Model projections on the impact of HCV treatment in the prevention of HCV transmission among people who inject drugs in Europe

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Graphical abstract
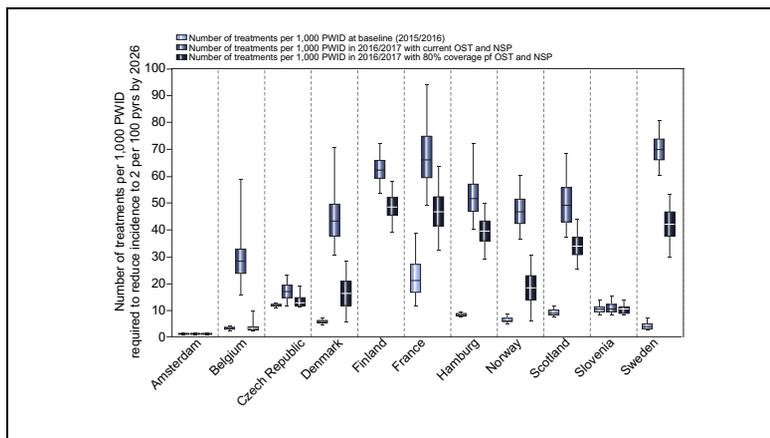
Highlights

- Chronic HCV prevalence and treatment rates among PWID vary widely across Europe.

- HCV treatment scale-up is required in most sites to reduce HCV transmission.

- Increasing OST/NSP coverage enhances HCV treatment prevention benefit.

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Lay summary

Measuring the amount of HCV in the population of PWID is uncertain. To reduce HCV infection to minimal levels in Europe will require scale-up of both HCV treatment and other interventions that reduce injecting risk (especially OST and provision of sterile injecting equipment).

Model projections on the impact of HCV treatment in the prevention of HCV transmission among people who inject drugs in Europe

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Background & Aims: Prevention of hepatitis C virus (HCV) transmission among people who inject drugs (PWID) is critical for eliminating HCV in Europe. We estimated the impact of current and scaled-up HCV treatment with and without scaling up opioid substitution therapy (OST) and needle and syringe programmes (NSPs) across Europe over the next 10 years.
Methods: We collected data on PWID HCV treatment rates, PWID prevalence, HCV prevalence, OST, and NSP coverage from 11 European settings. We parameterised an HCV transmission model to setting-specific data that project chronic HCV prevalence and incidence among PWID.
Results: At baseline, chronic HCV prevalence varied from <25% (Slovenia/Czech Republic) to >55% (Finland/Sweden), and <2% (Amsterdam/Hamburg/Norway/Denmark/Sweden) to 5% (Slovenia/Czech Republic) of chronically infected PWID were treated annually. The current treatment rates using new direct-acting antivirals (DAAs) may achieve observable reductions in chronic prevalence (38–63%) in 10 years in Czech Republic, Slovenia, and Amsterdam. Doubling the HCV treatment rates will reduce prevalence in other sites (12–24%; Belgium/Denmark/Hamburg/ Norway/Scotland), but is unlikely to reduce prevalence in Sweden and Finland. Scaling-up OST and NSP to 80% coverage with current treatment rates using DAAs could achieve observable reductions in HCV prevalence (18–79%) in all sites. Using DAAs, Slovenia and Amsterdam are projected to reduce incidence to 2 per 100 person years or less in 10 years. Moderate to substantial increases in the current treatment rates are required to achieve the same impact elsewhere, from 1.4 to 3 times (Czech Republic and France), 5–17 times (France, Scotland, Hamburg, Norway, Denmark, Belgium, and Sweden), to 200 times (Finland). Scaling-up OST and NSP coverage to 80% in all sites reduces treatment scale-up needed by 20–80%.
Conclusions: The scale-up of HCV treatment and other interventions is needed in most settings to minimise HCV transmission among PWID in Europe.
Lay summary: Measuring the amount of HCV in the population of PWID is uncertain. To reduce HCV infection to minimal levels in Europe will require scale-up of both HCV treatment and other interventions that reduce injecting risk (especially OST and provision of sterile injecting equipment).

Introduction

Chronic hepatitis C virus (HCV) infection is a leading cause of liver disease and morbidity, causing more deaths than HIV in the United States and other high-income countries.[1–4] Preventing HCV transmission among people who inject drugs (PWID) is critical for averting future liver disease in Europe and elsewhere[5] and new HCV infections in this group.[6] Primary prevention through opioid substitution therapy (OST) and high-coverage needle

and syringe programmes (NSPs) can reduce HCV transmission among PWID[7,8] and averts new HCV infections,[9] but substantial reductions in HCV prevalence are unlikely to be achieved without scaling-up HCV treatment.[10–15]

The arrival of highly effective and short-duration direct-acting antivirals (DAAs) with cure rates (sustained viral response [SVR]) above 90% for all genotypes has made HCV "treatment as prevention" more than a theoretical possibility.[16,17,12] However, the current high cost of DAA regimes (often >€30,000 per treatment regime in higher-income countries) is a barrier to scaling-up treatment in most countries. European guidelines previously recommended prioritising DAAs for patients with advanced liver disease. Now, they suggest that HCV treatment should also be provided to people with a risk of transmitting HCV, such as PWID.[18,19] A recent economic model suggested that, in general, it is more cost effective to delay treatment of a mild disease until more moderate stages of fibrosis.[20] However, when these individuals have an ongoing transmission risk, they should be prioritised for early treatment over other patient groups.[21]

In this paper, we estimate the current HCV treatment rates and coverage of OST and NSP in PWID across 11 sites in Europe. We assess the impact of these and scaled-up HCV treatment rates and other primary prevention on HCV prevalence and incidence over the next 10 years.

