based, analysis suggesting a link with prevention policies (Figure 2) [42]. Chronicity levels among PWID were found for 12 countries (44%) showing a large range (53–97%). Multiple studies at these extremes (six below 60%, two above 90%, out of 28) suggest substantial differences in progression to chronic infection may exist between countries, which might be explained by differences in gender and HIV co-infection prevalence distributions between study populations and the setting of the study, and may impact future treatment needs.

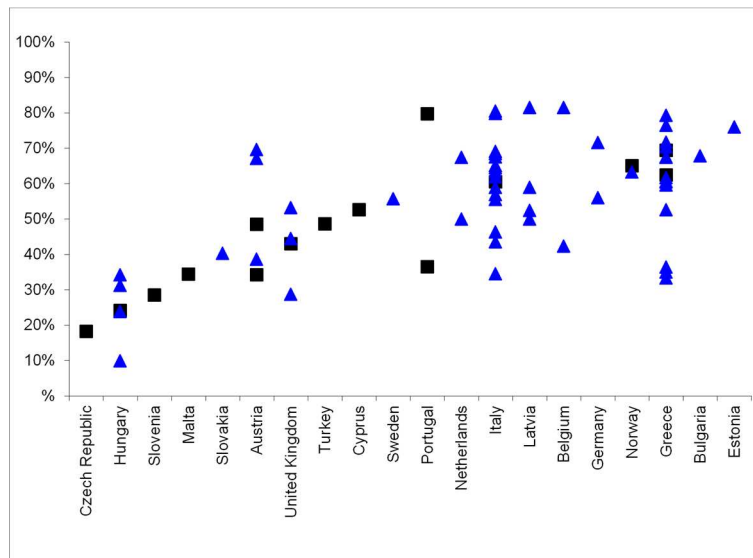
To actually estimate future treatment needs, modelling studies are important, particularly for assessing the potential impact of treatment on prevention. Only two of the 27 countries appear to have carried out a modelling study to estimate the effect of HCV treatment on the future burden of disease. Without treatment, a study in The Netherlands (Amsterdam) projected a 36% increase in the burden of liver disease between 2011 and 2025, whereas in Glasgow this was projected to be 56–64% for 2010–2025. Both studies included competing mortality in their model and showed that HCV treatment would substantially reduce this liver disease burden.

Mortality in PWID with HCV infection is dependent on competing mortality (e.g. HIV or drug-related death [222–224])

and duration of persistent HCV infection. The all-cause mortality rates were estimated at 2.1–2.4/100PY in Spain and The Netherlands, but were 12.2/100PY among HIV co-infected PWID in Denmark. The high rate in the Danish study could be explained by high rates of overdose mortality [49] or differences in cART initiation, given that a Spanish study reported a CMR of 2.4/100PY among HIV co-infected PWID during a comparable study period. This suggests significant country differences for PWID with HCV, in line with findings on mortality among all PWID [224] and the importance of obtaining country-specific mortality estimates. Available data on the morbidity and mortality risk due to HCV among PWID are scarce but are urgently needed for future planning.

The data reported here are related to the EU and therefore our results are most probably not generalisable to other regions globally. However, it is likely that data availability in low and middle income countries will be lower, despite the often more serious epidemiological situation among PWID regarding blood-borne infections e.g. in Eastern Europe and Central Asia [33,43,225–227]. Our study provides a framework and methodology for combining a series of complementary systematic reviews using standardised and validated methods that may be applied to other regions, or topic areas, where a comprehensive view may be beneficial [57], for example when the aim is to support national public health policies. We are unaware of a similar systematic review of the literature comparing multiple related topic areas around a key public health issue in a large number of countries.

Our study is subject to important limitations. We have primarily focused on published studies, available through the MEDLINE, EMBASE and the Cochrane Library databases, which are subject to publication bias and delay. To minimise this problem, we contacted a network of drug and infectious disease experts in Europe, to identify missed studies and we included publications in all languages. Another limitation relates to our inclusion criterion of having an unselected population of PWID with regard to gender



**Figure 9. HCV antibody prevalence (%) among PWID in the EU, 2006–2011.** Note Figure 9: Source EMCDDA, 2013 (<http://www.emcdda.europa.eu/stats13#inf:displayTables>); black squares are data with national coverage, blue triangles are data with sub-national (local, regional) coverage.

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or HBV/HIV infection and to restricting our review to data of PWID (ever injectors) only. There are many more reports on populations of people who use drugs where injection status is not known or that are limited to HIV co-infected patients which we could mostly not include, although we believe by being restrictive we may have minimised potential bias. We were also mostly (except for Incidence) unable to distinguish studies based on ever or recent (active/current) injectors as this information was usually not available. However, as most of our outcomes relate to HCV chronicity we believe the data here presented are not seriously affected by recent injecting status of the ever PWID in our study and ever-PWID are the more appropriate group to study. Data in the Diagnosis and Treatment sections would ideally have been adjusted for duration of follow-up in the studies, however these data were mostly not available for the data we extracted. Our data are further limited regarding the comparability of studies found. In particular the geographic coverage of studies was usually partial, with few national studies (Table 4), and they were often undertaken in health services; so participants may not be representative of all PWID. Thus some of the differences between and within countries found here may reflect differences in study design and methodologies rather than true differences. Finally, we selected the topic areas for our review on the basis of informed expert discussions among the authors on what are the key data elements for treatment scale-up that are not available from routine monitoring (Table 1 and Table S2). Further work may be necessary to develop consensus guidance on the information needed to guide HCV treatment policies.

In this review we focused on data from the literature, as a complement to data on HCV infection that is routinely collected by EU bodies, and is likely to be used in national policy decision making. The routine data include hepatitis C notifications, HCV antibody prevalence among PWID, PWID population size, HIV prevalence in PWID (as a proxy for co-infection levels), and the provision and coverage of needle and syringe programmes and opioid substitution treatment as primary HCV prevention measures for PWID (Table S2 in Web-appendix S1). Although some of these data are widely available, for example most

countries have an estimate of HCV antibody prevalence among PWID [43,44,49], other available data can be difficult to interpret. Acute hepatitis notifications are likely to represent only a very small proportion of real incidence, due to the asymptomatic nature of acute HCV infection and underreporting [228], while trends in chronic infections cannot be easily interpreted due to the long time to diagnosis and their dependence on testing patterns, in addition to potentially serious underreporting [4,229] and incomplete availability of risk information. Of particular interest is the HCV antibody prevalence in new injectors (injecting for less than 2 years) (Figure 8). This may provide a relatively cost-effective indicator of levels of new infection in PWID [44,192], as an addition to the regular prevalence data (Figure 9), particularly if it is supported and regularly validated by incidence studies using direct methods as here reviewed, or, in addition, indirect methods [211,230]. Finally, it should be noted that, although population size estimates of PWID are routinely monitored in Europe [49], few countries have estimates that are reasonably recent. This highlights an important need for improvement, given that population size estimates enable converting data from different sources into the absolute numbers needed for planning.

In conclusion, the availability of key data for informing the scale-up of HCV treatment among PWID in individual European countries is highly variable. Our study suggests that large proportions of HCV-infected PWID remain undiagnosed, and of those diagnosed, only one in ten receive antiviral treatment. Stronger national and international efforts, including operational research and collection of key data on PWID with HCV, are needed to develop sound HCV treatment policies for PWID in Europe.

## Supporting Information

**Web-appendix S1 Study protocol and Table S2 – availability of routine data.** References cited: [231,232]. (DOCX)

**Web-appendix S2 Tables S3 to S10 – full data per topic area.**

(XLSX)

**Web-appendix S3 Additional detail on the Chronicity analyses.**

(DOCX)

**Web-appendix S4 PRISMA checklist.**

(DOCX)

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\*Lucy Platt, Bethan McDonald, Andrea Low and PV have undertaken a separate systematic review of HIV and HCV co-infection which fed into the co-infection review included here. Sabine Van Houdt has assisted CM with the literature review on chronicity included here.

**Author Contributions**

Analyzed the data: LW MF BG MK IS KC AH MP PV JL VH CM. Wrote the paper: LW MF BG MK IS KC AH MP PV JL VH CM. Original idea: LW. Study planning: LW MF VH CM. Study coordination, manuscript writing, support on searches, data extraction and interpretation of results: LW. Study protocol development: LW MF. Study protocol advise: VH CM MK PV JL BG. Literature searches, data analysis and writing Incidence section: VH KC. Literature searches, data analysis and writing Chronicity section: CM. Literature searches, data analysis and writing Genotype section: MK AH. Literature searches, data analysis and writing HIV co-infection section: PV. Literature searches, data analysis and writing Diagnosis and Treatment entry sections: IS JL. Literature searches, data analysis and writing Burden of disease section: BG MP. Commenting on manuscript versions: MF BG MK IS KC AH MP PV JL VH CM. Comparisons of search strings and results to ensure consistency across topics: BG. Responding on two requests for additional literature by performing country-specific searches including grey literature and assisting with interpreting the non-English literature: The EMCDDA DRID group.