Materials and methods
Model
We used a dynamic deterministic mathematical model of HCV transmission among PWID, stratifying PWID according to intervention status (no OST or NSP, on OST, NSP, or both) alongside HCV infection and treatment status (susceptible and never infected, previously infected, chronically infected, on treatment, and treatment failure[9,10]). In three sites (Czech Republic, Finland, and Sweden), PWID are also stratified by drug type (opioid or methamphetamine/amphetamine). PWID enter the model through a constant rate that individuals initiate injecting. All PWID are assumed initially susceptible to HCV infection (Fig. 1A). Susceptible PWID can become infected at a per capita rate proportional to the background prevalence of the disease, which changes as HCV treatment increases. Transmission is reduced by a fixed multiplicative cofactor dependent on OST and NSP status (Fig. 1B). Once infected, PWID either transition

to the chronically infected group (Ab+, RNA+), or spontaneously clear infection and transition to the previously infected group (Ab+, RNA−). This previously infected group is assumed to be reinfected and clear infection at the same rate as susceptible PWID.[11,22,23] Chronically infected PWID (both primary and reinfection) can be treated. If treatment is successful and SVR is attained, PWID transition to the previously infected group. However, if SVR is not attained, PWID transition to the treatment-failure group. In the baseline model, treatment failures cannot be retreated (Fig. 1A). Once treatment is switched to DAAs, we assume that treatment failures can be retreated. PWID leave the model through permanent cessation of injecting, or drug-related or non-drug-related mortality. All PWID enter the model with no coverage of OST or NSP, and transition between the different intervention states (OST and/or NSP) at site-specific fixed per capita rates (Fig. 1B; Tables S1a–S1k). Further details of the model, including model equations, are in the Supplementary materials.

Model parameterisation and calibration
The model was parameterised to each of the 11 sites (see Table 1 and Tables S1a–S1l for site-specific information).

For sites with opioid injecting only, 2,500 model parameter sets were randomly sampled from the parameter uncertainty distributions (see Tables S1a–S1l). For each parameter set, the model was fit to the PWID population size by varying the rate that individuals initiate injecting, to OST and NSP coverage levels by varying the recruitment rates onto OST and NSP, and to either the chronic or antibody HCV prevalence at a site-specific time point by varying the transmission rate. For Czech Republic, Finland, and Sweden, the model was fit to more parameters (see Supplementary materials for further details). HCV incidence was estimated from model inputs assuming a stable epidemic, except for Amsterdam where additional data were available, suggesting a decreasing PWID population size and declining incidence.[15]

In sites with opioid and methamphetamine/amphetamine injecting, we assume that the baseline risk of HCV transmission is the same for all PWID.[24–26] There is an equal NSP coverage across both types of injectors, but only opioid users can be recruited into OST.

In all but four sites (Czech Republic, Finland, Sweden, and Norway), HCV treatment of PWID was modelled only among
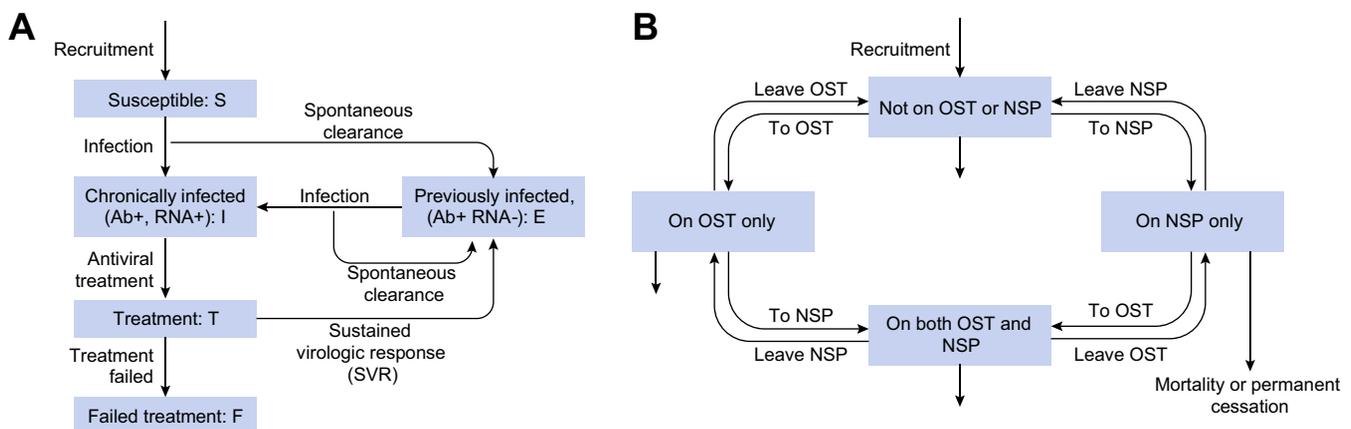
Fig. 1. Schematics of HCV transmission, and OST and NSP interventions in the model. (A) Infection component of the model. (B) OST and NSP intervention components of the model. HCV, hepatitis C virus; NSP, needle and syringe programme; OST, opioid substitution therapy; SVR, sustained viral response.