**References**

1. Thomas DL, Thio CL, Martin MP, Qi Y, Ge D, et al. (2009) Genetic variation in IL28B and spontaneous clearance of hepatitis C virus. *Nature* 461: 798–801. [nature08463 \[pii\]](https://doi.org/10.1038/nature08463); [10.1038/nature08463 \[doi\]](https://doi.org/10.1038/nature08463).
2. Lavanchy D (2011) Evolving epidemiology of hepatitis C virus. *Clin Microbiol Infect* 17: 107–115. [10.1111/j.1469-0691.2010.03432.x \[doi\]](https://doi.org/10.1111/j.1469-0691.2010.03432.x).
3. Alter MJ (2011) HCV routes of transmission: what goes around comes around. *Semin Liver Dis* 31: 340–346. [10.1055/s-0031-1297923 \[doi\]](https://doi.org/10.1055/s-0031-1297923).
4. Wiessing L, Guarita B, Giraudon I, Brummer-Korvenkontio H, Salminen M, et al. (2008) European monitoring of notifications of hepatitis C virus infection in the general population and among injecting drug users (IDUs) - the need to improve quality and comparability. *Euro Surveill* 13: pii=18884. Available: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=18884>.
5. Stephenson J (2001) Former addicts face barriers to treatment for HCV. *JAMA* 285: 1003–1005.
6. King LA, Le SY, Meffre C, Delarocque-Astagneau E, Descenclos JC (2009) Assessment and proposal of a new combination of screening criteria for hepatitis C in France. *Eur J Public Health* 19: 527–533. [ckp112 \[pii\]](https://doi.org/10.1093/eurpub/ckp112); [10.1093/eurpub/ckp112 \[doi\]](https://doi.org/10.1093/eurpub/ckp112).
7. Shepard CW, Finelli L, Alter MJ (2005) Global epidemiology of hepatitis C virus infection. *Lancet Infect Dis* 5: 558–567. [S1473-3099\(05\)70216-4 \[pii\]](https://doi.org/10.1016/S1473-3099(05)70216-4); [10.1016/S1473-3099\(05\)70216-4 \[doi\]](https://doi.org/10.1016/S1473-3099(05)70216-4).
8. Blachier M, Leleu H, Peck-Radosavljevic M, Valla DC, Roudot-Thoraval F (2013) The burden of liver disease in Europe: a review of available epidemiological data. *J Hepatol* 58: 593–608. [S0168-8278\(12\)00924-5 \[pii\]](https://doi.org/10.1016/j.jhep.2012.12.005); [10.1016/j.jhep.2012.12.005 \[doi\]](https://doi.org/10.1016/j.jhep.2012.12.005).
9. Pawlotsky JM (2013) Treatment of chronic hepatitis C: current and future. *Curr Top Microbiol Immunol* 369: 321–342.
10. Hellard M, Sacks-Davis R, Gold J (2009) Hepatitis C treatment for injection drug users: a review of the available evidence. *Clin Infect Dis* 49: 561–573. [10.1086/600304 \[doi\]](https://doi.org/10.1086/600304).
11. Edlin BR (2002) Prevention and Treatment of Hepatitis C in Injection Drug Users. *Hepatology* 36: S210–S219. [10.1053/jhep.2002.36809 \[doi\]](https://doi.org/10.1053/jhep.2002.36809).