Table 1. Parameter table.

Parameter	Value
PWID population size[*]	
Amsterdam	2,621 (1,946–3,374) in 2009
	1,874 (1,341–2,455) in 2014
Belgium	9,080 (6,356–11,804)
Czech Republic	41,816–46,563
	(Range, no point estimate available)
Denmark	16,500 (13,000–19,000)
Finland	15,611 (13,770–22,655)
France	80,000 (65,000–95,000)
Hamburg	8,492 (7,582–9,436)
Norway	15,500 (10,500–20,150)
Scotland	16,000 (11,500–19,400)
Slovenia	6,000 (4,200–7,800)
Sweden	8,021–26,550
	(Maximum and minimum PWID population size estimates)
PWID mortality rate (% per year)[†]	
Amsterdam	2.4
Belgium	2.5
Czech Republic	0.8
Denmark	2.0
Finland	2.0
France	1.3
Hamburg	0.7
Norway	1.9
Scotland	1.0
Slovenia	0.7
Sweden	2.0
HCV antibody prevalence among PWID (%) and year prevalence fit to[‡]	
Amsterdam	59.4 (54.8–64.0) in 2007
Belgium	43.3 (34.3–52.4) in 2012
Czech Republic	35.0 (31.6–38.5) in 2005
Finland	76.0 (72.4–79.4) in 2014
France	66.4 (60.3–71.9) in 2011
Hamburg	67.7 (62.3–72.8) in 2014
Scotland	58.0 (55.8–60.2) in 2013/14
Slovenia	27.3 (19.1–35.5) in mid-2010
Sweden	81.7 (79.6–83.6) in 2014
HCV chronic prevalence among PWID (%) and year prevalence fit to[‡]	
Denmark	35.0–45.0 in 2014
Norway	45 (42.6–47.5) in 2007

Number PWID treated per year

	Total treated in each site per year	Number treated per 1,000 PWID per year
Amsterdam[§]	2005–2016: 15	2005–2016: 6.1–11.2
Belgium[§]	2004–2016: 30	2004–2016: 5.7–10.6
Czech Republic[α]	2002–2011: 370	2002–2011: 7.9–8.8
	2011–2016: 540	2011–2016: 11.6–12.9
Denmark[§]	2002–2014: 53	2002–2014: 2.8–4.1
	2014–2015: 50	2014–2015: 2.6–3.8
	2014–2016: 100	2014–2016: 5.3–7.7
Finland[§]	2006–2016: 5	2006–2016: 0.06
France[§]	2001–2016: 1,705 (923–3,148)	2001–2016: 10.5–43.3
		(These are the calculated numbers treated based on the treatment rate for people who have injected at least once in the last year)
Hamburg[§]	2005–2011: 60	2005–2011: 6.2–7.9
	2011–2016: 72	2011–2016: 7.6–9.5
Norway	2009–2016: 100	2009–2016: 5.0–9.5
		(70% treatments are amongst those on OST and 30% treatments amongst those not on OST)
Scotland[§]	2005–2008: 60	2005–2008: 3.1–5.2
	2008–2009: 90	2008–2009: 4.6–7.8
	2009–2016: 150	2009–2016: 7.7–13.0
Slovenia[α]	1997–1999: 2	1997–1999: 0.3–0.5
	1999–2008: 5	1999–2008: 0.6–1.2
	2008–2016: 62	2008–2016: 7.9–14.8
Sweden[α]	1997–2016: 90	1997–2016: 3.4–11.2

The key parameters used in the modelling for each of the sites; mean (95% CI) is shown from PWID population size and prevalence estimates unless otherwise stated. Mortality rates are given per year. The range for the number of PWID treated per 1,000 PWID is estimated using the number of treatments in each site and the PWID population size.

HCV, hepatitis C virus; OST, opioid substitution therapy; PWID, people who inject drugs.

[*] All sampled from a normal distribution.

[†] All sampled from a Poisson distribution.

[‡] All sampled from a normal distribution; in all cases, HCV antibody prevalence is adjusted to chronic prevalence by assuming a 26% (22–29%) spontaneous clearance rate.[49]

[§] Only those on OST are initially eligible for treatment.

[α] All PWID can be treated. References are given in S1a–S1k in Supplementary materials.

those on OST for initial analyses, as in these sites only PWID on OST are currently treated.

Model projections and analyses

Data on PWID treatment numbers for each site were scaled to give a rate per 1,000 PWID, as well as the percentage of chronic HCV infections treated in 2015/2016. By scaling to give a rate based on the total PWID population size, we can easily compare the current and projected future treatment numbers between all sites. All known increases in treatment prior to 2015 were included in the model.

We used the model to project the change in prevalence and incidence between 2016 and 2026 if treatment is switched from interferon-based therapies to new DAAs (SVR rate 90% [85–95%]). Current treatment rates per 1,000 PWID either are maintained, doubled, or increased to 50 per 1,000 PWID treated annually. Impact projections either assumed that current coverages of OST and NSP are maintained, or OST and NSP are scaled-up to 80% coverage (if not already achieved). We determined the annual treatment number (expressed as a rate of treatment per 1,000 PWID) needed to reduce incidence to 2 per 100 person years (pyr) by 2026. This is the number of treatments annually per 1,000 PWID and is, therefore, constant when projecting to 2026.