12. Dalgard O (2005) Follow-up studies of treatment for hepatitis C virus infection among injection drug users. *Clin Infect Dis* 40 Suppl 5: S336–S338. CID34655 [pii]; 10.1086/427449 [doi].
13. Bruggmann P (2012) Accessing Hepatitis C patients who are difficult to reach: it is time to overcome barriers. *J Viral Hepat* 19: 829–835. 10.1111/jvh.12008 [doi].
14. Mehta SH, Lucas GM, Mirel LB, Torbenson M, Higgins Y, et al. (2006) Limited effectiveness of antiviral treatment for hepatitis C in an urban HIV clinic. *AIDS* 20: 2361–2369. 10.1097/QAD.0b013e32801086da [doi]; 00002030-200611280-00013 [pii].
15. Mehta SH, Genberg BL, Astemborski J, Kavasery R, Kirk GD, et al. (2008) Limited uptake of hepatitis C treatment among injection drug users. *J Community Health* 33: 126–133. 10.1007/s10900-007-9083-3 [doi].
16. Grebely J, Raffa JD, Lai C, Kraiden M, Kerr T, et al. (2009) Low uptake of treatment for hepatitis C virus infection in a large community-based study of inner city residents. *J Viral Hepat* 16: 352–358. J VH1080 [pii]; 10.1111/j.1365-2893.2009.01080.x [doi].
17. Aspinall EJ, Corson S, Doyle JS, Grebely J, Hutchinson SJ, et al. (2013) Treatment of hepatitis C virus infection among people who are actively injecting drugs: a systematic review and meta-analysis. *Clin Infect Dis* 57 Suppl 2: S80–S89. cit306 [pii]; 10.1093/cid/cit306 [doi].
18. NCHECR (2003) HIV/AIDS, viral hepatitis and sexually transmissible infections in Australia. Annual Surveillance Report 2003. Sydney: National Centre in HIV Epidemiology and Clinical Research (NCHECR), The University of New South Wales.
19. Iversen J, Grebely J, Topp L, Wand H, Dore G, et al. (2014) Uptake of hepatitis C treatment among people who inject drugs attending Needle and Syringe Programs in Australia, 1999–2011. *J Viral Hepat* 21: 198–207. 10.1111/jvh.12129 [doi].
20. Strathdee SA, Latka M, Campbell J, O'Driscoll PT, Golub ET, et al. (2005) Factors associated with interest in initiating treatment for hepatitis C Virus (HCV) infection among young HCV-infected injection drug users. *Clin Infect Dis* 40 Suppl 5: S304–S312. CID34650 [pii]; 10.1086/427445 [doi].
21. Grebely J, Raffa JD, Lai C, Kraiden M, Kerr T, et al. (2007) Low uptake of treatment for hepatitis C virus (HCV) infection in a large community-based cohort of illicit drug users in Vancouver. *Hepatology* 46: 296A.
22. Cacoub P, Goderel I, Morlat P, Sene D, Myers RP, et al. (2005) Management of chronic hepatitis C in French departments of internal medicine and infectious diseases. *Epidemiol Infect* 133: 305–314.
23. Fenton MC, Keyes K, Geier T, Greenstein E, Skodol A, et al. (2012) Psychiatric comorbidity and the persistence of drug use disorders in the United States. *Addiction* 107: 599–609.
24. Tortajada S, Herrero MJ, Domingo-Salvany A, Molist G, Barrio G, et al. (2012) Psychiatric morbidity among cocaine and heroin users in the community. *Adicciones* 24: 201–210.
25. Marinho RT, Barreira DP (2013) Hepatitis C, stigma and cure. *World J Gastroenterol* 19: 6703–6709. 10.3748/wjg.v19.i40.6703 [doi].
26. McGowan CE, Fried MW (2012) Barriers to hepatitis C treatment. *Liver Int* 32 Suppl 1: 151–156. 10.1111/j.1478-3231.2011.02706.x [doi].
27. Barocas JA, Brennan MB, Hull SJ, Stokes S, Fangman JJ, et al. (2014) Barriers and facilitators of hepatitis C screening among people who inject drugs: a multi-city, mixed-methods study. *Harm Reduct J* 11: 1.
28. Martin NK, Vickerman P, Miners A, Foster GR, Hutchinson SJ, et al. (2012) Cost-effectiveness of hepatitis C virus antiviral treatment for injection drug user populations. *Hepatology* 55: 49–57.
29. Martin NK, Vickerman P, Foster GR, Hutchinson SJ, Goldberg DJ, et al. (2011) Can antiviral therapy for hepatitis C reduce the prevalence of HCV among injecting drug user populations? A modeling analysis of its prevention utility. *J Hepatol* 54: 1137–1144.
30. Martin NK, Vickerman P, Grebely J, Hellard M, Hutchinson SJ, et al. (2013) Hepatitis C virus treatment for prevention among people who inject drugs: Modeling treatment scale-up in the age of direct-acting antivirals. *Hepatology* 58: 1598–1609. 10.1002/hep.26431 [doi].
31. Zeiler I, Langlands T, Murray JM, Ritter A (2010) Optimal targeting of Hepatitis C virus treatment among injecting drug users to those not enrolled in methadone maintenance programs. *Drug Alcohol Depend* 110: 228–233. S0376-8716(10)00106-7 [pii]; 10.1016/j.drugalcdep.2010.03.006 [doi].
32. Hedrich D, Pirona A, Wiessing L (2008) From margin to mainstream: the evolution of harm reduction responses to problem drug use in Europe. *Drugs Educ Prev Policy* 15: 503–517.
33. Wiessing L, Likatavicius G, Klemopova D, Hedrich D, Nardone A, et al. (2009) Associations between availability and coverage of HIV-prevention measures and subsequent incidence of diagnosed HIV infection among injection drug users. *Am J Public Health* 99: 1049–1052. Available: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2679784/>.
34. Lettmeier B, Muhlberger N, Schwarzer R, Sroczynski G, Wright D, et al. (2008) Market uptake of new antiviral drugs for the treatment of hepatitis C. *J Hepatol* 49: 528–536. S0168-8278(08)00351-6 [pii]; 10.1016/j.jhep.2008.04.021 [doi].
35. WHO (2014) Guidelines for the Screening, Care and Treatment of Persons with Hepatitis Infection. Available: [http://apps.who.int/iris/bitstream/10665/111747/1/9789241548755\\_eng.pdf?ua=1&ua=1](http://apps.who.int/iris/bitstream/10665/111747/1/9789241548755_eng.pdf?ua=1&ua=1).
36. Pavlotsky JM, Aghemo A, Dusheiko G, Fornis X, Puoti M, et al. (2014) EASL Recommendations on Treatment of Hepatitis C - 2014.