We estimated the z-score associated with the mean difference in chronic prevalence given the uncertainty in chronic HCV generated by the model. We categorised a z-score <0.5 as a modest change (unlikely to be observed), between 0.5 and 1.5 as a moderate change (may be observable), and scores greater than 1.5 or 3.0 as changes that are increasingly and highly likely to be observed.

Uncertainty analysis

To consider the effect of uncertainty within the underlying parameters, we performed a linear-regression analysis of covariance on the relative decrease in HCV prevalence and incidence between 2016 and 2026 when current treatment rates are doubled. For each site, the proportion of the sum of squares contributed by each parameter of each model outcome was calculated to estimate the importance of each parameter to the uncertainty.[27]

For further details regarding the materials used, please refer to the CTAT table and Supplementary information.

Results

Baseline HCV treatment rates

HCV treatment of PWID started at different times across the sites, ranging from 1997 (Slovenia) to 2009 (Norway) with very few PWID having been treated in Finland. In Fig. 2, the percentage of chronic HCV prevalent cases among PWID that were treated in 2015/2016 based on data from each site is shown. They vary from <0.1% in Finland to 0.5–2% in Sweden, Denmark, Belgium, Norway, and Amsterdam, and to >5% in Czech Republic and Slovenia.
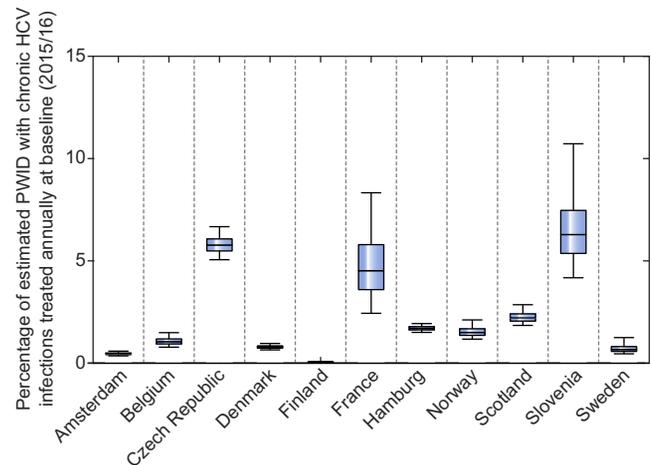
Fig. 2. Percentage of estimated PWID with chronic HCV infections treated annually at baseline (2015/2016) for each site. Bars indicate the median and interquartile range, and whiskers show the 95% credibility intervals. HCV, hepatitis C virus; PWID, people who inject drugs.

Model projections

Chronic HCV prevalence among PWID

At baseline in 2016, the projected chronic prevalence varied from <25% in Czech Republic (20.9% [95% CI 18.2–23.8%]) and Slovenia (16.2% [10.7–21.7%]) to >55% in Finland (56.1% [53.1–59.4%]) and Sweden (60.0% [57.4–62.9%]). In Fig. 3, the projected baseline and 10-year chronic HCV prevalence among PWID in each setting for different levels of scale-up of HCV treatment with new DAAs are shown. In Fig. 4, the same projections are shown, but with scale-up in OST and NSP coverage to 80%.

Switching to DAAs with treatment rate maintained

In the majority (8/11) of the sites, the difference in projected chronic HCV prevalence after 10 years if the current treatment rates with DAAs remain constant is <5%. In these sites, the median absolute difference ranges from <1.5% in Finland, Sweden, and Belgium up to 3–4% in Norway, Denmark, France, Hamburg, and Scotland. This difference is substantially smaller than the uncertainty in the baseline chronic HCV prevalence in the sites. This equates to a relative decrease of <10% at each site (see Supplementary materials).

In the remaining three sites (Amsterdam, Czech Republic, and Slovenia), there is a much greater relative decrease in chronic HCV prevalence between 2016 and 2026 from switching to DAAs: 37.5% (26.6–51.8%) in Czech Republic and 49.3% (25.0–98.0%) in Slovenia. In Amsterdam, the decreasing population size and concurrent decrease in transmission contribute around 90% of the relative decrease of 51.8% (28.7–65.7%) in chronic prevalence between 2016 and 2026. These sites have a z score >3.0, indicating that an observable change in chronic prevalence will likely occur by switching to DAAs with the current treatment rates.
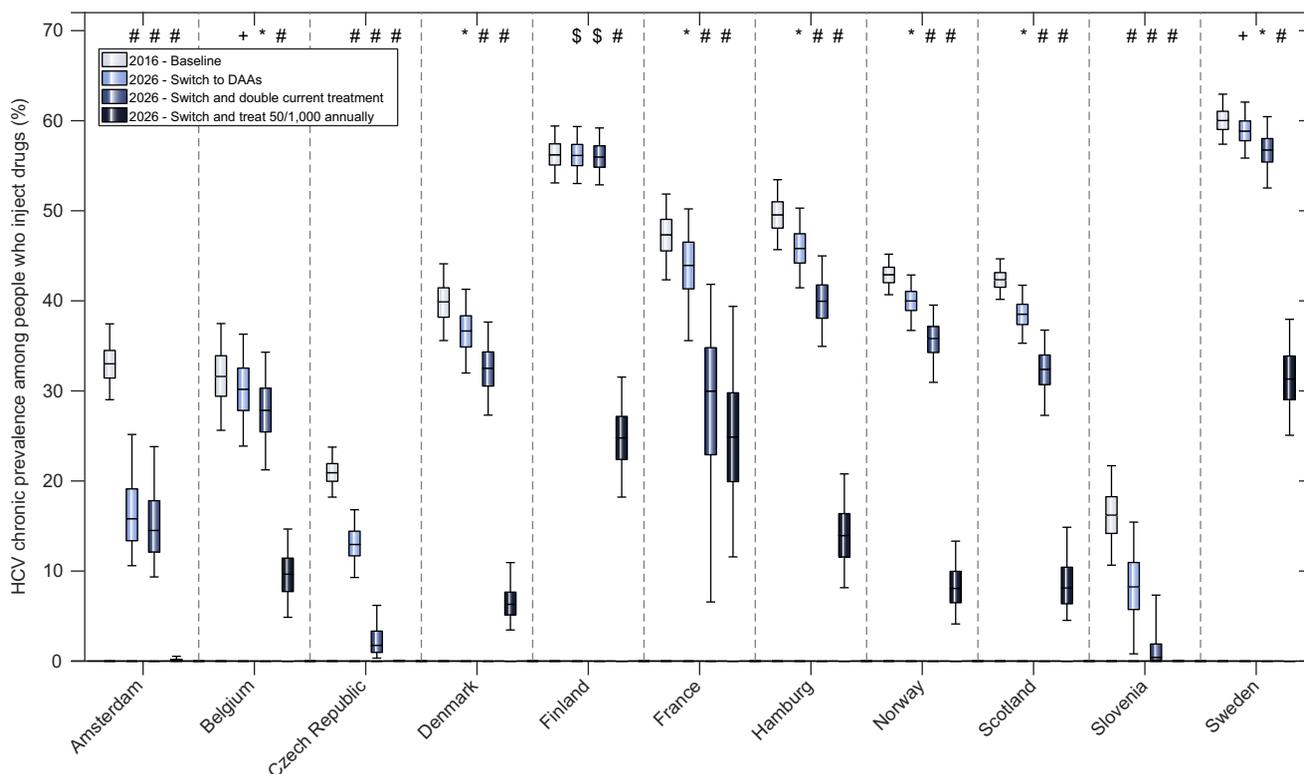
Fig. 3. Baseline and projected 10-year chronic HCV prevalence among PWID in multiple sites in Europe for various treatment-intervention scenarios. Baseline chronic prevalence (white boxes) and projected 10-year chronic prevalence if either current treatment rates continue with new DAAs (pale blue boxes), treatment rates are doubled with new DAAs (mid-blue boxes), or increased to 50 per 1,000 PWID annually with new DAAs (dark blue boxes). Bars indicate the median and interquartile range, and whiskers show the 95% credibility intervals. $, z-score <0.5 (unlikely to observe a difference, 2016–2026); +, z-score 0.5–1.5 (may be able to observe a difference, 2016–2026); *, z-score 1.5–3 (increasingly likely to be able to observe a difference, 2016–2026); #, z-score >3 (highly likely to be able to observe a difference, 2016–2026). DAA, direct-acting antiviral; HCV, hepatitis C virus; PWID, people who inject drugs.

If all sites switched to DAAs with the current treatment rates and concurrently increased OST and NSP coverage to 80%, the model projects a reduction in prevalence in all sites. This reduction is from <20% in Finland (17.6% [10.0–27.9%]) and Hamburg (19.5% [11.7–27.6%]), 30–50% in Scotland, Sweden, France, Norway, Denmark, and Belgium, to >50% in Czech Republic and Amsterdam, and >75% in Slovenia. The differential benefit of scaling-up OST and NSP alongside treatment on reducing chronic HCV prevalence ranges from >10 to <1.5 times because of baseline coverage. For example, in Finland, Sweden, and Belgium, scaling-up OST and NSP with the current HCV treatment rates reduces chronic HCV prevalence in 10 years by 17.1%, 31.1%, and 48.4%, respectively, compared to 0.1%, 1.8%, and 4.4% reduction without OST and NSP scale-up. In contrast, there is only a small projected improvement in Amsterdam and Czech Republic, which already have high coverage of OST and NSP (Tables S1a–S1k). Other sites are projected to improve reductions in chronic HCV prevalence from two to three times (Slovenia, Hamburg, and Scotland) and five to six times in France, Denmark, and Norway (Table S3).

*Switching to DAAs with treatment rate doubled*
For sites with high baseline chronic prevalence (>55% at baseline) and low treatment rates (<1% of chronic infections treated at baseline) (*e.g.* Sweden and Finland), doubling the DAA treatment rates has little effect on the projected prevalence in 2026 (0.4% [0.3–0.6%] and 5.2% [3.3–10.4%] relative decrease, respectively) if OST and NSP are maintained at current coverage. For

sites with moderate chronic prevalence (30–50% at baseline) and <2.5% of chronic infections being treated annually in 2015/2016 (Belgium, Denmark, Hamburg, Norway, and Scotland), doubling the DAA treatment rates could reduce chronic HCV prevalence from 11.6% relative decrease (Belgium) up to 23.5% (Scotland).