37. Reimer J, Schulte B, Castells X, Schafer I, Polywka S, et al. (2005) Guidelines for the treatment of hepatitis C virus infection in injection drug users: status quo in the European Union countries. *Clin Infect Dis* 40 Suppl 5: S373–S378.
38. Wiessing L (2001) The access of injecting drug users to hepatitis C treatment is low and should be improved. *Euro Surveill* 5: pii = 1709. Available: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=1709>.
39. The Scottish Government (2008) Hepatitis C Action Plan for Scotland, Phase II: May 2008 – March 2011. Edinburgh: The Scottish Government.
40. Galmiche JP (1998) French consensus conference on hepatitis C: screening and treatment. *Gut* 42: 892–898.
41. Lindenburg CEA, Lambers FAE, Urbanus AT, Schinkel J, Jansen PLM, et al. (2011) Hepatitis C testing and treatment among active drug users in Amsterdam: Results from the DUTCH-C project. *European Journal of Gastroenterology and Hepatology* 23: January. Available: <http://dx.doi.org/10.1097/MEG.0b013e328340c451>.
42. Norden L, van Veen M, Lidman C, Todorov I, Guarita B, et al. (2013) Hepatitis C among injecting drug users is two times higher in Stockholm, Sweden than in Rotterdam, the Netherlands. *Subst Use Misuse* 48: 1469–1474. 10.3109/10826084.2013.793356 [doi].
43. Nelson PK, Mathers BM, Cowie B, Hagan H, Des Jarlais D, et al. (2011) Global epidemiology of hepatitis B and hepatitis C in people who inject drugs: results of systematic reviews. *Lancet* 378: 571–583. S0140-6736(11)61097-0 [pii]; 10.1016/S0140-6736(11)61097-0 [doi].
44. Wiessing L, Likatavicius G, Hedrich D, Guarita B, van de Laar MJ, et al. (2011) Trends in HIV and hepatitis C virus infections among injecting drug users in Europe, 2005 to 2010. *Euro Surveill* 16: pii = 20031. Available: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20031>.
45. Hahne SJ, Veldhuijzen IK, Wiessing L, Lim TA, Salminen M, et al. (2013) Infection with hepatitis B and C virus in Europe: a systematic review of prevalence and cost-effectiveness of screening. *BMC Infect Dis* 13: 181. 1471-2334-13-181 [pii]; 10.1186/1471-2334-13-181 [doi].
46. Stroffolini T, D'Egidio PF, Aceti A, Filippini P, Puoti M, et al. (2012) Hepatitis C virus infection among drug addicts in Italy. *J Med Virol* 84: 1608–1612. 10.1002/jmv.23370 [doi].
47. Graham CS, Baden LR, Yu E, Mrus JM, Carnie J, et al. (2001) Influence of human immunodeficiency virus infection on the course of hepatitis C virus infection: a meta-analysis. *Clin Infect Dis* 33: 562–569.
48. Rantala M, van de Laar MJ (2008) Surveillance and epidemiology of hepatitis B and C in Europe - a review. *Euro Surveill* 13.
49. European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) (2014) European Drug Report 2014. Available: <http://www.emcdda.europa.eu/edr2014>.
50. John-Baptiste A, Yeung MW, Leung V, van der Velde G, Krahn M (2012) Cost effectiveness of hepatitis C-related interventions targeting substance users and other high-risk groups: a systematic review. *Pharmacoeconomics* 30: 1015–1034. 1 [pii]; 10.2165/11597660-000000000-00000 [doi].
51. Grebely J, Dore GJ (2011) What is killing people with hepatitis C virus infection? *Semin Liver Dis* 31: 331–339.
52. Chou R, Hartung D, Rahman B, Wasson N, Cottrell EB, et al. (2013) Comparative effectiveness of antiviral treatment for hepatitis C virus infection in adults: a systematic review. *Ann Intern Med* 158: 114–123.
53. Grebely J, Prins M, Hellard M, Cox AL, Osburn WO, et al. (2012) Hepatitis C virus clearance, reinfection, and persistence, with insights from studies of injecting drug users: towards a vaccine. *Lancet Infect Dis* 12: 408–414.
54. Pellicelli AM, Barbaro G, Barbarini G, Soccorsi F (2008) Management of chronic hepatitis in drug addicts: a systematic review. *Clin Ter* 159: 41–49.
55. Hutchinson SJ, Roy KM, Wadd S, Bird SM, Taylor A, et al. (2006) Hepatitis C virus infection in Scotland: epidemiological review and public health challenges. *Scott Med J* 51: 8–15.
56. Micallef JM, Macdonald V, Jauncey M, Amin J, Rawlinson W, et al. (2007) High incidence of hepatitis C virus reinfection within a cohort of injecting drug users. *J Viral Hepat* 14: 413–418.
57. Weir MC, Grimshaw JM, Mayhew A, Fergusson D (2012) Decisions about lumping vs. splitting of the scope of systematic reviews of complex interventions are not well justified: a case study in systematic reviews of health care professional reminders. *J Clin Epidemiol* 65: 756–763.
58. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, et al. (2009) The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol* 62: e1–34. S0895-4356(09)00180-2 [pii]; 10.1016/j.jclinepi.2009.06.006 [doi].
59. Ebner N, Wanner C, Winklbaur B, Matzenauer C, Jachmann CA, et al. (2009) Retention rate and side effects in a prospective trial on hepatitis C treatment with pegylated interferon alpha-2a and ribavirin in opioid-dependent patients. *Addict Biol* 14: 227–237. ADB148 [pii]; 10.1111/j.1369-1600.2009.00148.x [doi].
60. McHutchison JG, Gordon SC, Schiff ER, Shiffman ML, Lee WM, et al. (1998) Interferon alfa-2b alone or in combination with ribavirin as initial treatment for chronic hepatitis C. Hepatitis Interventional Therapy Group. *N Engl J Med* 339: 1485–1492. 10.1056/NEJM199811193392101 [doi].
61. Mravcik V, Sebakova H (2002) Vyskyt virovych hepatitid typu B a C ve skupine injekcnich uzivatelu drog v okrese Karvina (HBV and HCV prevalence and incidence in IDUs in Karvina District, the Czech Republic). *Adiktologie* 2: 19–27.

62. Mravcik V, Petrošová B, Zábranský T, Rehak V, Coufalová M (2009) Výskyt VHC U I Njekcnich Uživateľu Drog. Edisko Pro Drogov A Drogove Závislosti 1–80.
63. Lucidarme D, Bruandet A, Ilef D, Harbonnier J, Jacob C, et al. (2004) Incidence and risk factors of HCV and HIV infections in a cohort of intravenous drug users in the North and East of France. *Epidemiol Infect* 132: 699–708.
64. Bruandet A, Lucidarme D, Decoster A, Ilef D, Harbonnier J, et al. (2006) [Incidence and risk factors of HCV infection in a cohort of intravenous drug users in the North and East of France]. *Rev Epidemiol Sante Publique* 54 Spec No1: 1S15–1S22.
65. Partanen A, Malin K, et al (2006) A-klinikasäätiön raporttisarja. 52.
66. Smyth BP, O'Connor JJ, Barry J, Keenan E (2003) Retrospective cohort study examining incidence of HIV and hepatitis C infection among injecting drug users in Dublin. *J Epidemiol Community Health* 57: 310–311.
67. Grogan L, Tiernan M, Geoghegan N, Smyth B, Keenan E (2005) Bloodborne virus infections among drug users in Ireland: a retrospective cross-sectional survey of screening, prevalence, incidence and hepatitis B immunisation uptake. *Ir J Med Sci* 174: 14–20.
68. Bravo MJ, Vallejo F, Barrio G, Brugal MT, Molist G, et al. (2012) HCV seroconversion among never-injecting heroin users at baseline: no predictors identified other than starting injection. *Int J Drug Policy* 23: 415–419.
69. Blome MA, Bjorkman P, Flamholz L, Jacobsson H, Molnégren V, et al. (2011) Minimal transmission of HIV despite persistently high transmission of hepatitis C virus in a Swedish needle exchange program. *J Viral Hepat* 18: 831–839.
70. Mansson AS, Moestrup T, Nordenfelt E, Widell A (2000) Continued transmission of hepatitis B and C viruses, but no transmission of human immunodeficiency virus among intravenous drug users participating in a syringe/needle exchange program. *Scand J Infect Dis* 32: 253–258.
71. van den Berg C, Smit C, Van BG, Coutinho R, Prins M (2007) Full participation in harm reduction programmes is associated with decreased risk for human immunodeficiency virus and hepatitis C virus: evidence from the Amsterdam Cohort Studies among drug users. *Addiction* 102: 1454–1462.
72. van den Berg CH, Smit C, Bakker M, Geskus RB, Berkhout B, et al. (2007) Major decline of hepatitis C virus incidence rate over two decades in a cohort of drug users. *Eur J Epidemiol* 22: 183–193.
73. Allen EJ, Palmateer NE, Hutchinson SJ, Cameron S, Goldberg DJ, et al. (2012) Association between harm reduction intervention uptake and recent hepatitis C infection among people who inject drugs attending sites that provide sterile injecting equipment in Scotland. *Int J Drug Policy* 23: 346–352.
74. Turner KM, Hutchinson S, Vickerman P, Hope V, Craine N, et al. (2011) The impact of needle and syringe provision and opiate substitution therapy on the incidence of hepatitis C virus in injecting drug users: pooling of UK evidence. *Addiction* 106: 1978–1988. 10.1111/j.1360-0443.2011.03515.x [doi].
75. Roy KM, Goldberg D, Taylor A, Hutchinson S, MacDonald L, et al. (2001) A method to detect the incidence of hepatitis C infection among injecting drug users in Glasgow 1993–98. *J Infect* 43: 200–205. 10.1053/jinf.2001.0908 [doi];S0163-4453(01)90908-9 [pii].
76. Roy KM, Hutchinson SJ, Wadd S, Taylor A, Cameron SO, et al. (2007) Hepatitis C virus infection among injecting drug users in Scotland: a review of prevalence and incidence data and the methods used to generate them. *Epidemiol Infect* 135: 433–442. S0950268806007035 [pii]; 10.1017/S0950268806007035 [doi].
77. Abou-Saleh M, Davis P, Rice P, Checinski K, Drummond C, et al. (2008) The effectiveness of behavioural interventions in the primary prevention of hepatitis C amongst injecting drug users: a randomised controlled trial and lessons learned. *Harm Reduct J* 5: 25.
78. Brant LJ, Ramsay ME, Balogun MA, Boxall E, Hale A, et al. (2008) Diagnosis of acute hepatitis C virus infection and estimated incidence in low- and high-risk English populations. *J Viral Hepat* 15: 871–877.
79. Health Protection Agency, Health Protection Scotland, Public Health Wales, Public Health Agency Northern Ireland (2012) Hepatitis C in the UK, 2012 Report.
80. Craine N, Hickman M, Parry JV, Smith J, Walker AM, et al. (2009) Incidence of hepatitis C in drug injectors: the role of homelessness, opiate substitution treatment, equipment sharing, and community size. *Epidemiol Infect* 137: 1255–1265.
81. Hope VD, Hickman M, Ngui SL, Jones S, Telfer M, et al. (2011) Measuring the incidence, prevalence and genetic relatedness of hepatitis C infections among a community recruited sample of injecting drug users, using dried blood spots. *J Viral Hepat* 18: 262–270.
82. Balogun MA, Murphy N, Nunn S, Grant A, Andrews NJ, et al. (2009) Prevalence and incidence of hepatitis C in injecting drug users attending genitourinary medicine clinics. *Epidemiol Infect* 137: 980–987. S0950268808001660 [pii]; 10.1017/S0950268808001660 [doi].
83. McDonald SA, Hutchinson SJ, Cameron SO, Innes HA, McLeod A, et al. (2012) Examination of the risk of reinfection with hepatitis C among injecting drug users who have been tested in Glasgow. *Int J Drug Policy* 23: 353–357.
84. Aarons E, Grant P, Soldan K, Luton P, Tang J, et al. (2004) Failure to diagnose recent hepatitis C virus infections in London injecting drug users. *J Med Virol* 73: 548–553.
85. Judd A, Hickman M, Jones S, McDonald T, Parry JV, et al. (2005) Incidence of hepatitis C virus and HIV among new injecting drug users in London: prospective cohort study. *BMJ* 330: 24–25. bmj.38286.841227.7C [pii]; 10.1136/bmj.38286.841227.7C [doi].
86. Christensen PB, Krarup HB, Niesters HG, Norder H, Georgsen J (2000) Prevalence and incidence of bloodborne viral infections among Danish prisoners. *Eur J Epidemiol* 16: 1043–1049.
87. Champion JK, Taylor A, Hutchinson S, Cameron S, McMenamin J, et al. (2004) Incidence of hepatitis C virus infection and associated risk factors among Scottish prison inmates: a cohort study. *Am J Epidemiol* 159: 514–519.
88. Grady BP, Vanhommerig JW, Schinkel J, Weegink CJ, Bruisten SM, et al. (2012) Low incidence of reinfection with the hepatitis C virus following treatment in active drug users in Amsterdam. *Eur J Gastroenterol Hepatol* . 10.1097/MEG.0b013e32835702a8 [doi].
89. Backmund M, Meyer K, Edlin BR (2004) Infrequent reinfection after successful treatment for hepatitis C virus infection in injection drug users. *Clin Infect Dis* 39: 1540–1543. CID33778 [pii]; 10.1086/425361 [doi].
90. Gombas W, Fischer G, Jagsch R, Eder H, Okamoto I, et al. (2000) Prevalence and distribution of hepatitis C subtypes in patients with opioid dependence. *Eur Addict Res* 6: 198–204.
91. Mathei C, Wollants E, Verbeeck J, Van RM, Robaey G, et al. (2005) Molecular epidemiology of hepatitis C among drug users in Flanders, Belgium: association of genotype with clinical parameters and with sex- and drug-related risk behaviours. *Eur J Clin Microbiol Infect Dis* 24: 514–522.
92. Micalessi MI, Gerard C, Amey L, Plasschaert S, Brochier B, et al. (2008) Distribution of hepatitis C virus genotypes among injecting drug users in contact with treatment centers in Belgium, 2004–2005. *J Med Virol* 80: 640–645.
93. Bourgeois S, Schrooten W, Robaey G (2010) High viral response in a multidisciplinary network not organized under one roof for antiviral management of chronic hepatitis C viral patients infected after substance use. *Journal of Hepatology* 52: S103.
94. Reitox National Focal Point Bulgaria (2009) 2009 National Report (2008 Data) to the EMCDDA. Available: [http://www.emcdda.europa.eu/attachements.cfm/att\\_142615\\_EN\\_BG-NR2009.pdf](http://www.emcdda.europa.eu/attachements.cfm/att_142615_EN_BG-NR2009.pdf).
95. Teoharov P, Pavlov I (2009) Genetic diversity of hepatitis C virus among Bulgarian injecting drug users with hepatitis C. *Clinical Microbiology and Infection*. Conference: 19<sup>th</sup> European Congress of Clinical Microbiology and Infectious Diseases (ECCMID) Helsinki Finland. Conference Start: 20090516 Conference End: 20090519. Conference Publication: (var.pagings). 15 (pp S594), 2009. Date of Publication: May 2009. [Journal: Conference Abstract]. *Clinical Microbiology and Infection*.
96. Demetriou VL, van de Vijver DA, Hezka J, Kostrikis LG, Kostrikis LG (2010) Hepatitis C infection among intravenous drug users attending therapy programs in Cyprus. *J Med Virol* 82: 263–270.
97. Krekulova L, Rehak V, Strunecky O, Nemecek V (2009) Current situation and trends in the hepatitis C virus genotype distribution among injecting drug users in the Czech Republic. *Epidemiol Mikrobiol Immunol* 58: 84–89.
98. Nechanska B (2013) Udaje v Narodnim registru uzivateľu lekárskej indikovaných substitučných latek - rok 2012 (Information in the National Register of Medically Indicated Substitution Substances - 2012). Aktuální informace.
99. Mossner BK, Skamling M, Jorgensen TR, Georgsen J, Pedersen C, et al. (2010) Decline in hepatitis B infection observed after 11 years of regional vaccination among Danish drug users. *J Med Virol* 82: 1635–1639.
100. Omland LH, Christensen PB, Krarup H, Jepsen P, Weis N, et al. (2011) Mortality among patients with cleared hepatitis C virus infection compared to the general population: a Danish nationwide cohort study. *PLoS One* 6: e22476.
101. Alric L, Fort M, Izopet J, Vinel JP, Bureau C, et al. (2000) Study of host- and virus-related factors associated with spontaneous hepatitis C virus clearance. *Tissue Antigens* 56: 154–158.
102. Elghouzzi MH, Bouchardeau F, Pilonel J, Boiret E, Tirtaine C, et al. (2000) Hepatitis C virus: routes of infection and genotypes in a cohort of anti-HCV-positive French blood donors. *Vox Sang* 79: 138–144.
103. Cournot M, Glibert A, Castel F, Druart F, Imani K, et al. (2004) Management of hepatitis C in active drug users: experience of an addiction care hepatology unit. *Gastroenterol Clin Biol* 28: 533–539.
104. Lucidarme D, Decoster A, Fremaux D, Harbonnier J, Jacob C, et al. (2007) Routine practice HCV infection screening with saliva samples: multicentric study in an intravenous drug user population. *Gastroenterol Clin Biol* 31: 480–484.
105. Moussalli J, Delaquaize H, Boubilly D, Lhomme JP, Merleau PJ, et al. (2010) Factors to improve the management of hepatitis C in drug users: an observational study in an addiction centre. *Gastroenterol Res Pract* 2010: 10.1155/2010/261472 [doi].
106. Christofidou M, Jelastopulu E, Economides G, Spiliopoulou I, Siagris D, et al. (2008) Epidemiology of Chronic Hepatitis C Virus Infection in High Risk Groups. *Hepatitis Monthly* 8: 11–16.
107. Cullen W, Stanley J, Langton D, Kelly Y, Bury G (2007) Management of hepatitis C among drug users attending general practice in Ireland: baseline data from the Dublin area hepatitis C in general practice initiative. *Eur J Gen Pract* 13: 5–12.
108. Keating S, Coughlan S, Connell J, Sweeney B, Keenan E (2005) Hepatitis C viral clearance in an intravenous drug-using cohort in the Dublin area. *Ir J Med Sci* 174: 37–41.