France has a moderate chronic prevalence (47.3%) at baseline and high initial treatment rate (4.5% [2.4–8.3%] of all chronic infections treated annually). When their treatment rate is doubled with DAAs, this yields a greater relative decrease in chronic prevalence than other sites with moderate prevalence (36.4% [16.7–85.5%]). The credibility intervals are wide because of uncertainty in the estimates of HCV treatment rates.

In Czech Republic and Slovenia, doubling the DAA treatment rates is projected to reduce chronic prevalence by >90% (Fig. 3), and in Amsterdam by 55.8% (32.8–69.6%).

Increasing OST and NSP to 80% coverage and doubling the DAA treatment rates are projected to reduce chronic prevalence between 17.9% (10.3–28.2%) in Finland and 99.5% (91.8–99.9%) in Slovenia. In sites with high baseline treatment rates (Czech Republic and Slovenia), the decrease in prevalence is primarily caused by doubling treatment rates (97.3% and 91.6% decrease in Czech Republic with and without scaled-up OST and NSP, respectively, and 99.5% and 97.4% in Slovenia). For sites with low baseline treatment rates and low coverage of OST and NSP, it is the increase in OST and NSP that drives the decrease in chronic prevalence rather than the doubling in treatment rates. In Finland, the decrease changes from 0.4% to 17.9% when
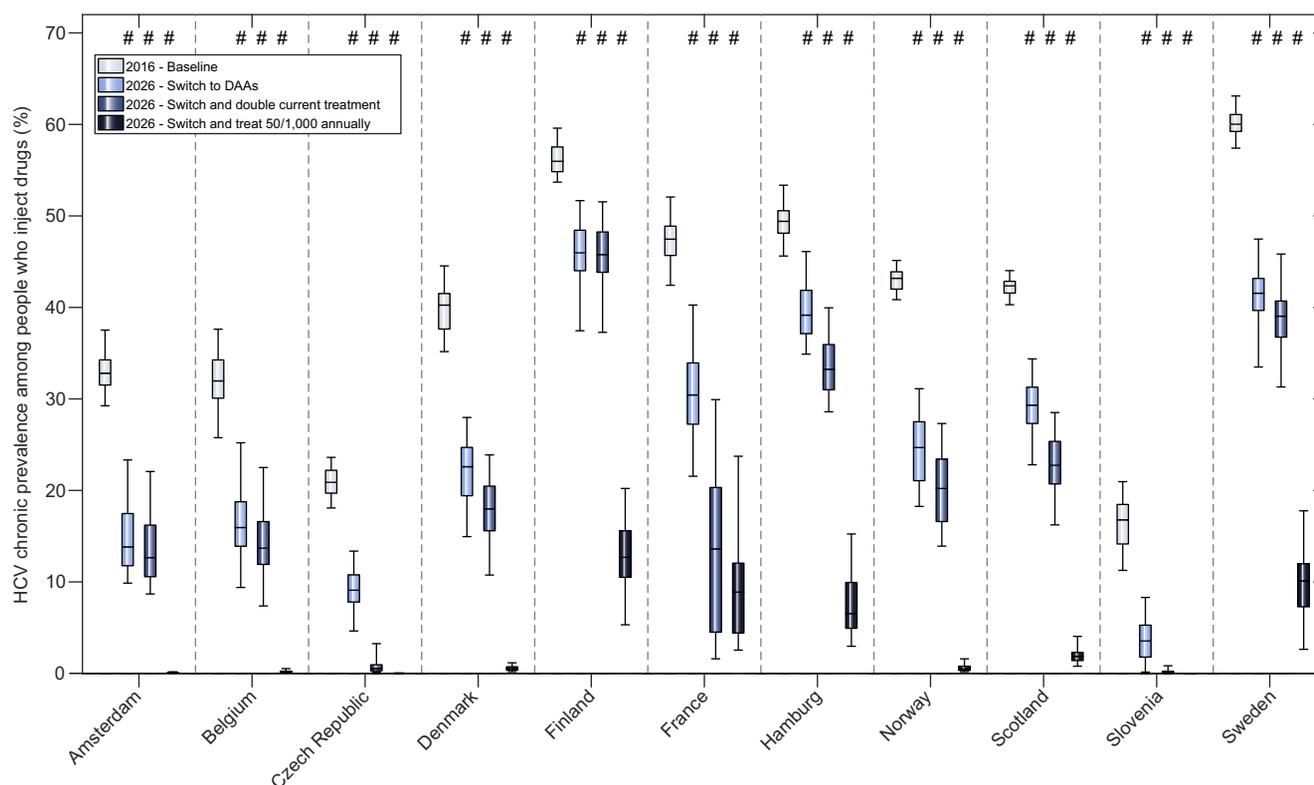
Fig. 4. Baseline and projected 10-year chronic HCV prevalence among PWID in multiple sites in Europe for various treatment-intervention scenarios with OST and NSP scaled-up to 80% coverage. Baseline chronic prevalence (white boxes) and projected 10-year chronic prevalence if either current treatment rates continue with new DAAs (pale blue boxes), treatment rates are doubled with new DAAs (mid-blue boxes), or increased to 50 per 1,000 PWID annually with new DAAs (dark blue boxes) with OST and NSP scaled-up to 80% coverage. Bars indicate the median and interquartile range, and whiskers show the 95% credibility intervals. $, z-score <0.5 (unlikely to observe a difference, 2016–2026); +, z-score 0.5–1.5 (may be able to observe a difference, 2016–2026); *, z-score 1.5–3 (increasingly likely to be able to observe a difference, 2016–2026); #, z-score >3 (highly likely to be able to observe a difference, 2016–2026). DAA, direct-acting antiviral; HCV, hepatitis C virus; NSP, needle and syringe programme; OST, opioid substitution therapy; PWID, people who inject drugs.

additionally scaling-up OST and NSP, from 5.2 to 35.5% in Sweden, and from 11.6% to 55.6% in Belgium.