109. Santolamazza M, Delle MM, Alvino A, Bacosi M, D'Innocenzo S, et al. (2001) Multiple viral infections in a group of intravenous drug users: hepatitis B virus exposure is the risk factor. *Eur J Gastroenterol Hepatol* 13: 1347–1354.
110. van den Berg CH, Grady BP, Schinkel J, van de Laar T, Molenkamp R, et al. (2011) Female sex and IL28B, a synergism for spontaneous viral clearance in hepatitis C virus (HCV) seroconverters from a community-based cohort. *PLoS One* 6: e27555.
111. Sultana C, Vagu C, Temereanca A, Grancea C, Slobozeanu J, et al. (2011) Hepatitis C Virus Genotypes in Injecting Drug Users from Romania. *Cent Eur J Med* 6: 672–678.
112. Lidman C, Norden L, Kaberg M, Kall K, Franck J, et al. (2009) Hepatitis C infection among injection drug users in Stockholm Sweden: prevalence and gender. *Scand J Infect Dis* 41: 679–684.
113. van de Laar TJ, Molenkamp R, van den Berg C, Schinkel J, Beld MG, et al. (2009) Frequent HCV reinfection and superinfection in a cohort of injecting drug users in Amsterdam. *J Hepatol* 51: 667–674.
114. Cullen BL, Hutchinson SJ, Cameron SO, Anderson E, Ahmed S, et al. (2012) Identifying former injecting drug users infected with hepatitis C: an evaluation of a general practice-based case-finding intervention. *J Public Health (Oxf)* 34: 14–23.
115. Jowett SL, Agarwal K, Smith BC, Craig W, Hewett M, et al. (2001) Managing chronic hepatitis C acquired through intravenous drug use. *QJM* 94: 153–158.
116. McDonald SA, Hutchinson SJ, Mills PR, Bird SM, Cameron S, et al. (2011) The influence of hepatitis C and alcohol on liver-related morbidity and mortality in Glasgow's injecting drug user population. *J Viral Hepat* 18: e126–e133.
117. Hofer H, Watkins-Riedel T, Janata O, Penner E, Holzmann H, et al. (2003) Spontaneous viral clearance in patients with acute hepatitis C can be predicted by repeated measurements of serum viral load. *Hepatology* 37: 60–64.
118. Vitous A, Hobstova J (2007) [Infectious diseases in problem drug users hospitalized in the infectious ward of the Motol University Hospital in 2002–2005]. *Klin Mikrobiol Infekc Lek* 13: 70–75.
119. Santantonio T, Medda E, Ferrari C, Fabris P, Cariti G, et al. (2006) Risk factors and outcome among a large patient cohort with community-acquired acute hepatitis C in Italy. *Clin Infect Dis* 43: 1154–1159.
120. Haushofer AC, Koptcy C, Hauer R, Brunner H, Halbmayr WM (2001) HCV genotypes and age distribution in patients of Vienna and surrounding areas. *J Clin Virol* 20: 41–47.
121. Ciccozzi M, Zehender G, Cento V, Lo PA, Teoharov P, et al. (2011) Molecular analysis of hepatitis C virus infection in Bulgarian injecting drug users. *J Med Virol* 83: 1565–1570.
122. Krekulova L, Rehak V, Madrigal N, Johnson M, Killoran P, et al. (2001) Genotypic and epidemiologic characteristics of hepatitis C virus infections among recent injection drug user and nonuser populations. *Clin Infect Dis* 33: 1435–1438.
123. Tallo T, Norder H, Tefanova V, Krispin T, Schmidt J, et al. (2007) Genetic characterization of hepatitis C virus strains in Estonia: fluctuations in the predominating subtype with time. *J Med Virol* 79: 374–382.
124. Bourliere M, Barberin JM, Rotily M, Guagliardo V, Portal I, et al. (2002) Epidemiological changes in hepatitis C virus genotypes in France: evidence in intravenous drug users. *J Viral Hepat* 9: 62–70.
125. Payan C, Roudot-Thoraval F, Marcellin P, Bled N, Duverlie G, et al. (2005) Changing of hepatitis C virus genotype patterns in France at the beginning of the third millennium: The GEMHEP GenoCII Study. *J Viral Hepat* 12: 405–413.
126. Backmund M, Meyer K, Von Zielonka M, Eichenlaub D (2001) Treatment of hepatitis C infection in injection drug users. *Hepatology* 34: 188–193. S0270-9139(01)99075-5 [pii]; 10.1053/jhep.2001.25882 [doi].
127. Ross RS, Viazov S, Renzing-Kohler K, Roggendorf M (2000) Changes in the epidemiology of hepatitis C infection in Germany: shift in the predominance of hepatitis C subtypes. *J Med Virol* 60: 122–125.
128. Schroter M, Zollner B, Schafer P, Reimer A, Muller M, et al. (2002) Epidemiological dynamics of hepatitis C virus among 747 German individuals: new subtypes on the advance. *J Clin Microbiol* 40: 1866–1868.
129. Gigi E, Sinakos E, Lalla T, Vrettou E, Orphanou E, et al. (2007) Treatment of intravenous drug users with chronic hepatitis C: treatment response, compliance and side effects. *Hippokratia* 11: 196–198.
130. Katsoulidou A, Sypsa V, Tassopoulos NC, Boletis J, Karafoulidou A, et al. (2006) Molecular epidemiology of hepatitis C virus (HCV) in Greece: temporal trends in HCV genotype-specific incidence and molecular characterization of genotype 4 isolates. *J Viral Hepat* 13: 19–27.
131. Manolakopoulos S, Deutsch MJ, Anagnostou O, Karatapanis S, Tiniakou E, et al. (2010) Substitution treatment or active intravenous drug use should not be contraindications for antiretroviral treatment in drug users with chronic hepatitis C. *Liver International* 30: November. Available: <http://dx.doi.org/10.1111/j.1478-3231.2010.02341.x>.
132. Papadopoulos V, Gogou A, Mylopoulou T, Mimidis K (2010) Should active injecting drug users receive treatment for chronic hepatitis C? *Arq Gastroenterol* 47: 238–241.
133. Raptopoulou M, Touloumi G, Tzourmakliotis D, Nikolopoulou G, Dimopoulou M, et al. (2011) Significant epidemiological changes in chronic hepatitis C infection: results of the nationwide HEPNET-GREECE cohort study. *Hippokratia* 15: 26–31.
134. Savvas SP, Koskinas J, Sinani C, Hadziyannis A, Spanou F, et al. (2005) Changes in epidemiological patterns of HCV infection and their impact on liver disease over the last 20 years in Greece. *J Viral Hepat* 12: 551–557.
135. Dal Molin G, Ansaldo F, Biagi C, D'Agaro P, Comar M, et al. (2002) Changing molecular epidemiology of hepatitis C virus infection in Northeast Italy. *J Med Virol* 68: 352–356.
136. Saracco G, Sostegni R, Ghisetti V, Rocca G, Cariti G, et al. (2000) Hepatitis C virus genotypes in a non-cirrhotic Italian population with chronic hepatitis C: correlation with clinical, virological and histological parameters. Results of a prospective multicentre study. *J Viral Hepat* 7: 124–129.
137. Sereno S, Perinelli P, Laghi V (2009) Changes in the prevalence of hepatitis C virus genotype among Italian injection drug users—relation to period of injection started. *J Clin Virol* 45: 354–357.
138. Liakina V, Speiciene D, Irmus A, Valantinas J (2009) Changes in hepatitis C virus infection routes and genotype distribution in a Lithuanian cohort with chronic hepatitis C. *Med Sci Monit* 15: H17–H23.
139. Chlabicz S, Flisiak R, Kowalczyk O, Grzeszczuk A, Pytel-Krolczuk B, et al. (2008) Changing HCV genotypes distribution in Poland—relation to source and time of infection. *J Clin Virol* 42: 156–159.
140. Calado RA, Rocha MR, Parreira R, Piedade J, Venenno T, et al. (2011) Hepatitis C virus subtypes circulating among intravenous drug users in Lisbon, Portugal. *J Med Virol* 83: 608–615.
141. Seme K, Vrhovac M, Mocilnik T, Maticic M, Lesnicar G, et al. (2009) Hepatitis C virus genotypes in 1,504 patients in Slovenia, 1993–2007. *J Med Virol* 81: 634–639.
142. Serra MA, Rodriguez F, del Olmo JA, Escudero A, Rodrigo JM (2003) Influence of age and date of infection on distribution of hepatitis C virus genotypes and fibrosis stage. *J Viral Hepat* 10: 183–188.
143. Touceda S, Pereira M, Agulla A (2002) Prevalence of hepatitis C virus genotypes in the area of El Ferrol (La Coruna, Spain). *Enferm Infecc Microbiol Clin* 20: 200–204.
144. van de Laar TJ, Langendam MW, Bruisten SM, Welp EA, Verhaest I, et al. (2008) Changes in risk behavior and dynamics of hepatitis C virus infections among young drug users in Amsterdam, the Netherlands. *J Med Virol* 77: 509–518.
145. Balogun MA, Laurichesse H, Ramsay ME, Sellwood J, Westmoreland D, et al. (2003) Risk factors, clinical features and genotype distribution of diagnosed hepatitis C virus infections: a pilot for a sentinel laboratory-based surveillance. *Commun Dis Public Health* 6: 34–39.
146. Jack K, Willott S, Manners J, Varnam MA, Thomson BJ (2009) Clinical trial: a primary-care-based model for the delivery of anti-viral treatment to injecting drug users infected with hepatitis C. *Aliment Pharmacol Ther* 29: 38–45. APT3872 [pii]; 10.1111/j.1365-2036.2008.03872.x [doi].
147. Mohsen AH (2001) The epidemiology of hepatitis C in a UK health regional population of 5.12 million. *Gut* 48: 707–713.
148. Öbig (2013) Gesundheit Österreich GmbH/ Österreichisches Bundesinstitut für Gesundheitswesen - GÖG/ÖBIG (unpublished data).
149. Mathei C (2011) Internal document. Free Clinic: Antwerp.
150. National Focal Point (2010) Annual report on the state of drug related problems in Bulgaria.
151. Huik K, Sadam M, Karki T, Avi R, Krispin T, et al. (2010) CCL3L1 copy number is a strong genetic determinant of HIV seropositivity in Caucasian intravenous drug users. *J Infect Dis* 201: 730–739.
152. Defosse G, Verneau A, Ingrand I, Silvain C, Ingrand P, et al. (2008) Evaluation of the French national plan to promote screening and early management of viral hepatitis C, between 1997 and 2003: a comparative cross-sectional study in Poitou-Charentes region. *Eur J Gastroenterol Hepatol* 20: 367–372. 10.1097/MEG.0b013e3282f479ab [doi]; 00042737-200805000-00001 [pii].
153. Jauffret-Roustide M, Le SY, Couturier E, Thierry D, Rondy M, et al. (2009) A national cross-sectional study among drug-users in France: epidemiology of HCV and highlight on practical and statistical aspects of the design. *BMC Infect Dis* 9: 113.
154. Backmund M, Meyer K, Henkel C, Reimer J, Wachtler M, et al. (2005) Risk Factors and predictors of human immunodeficiency virus infection among injection drug users. *Eur Addict Res* 11: 138–144.
155. Muller MC, Pichler M, Martin G, Plover D, Winter C, et al. (2009) Burden of disease and level of patient's medical care in substitution treatment for opiates. *Med Klin* 104: 913–917.
156. Zimmermann R (2012) DRUCK-Studie - Drogen und chronische Infektionskrankheiten in Deutschland. Ergebnisse der Pilotierung eines Serov- und Verhaltenssurveys bei i.v. Drogengebrauchern. *Epidem Bull* 33.
157. Giotakos O, Bourtsoukli P, Paraskeyopoulou T, Spandoni P, Stasinou S, et al. (2003) Prevalence and risk factors of HIV, hepatitis B and hepatitis C in a forensic population of rapists and child molesters. *Epidemiol Infect* 130: 497–500.
158. Focal Point (2009) Greek REITOX Focal Point (EKTEPN), University Mental Health Research Institute (UMHRI) (unpublished data).
159. Gyarmathy VA, Neaigus A, Ujhelyi E (2009) Vulnerability to drug-related infections and co-infections among injecting drug users in Budapest, Hungary. *Eur J Public Health* 19: 260–265.
160. Tresó B, Barcsay E, Tarjan A, Horvath G, Dencs A, et al. (2012) Prevalence and correlates of HCV, HVB, and HIV infection among prison inmates and staff, Hungary. *J Urban Health* 89: 108–116.

161. Camoni L, Regine V, Saffa MC, Nicoletti G, Canuzzi P, et al. (2010) Continued high prevalence of HIV, HBV and HCV among injecting and noninjecting drug users in Italy. *Ann Ist Super Sanita* 46: 59–65.
162. Napoli C, Tafuri S, Pignataro N, Tedesco G, Maria AS, et al. (2010) Risk factors for HBV/HIV/HCV in drug addicts: a survey of attendees of a department of pathological dependence. *J Prev Med Hyg* 51: 101–104.
163. Quaglio G, Lugoboni F, Pajusko B, Sarti M, Talamini G, et al. (2003) Factors associated with hepatitis C virus infection in injection and noninjection drug users in Italy. *Clin Infect Dis* 37: 33–40.
164. Babudieri S, Longo B, Sarmati L, Starnini G, Dori L, et al. (2005) Correlates of HIV, HBV, and HCV infections in a prison inmate population: results from a multicentre study in Italy. *J Med Virol* 76: 311–317.
165. Trapencieris M, Snikere S, Petersons A, Kaupe R (2013) Drug use patterns and trends in Latvia. Drug users cohort study 6th phase results (Narkotiku lietasanas paradumi un tendences Latvija. Narkotiku lietotaju kohortas petijuma 6. posma rezultati).
166. National Institute of Health Development (2009) Prevalence of HIV and other Infections and Risk Behaviour Among Injecting Drug Users In Latvia, Lithuania And Estonia in 2007 Study report, 2009. Available: [http://balthiv.com/download-doc.php?file=ENCAP\\_ENG.pdf](http://balthiv.com/download-doc.php?file=ENCAP_ENG.pdf).
167. Karnite A, Uuskula A, Luizov A, Rusev A, Talu A, et al. (2013) Assessment on HIV and TB knowledge and the barriers related to access to care among vulnerable groups. Report on a cross-sectional study among injecting drug users. (Zinašanas par HIV un tuberkulozi un šķ, e-rsl, i apru-pes san, emšanai socia-la-s atstumti-bas riska grupa-s. Injice-jamo narkotiku lietota-ju viduveikta šķ, e-rsgriezuma pe-ti-juma rezulta-ti) (in press).
168. Removille N, Origer A, Couffignal S, Vaillant M, Schmit JC, et al. (2011) A hepatitis A, B, C and HIV prevalence and risk factor study in ever injecting and non-injecting drug users in Luxembourg associated with HAV and HBV immunisations. *BMC Public Health* 11: 351.
169. Bielak A, Zielinski A (2002) Występowanie chorób zakaźnych (wzr typu B i C, HIV) wśród narkomanów przyjmujących dożylnie środki odurzające. [Infectious diseases (HBV, HCV and HIV) among injecting drug users.] (unpublished data).
170. Rosinska M, Zielinski A (2004) Estimating the prevalence of infectious diseases (hepatitis C and B, HIV) among drug users taking drugs by injection in cities with varying degrees of implementation of harm reduction programs (Oszacowanie występowania chorób zakaźnych (wirusowe zapalenie wątroby typu C i B, HIV) wśród narkomanów przyjmujących środki odurzające w iniekcji w miastach o różnym stopniu realizacji programów redukcji szkód).
171. Rosinska M (2005) Estimating the prevalence of infectious diseases (hepatitis C and B, HIV) among drug users taking drugs by injection with a special emphasis on migration between countries (Oszacowanie występowania chorób zakaźnych (wirusowe zapalenie wątroby typu C i B, HIV) wśród narkomanów przyjmujących środki odurzające w iniekcji ze szczególnym uwzględnieniem migracji pomiędzy krajami).
172. Rosinska M (2009) Estimating the prevalence of infectious diseases (hepatitis C and B, HIV) among people who injected drugs in Gdansk and Krakow (Oszacowanie występowania chorób zakaźnych (wirusowe zapalenie wątroby typu C i B, HIV) wśród osób przyjmujących środki odurzające we wstrzyknięciach w Gdansk i w Krakowie).
173. Barros H, Ramos E, Lucas R (2008) A survey of HIV and HCV among female prison inmates in Portugal. *Cent Eur J Public Health* 16: 116–120.
174. Institute of Public Health (2008) Report on the Drug Situation 2008 of the Republic of Slovenia. 68–69.
175. Saiz de la Hoya P, Bedia M, Murcia J, Cebria J, Sanchez-Paya J, et al. (2005) [Predictive markers of HIV and HCV infection and co-infection among inmates in a Spanish prison]. *Enferm Infecc Microbiol Clin* 23: 53–57.
176. Rodriguez-Vidal FF, Baz MJ, Fernandez EJ, Najarro F (2003) [Hepatitis C virus infection in a first level rural hospital: descriptive study in the decade 1991–1999]. *Enferm Infecc Microbiol Clin* 21: 142–146.
177. Lumberras B, Jarrin I, Del AJ, Perez-Hoyos S, Muga R, et al. (2006) Impact of hepatitis C infection on long-term mortality of injecting drug users from 1990 to 2002: differences before and after HAART. *AIDS* 20: 111–116.
178. Bassani S, Toro C, de la Fuente L, Brugal MT, Jimenez V, et al. (2004) Rate of infection by blood-borne viruses in active heroin users in 3 Spanish cities. *Med Clin (Barc)* 122: 570–572.
179. de los Cobos CT, Casanueva GM, Jove GC (2003) Profile of drug users admitted to a hospital. *An Med Interna* 20: 504–509.
180. Folch C, Casabona J, Espelt A, Majo X, Meroño M, et al. (2013) Gender differences in HIV risk behaviours among intravenous drug users in Catalonia, Spain. *Gac Sanit*.
181. Hernandez-Aguado I, Ramos-Rincon JM, Avinio MJ, Gonzalez-Aracil J, Perez-Hoyos S, et al. (2001) Measures to reduce HIV infection have not been successful to reduce the prevalence of HCV in intravenous drug users. *Eur J Epidemiol* 17: 539–544.
182. Huntington S, Folch C, Gonzalez V, Meroño M, Ncube F, et al. (2010) [Prevalence of human immunodeficiency virus and hepatitis C virus, and associated factors among injecting drug users in Catalonia]. *Enferm Infecc Microbiol Clin* 28: 236–238.
183. Folch C, Casabona J, Brugal MT, Majó X, Meroño M, et al. (2009) Prevalencia de VIH, VHC y de otras ITS en usuarios de droga por vía parenteral reclutados en centros de reducción de daños [Prevalence of HIV, HCV and other STIs among IDUs recruited from harm reduction centres].
184. Sanvisens A, Fuster D, Serra I, Tor J, Tural C, et al. (2011) Estimated liver fibrosis and its impact on all-cause mortality of HCV-monoinfected and HCV/HIV-coinfected drug users. *Curr HIV Res* 9: 256–262.
185. Hope VD, Judd A, Hickman M, Lamagni T, Hunter G, et al. (2001) Prevalence of hepatitis C among injection drug users in England and Wales: is harm reduction working? *Am J Public Health* 91: 38–42.
186. Marongiu A, Hope VD, Parry JV, Ncube F (2012) Male IDUs who have sex with men in England, Wales and Northern Ireland: are they at greater risk of bloodborne virus infection and harm than those who only have sex with women? *Sex Transm Infect* 88: 456–461.
187. Health Protection Scotland (2008) The Needle Exchange Surveillance Initiative (NESI): Prevalence of HCV, HIV and injecting risk behaviours among injecting drug users attending needle exchanges in Scotland, 2007.
188. Wilkinson M, Crawford V, Tippet A, Jolly F, Turton J, et al. (2009) Community-based treatment for chronic hepatitis C in drug users: High rates of compliance with therapy despite ongoing drug use. *Alimentary Pharmacology and Therapeutics* 29: January. Available: <http://dx.doi.org/10.1111/j.1365-2036.2008.03834.x>.
189. HPA HPS, National Public Health Service for Wales, CDSC Northern Ireland, CRDHB (2009) Shooting Up: Infections among injecting drug users in the United Kingdom 2008.
190. Christensen PB, Hay G, Jepsen P, Omland LH, Just SA, et al. (2012) Hepatitis C prevalence in Denmark -an estimate based on multiple national registers. *BMC Infect Dis* 12: 178.
191. Jauffret-Roustide M, Emmanuelli J, Quaglia M, Barin F, Arduin P, et al. (2006) Impact of a harm-reduction policy on HIV and hepatitis C virus transmission among drug users: recent French data—the ANRS-Coquelicot Study. *Subst Use Misuse* 41: 1603–1621. W46167756681022 [pii]; 10.1080/10826080600847951 [doi].
192. Hope V, Parry JV, Marongui A, Ncube F (2012) Hepatitis C infection among recent initiates to injecting in England 2000–2008: Is a national hepatitis C action plan making a difference? *J Viral Hepat* 19: 55–64.
193. Health Protection Agency, Health Protection Scotland, Public Health Wales, Public Health Agency Northern Ireland (2012) Unlinked Anonymous Monitoring Survey of People Who Inject Drugs in contact with specialist services: data tables update July 2012. Available: [http://www.hpa.org.uk/web/HPAwebFile/HPAweb\\_C/1317135226434](http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1317135226434).
194. McDonald SA, Hutchinson SJ, Mills PR, Bird SM, Robertson C, et al. (2010) Diagnosis of hepatitis C virus infection in Scotland's injecting drug user population. *Epidemiol Infect* 138: 393–402.
195. McDonald SA, Hutchinson SJ, Palmateer NE, Allen E, Cameron SO, et al. (2013) Decrease in health-related quality of life associated with awareness of hepatitis C virus infection among people who inject drugs in Scotland. *J Hepatol* 58: 460–466. S0168-8278(12)00836-7 [pii]; 10.1016/j.jhep.2012.11.004 [doi].
196. Agostini H, Castera L, Melin P, Cattan L, Roudot-Thoraval F (2007) HEPACOM: multicenter, observational prospective study of outcome and monitoring of HCV positive antiviral-naïve patients managed in the French health care system. *Gastroenterologie Clinique et Biologique* 31: 1074–1080.
197. Grando-Lemaire V, Goisset P, Sorge F, Trinchet JC, Castera L, et al. (2002) Hepatitis C virus screening in drug users in an addiction out-patient unit. *Gastroenterol Clin Biol* 26: 1091–1096. MDOI-GCB-12-2002-26-12-0399-8320-101019-ART5 [pii].
198. Perut V, Labalette C, Sogni P, Ferrand I, Salmon-Ceron D, et al. (2009) Access to care of patients with chronic hepatitis C virus infection in a university hospital: Is opioid dependence a limiting condition? *Drug Alcohol Depend* 104: 78–83.
199. Schulte B, Schutt S, Brack J, Isernhagen K, Deibler P, et al. (2010) Successful treatment of chronic hepatitis C virus infection in severely opioid-dependent patients under heroin maintenance. *Drug Alcohol Depend* 109: 248–251. S0376-8716(10)00036-0 [pii]; 10.1016/j.drugalcdep.2010.01.009 [doi].
200. Gazdag G, Horvath G, Szabo O, Ungvari GS (2011) Difficulties with interferon treatment in former intravenous drug users. *Braz J Infect Dis* 15: 163–166.
201. Gazdag G, Horvath G, Szabo O, Ungvari GS (2012) Referral of intravenous drug users for antiviral treatment: effectiveness of hepatitis C case-finding programmes. *Cent Eur J Public Health* 20: 223–225.
202. Cullen W, Kelly Y, Stanley J, Langton D, Bury G (2005) Experience of hepatitis C among current or former heroin users attending general practice. *Ir Med J* 98: 73–74.
203. Guadagnino V, Trotta MP, Montesano F, Babudieri S, Caroleo B, et al. (2007) Effectiveness of a multi-disciplinary standardized management model in the treatment of chronic hepatitis C in drug addicts engaged in detoxification programmes. *Addiction* 102: 423–431. ADD1698 [pii]; 10.1111/j.1360-0443.2006.01698.x [doi].
204. Crespo J, Garcia F, Castro B, Pons F (2001) Chronic hepatitis (HCV) among intravenous drug users (IDU); reasons for not initiating the antiviral treatment. [Spanish]. *Adicciones* 13: 2001.
205. Croes E, Veen van de C (2012) Hepatitis C in de verslavingszorg. De effectiviteit van de hepatitis C informatiecampagne.
206. Van Veen M (2009) Briefrapport Infectieziektebestrijding in de verslavingszorg in Nederland.