DAA treatment rate 50 per 1,000 PWID
Increasing the annual DAA treatment rates to 50 per 1,000 PWID with the current OST and NSP coverage leads to substantial reductions in chronic HCV in all sites (Fig. 3). In the high-prevalence sites of Finland and Sweden, chronic prevalence reduces by about half by 2026. Conversely, chronic HCV prevalence decreases by 70% or more in most moderate-prevalence sites (Belgium, Hamburg, Scotland, Norway, and Denmark). In France, however, the decrease is smaller and more uncertain (47.6% [21.7–73.8%]). In low-prevalence settings (Czech Republic and Slovenia), chronic prevalence is projected to decrease by around 99% by 2026.

In projections with OST/NSP scale-up to 80%, prevalence decreases by more than three quarters in all sites, with 7/11 sites (Scotland, Denmark, Norway, Belgium, Amsterdam, Czech Republic, and Slovenia) projecting a decrease of >95%.

HCV incidence among PWID
Baseline projections of incidence before 2015 agree with observed incidence estimates where data were available (Supplementary materials). Projected changes in incidence from 2016 to 2026 are shown in Figs. S2 and S3, without and with scale-up of OST and NSP to 80% coverage using DAAs. HCV incidence is projected to remain largely unchanged with the current

OST and NSP coverage in all but three sites if the current HCV treatment rates are maintained using DAAs. However, if OST and NSP are scaled-up to 80% coverage, projections estimate a relative decrease in incidence of over 35% at all sites.

The treatment number per 1,000 PWID required in 2016/2017 to reduce incidence to 2 per 100 pyr (2%) among PWID by 2026 with and without scale-up of OST and NSP to 80% coverage is shown in Fig. 5. In Amsterdam, an incidence of 2% (1–3%) was already estimated in 2016, and so just switching to DAAs ensured an incidence <2% by 2026 in 99% of model runs. In Slovenia, just switching to the new DAAs and maintaining the current treatment rates are likely to decrease incidence to <2% by 2026 (projected by 78% of model fits), with an increase in treatments rates by 20% being needed to ensure this impact in the other 22% of model fits. In Czech Republic, switching to DAAs would achieve 2% incidence in <10% of model fits. Increasing the current treatment rates by 43% over all model runs would ensure the decrease. In all other sites, a substantial increase in HCV treatment rates (in the absence of any increase in OST and NSP coverage) is needed to reduce HCV incidence to 2%. This ranges from three to five times the current treatment rates in France and Scotland, to between six and nine times in Hamburg, Norway, Denmark, Belgium, 17 times in Sweden, and 200 times in Finland. If OST and NSP are scaled-up to 80% coverage, maintaining the current treatment rates is sufficient to achieve an incidence of 2% in 2026 in Amsterdam and Slovenia (100% of model fits), may achieve this impact in Belgium and
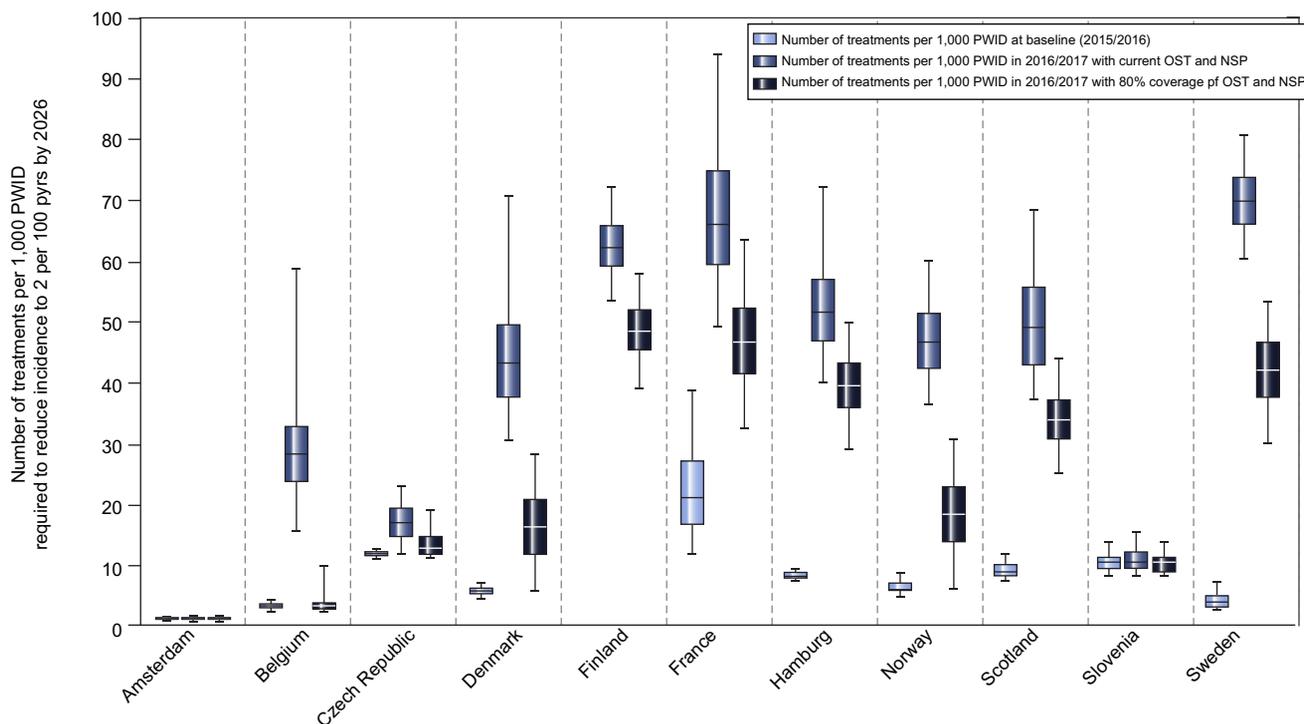
Fig. 5. Current and projected number of treatments per 1,000 PWID to reduce incidence to 2 per 100 pyr by 2026. Current number of treatments per 1,000 PWID at baseline (2015/2016, pale blue) and required scale-up in number of treatments per 1,000 PWID initially needed per year (2016/2017) if current OST and NSP coverage is maintained (mid-blue, median and 95% credibility interval shown in the figure), or if OST and NSP are scaled to 80% coverage (dark blue) to reduce incidence to 2 per 100 pyr (2%) by 2026. Based on data from the sites, we have treatment initially given only to those on OST, treatment initially given to all PWID, and 70% treatment to PWID on OST and 30% treatment to PWID not on OST. NSP, needle and syringe programme; OST, opioid substitution therapy; PWID, people who inject drugs; pyr, person years.