207. Omland LH, Jepsen P, Weis N, Christensen PB, Laursen AL, et al. (2010) Mortality in HIV-infected injection drug users with active vs cleared hepatitis C virus-infection: a population-based cohort study. *J Viral Hepat* 17: 261–268.
208. Hernando V, Perez-Cachafeiro S, Lewden C, Gonzalez J, Segura F, et al. (2012) All-cause and liver-related mortality in HIV positive subjects compared to the general population: differences by HCV co-infection. *J Hepatol* 57: 743–751.
209. Grady B, van den Berg C, van der Helm J, Schinkel J, Coutinho R, et al. (2011) No impact of hepatitis C virus infection on mortality among drug users during the first decade after seroconversion. *Clin Gastroenterol Hepatol* 9: 786–792.
210. Matser A, Urbanus A, Geskus R, Kretzschmar M, Xiridou M, et al. (2012) The effect of hepatitis C treatment and human immunodeficiency virus (HIV) co-infection on the disease burden of hepatitis C among injecting drug users in Amsterdam. *Addiction* 107: 614–623. 10.1111/j.1360-0443.2011.03654.x [doi].
211. Hutchinson SJ, Bird SM, Goldberg DJ (2005) Modeling the current and future disease burden of hepatitis C among injection drug users in Scotland. *Hepatology* 42: 711–723.
212. Rondy M, Wiessing L, Hutchinson SJ, Mathei C, Mathis F, et al. (2013) Hepatitis C prevalence in injecting drug users in Europe, 1990–2007: impact of study recruitment setting. *Epidemiol Infect* 141: 563–572. S0950268812000921 [pii]; 10.1017/S0950268812000921 [doi].
213. Lattimore S, Irving W, Collins S, Penman C, Ramsay M (2014) Using surveillance data to determine treatment rates and outcomes for patients with chronic hepatitis C virus infection. *Hepatology* 59: 1343–1350. 10.1002/hep.26926 [doi].
214. Barreiro P, Fernandez-Montero JV, de Mendoza C, Labarga P, Soriano V (2014) Towards hepatitis C eradication from the HIV-infected population. *Antiviral Res* 105: 1–7. S0166-3542(14)00038-2 [pii]; 10.1016/j.antiviral.2014.02.004 [doi].
215. Janssen-Cilag International NV (2014) OLYSIO (simeprevir) receives marketing authorisation in the European Union for the treatment of adults with hepatitis C genotype 1 and 4 infection. Available: <https://www.jnj.com/news/all/OLYSIO-simeprevir-receives-marketing-authorisation-in-the-European-Union-for-the-treatment-of-adults-with-hepatitis-C-genotype-1-and-4-infection>.
216. Hill A, Khoo S, Simmons B, Ford N (2013) What is the minimum cost per person to cure HCV?
217. Pybus OG, Cochrane A, Holmes EC, Simmonds P (2005) The hepatitis C virus epidemic among injecting drug users. *Infect Genet Evol* 5: 131–139.
218. van Asten L, Verhaest I, Lamzira S, Hernandez-Aguado I, Zangerle R, et al. (2004) Spread of hepatitis C virus among European injection drug users infected with HIV: a phylogenetic analysis. *J Infect Dis* 189: 292–302.
219. de Bruijne J, Schinkel J, Prins M, Koekkoek SM, Aronson SJ, et al. (2009) Emergence of hepatitis C virus genotype 4: phylogenetic analysis reveals three distinct epidemiological profiles. *J Clin Microbiol* 47: 3832–3838.
220. Eriksen MB, Jorgensen LB, Krarup H, Laursen AL, Christensen PB, et al. (2010) Molecular and epidemiological profiles of hepatitis C virus genotype 4 in Denmark. *J Med Virol* 82: 1869–1877.
221. Vickerman P, Grebely J, Dore GJ, Sacks-Davis R, Page K, et al. (2012) The more you look, the more you find: effects of hepatitis C virus testing interval on reinfection incidence and clearance and implications for future vaccine study design. *J Infect Dis* 205: 1342–1350. jis213 [pii]; 10.1093/infdis/jis213 [doi].
222. Kiehlend KB, Skaug K, Amundsen EJ, Dalgard O (2013) All-cause and liver-related mortality in hepatitis C infected drug users followed for 33 years: a controlled study. *J Hepatol* 58: 31–37. S0168-8278(12)00687-3 [pii]; 10.1016/j.jhep.2012.08.024 [doi].
223. Alavi M, Law MG, Grebely J, Thein HH, Walter S, et al. (2014) Lower life expectancy among people with an HCV notification: a population-based linkage study. *J Viral Hepat* 21: e10–e18. 10.1111/jvh.12245 [doi].
224. Mathers BM, Degenhardt L, Bucello C, Lemon J, Wiessing L, et al. (2013) Mortality among people who inject drugs: a systematic review and meta-analysis. *Bull World Health Organ* 91: 102–123.
225. Hope VD, Eramova I, Capurro D, Donoghoe MC (2014) Prevalence and estimation of hepatitis B and C infections in the WHO European Region: a review of data focusing on the countries outside the European Union and the European Free Trade Association. *Epidemiol Infect* 142: 270–286. S0950268813000940 [pii]; 10.1017/S0950268813000940 [doi].
226. Mathers BM, Degenhardt L, Phillips B, Wiessing L, Hickman M, et al. (2008) Global epidemiology of injecting drug use and HIV among people who inject drugs: a systematic review. *Lancet* 372: 1733–1745. S0140-6736(08)61311-2 [pii]; 10.1016/S0140-6736(08)61311-2 [doi].
227. Wiessing L, van de Laar MJ, Donoghoe MC, Guarita B, Klempova D, et al. (2008) HIV among injecting drug users in Europe: increasing trends in the East. *Euro Surveill* 13.
228. Hagan H, Snyder N, Hough E, Yu T, McKeirnan S, et al. (2002) Case-reporting of acute hepatitis B and C among injection drug users. *J Urban Health* 79: 579–585. 10.1093/jurban/79.4.579 [doi].
229. Hansen N, Cowan S, Christensen PB, Weis N (2008) Reporting chronic hepatitis B and C in Denmark. *Ugeskr Laeger* 170: 1567–1570. VP52123 [pii].
230. Sutton AJ, Hope VD, Mathei C, Mravcic V, Sebakova H, et al. (2008) A comparison between the force of infection estimates for blood-borne viruses in injecting drug user populations across the European Union: a modelling study. *J Viral Hepat* 15: 809–816. JVH1041 [pii]; 10.1111/j.1365-2893.2008.01041.x [doi].
231. ECDC (2013) Hepatitis B and C surveillance in Europe 2006–2011. Available: <http://www.ecdc.europa.eu/en/publications/Publications/Hepatitis-B-C-surveillance-report-2006-2011.pdf>.
232. Mathers BM, Degenhardt L, Ali H, Wiessing L, Hickman M, et al. (2010) HIV prevention, treatment, and care services for people who inject drugs: a systematic review of global, regional, and national coverage. *Lancet* 375: 1014–1028.