Czech Republic (84% and 50% of model fits), but is unlikely to (<10% of model fits) in other settings. Alongside increased OST and NSP, France, Denmark, Norway, Scotland, Hamburg, Sweden, and Finland would need to scale-up their baseline treatment rates by 2.2-, 2.8-, 2.8-, 3.6-, 4.7-, 10.3-, and 159-fold, respectively. This is 20–60% less than if OST and NSP had not been scaled-up.

Uncertainty analysis
The sensitivity analysis indicates that, for most sites, uncertainty in three main factors contributes to variation in the relative decrease in chronic prevalence and incidence between 2016 and 2026 when treatment rates are doubled, but with differing levels of influence between the sites (Fig. S4). The PWID population size contributes 34–63% of the variation in Finland, Belgium, Scotland, Slovenia, and Norway, and 80% in Sweden, whilst the prevalence estimates contribute 32–53% of the variation in five of the sites (Slovenia, Belgium, Czech Republic, Denmark, and Hamburg). The duration of injection is most important in Amsterdam, contributing 85% of the variation, but also contributes 25–48% in Scotland, Hamburg, Denmark, Norway, Belgium, and Finland. In France, the estimated treatment rate contributes 80% of the variation.

Discussion
Main findings
Treatment scale-up is needed to achieve observable reductions in chronic HCV prevalence among PWID in most sites in Europe,

even with new DAAs. Doubling the DAA treatment rates may lead to observable reductions (12–24% decrease) in chronic prevalence by 2026 in Belgium, Denmark, Hamburg, Norway, and Scotland; but not in Finland or Sweden. Exceptions include Czech Republic, Slovenia, and Amsterdam, which, at current HCV treatment rates, are projected to reduce chronic HCV prevalence from a third to a half by 2026. This is because of the low or decreasing prevalence of infection in these settings. Alternatively, increasing OST and NSP coverage to 80% with the current HCV treatment rates would reduce chronic HCV prevalence by 17–20% in Finland and Hamburg, and 30–79% in all other sites. Reducing HCV incidence to <2% by 2026 requires little action in Amsterdam, Czech Republic, and Slovenia, whereas in Belgium, Denmark, Hamburg, Norway, and Scotland it will require at least a fivefold increase in the current HCV treatment rates, or 1.8- to 4.7-fold if OST and NSP are scaled-up to 80% coverage.

Strengths and limitations
Our model projections and their interpretation are influenced strongly by uncertainty in the parameters and evidence base. First, we collected information from a range of sources and obtained data not routinely collected across Europe (*e.g.* number of PWID treated for HCV).[6,28] Unfortunately, data collection was inconsistent across sites, particularly estimates of PWID population size, which were used to estimate HCV treatment rates. Reliable PWID population-size estimates are difficult to obtain. Except for Amsterdam where evidence suggests a falling population[15,29] we had to assume stable populations.

Second, uncertainty in the chronic HCV prevalence among PWID contributed substantially to the uncertainty in our projections, with estimates generated from a diverse range of sources and rarely (except for Scotland) from ongoing community-based surveillance.[6,30]

Third, the duration of injecting drug use is difficult to estimate precisely and contributed to model uncertainty. We sampled the average injecting duration from a range extending from 6 to over 20 years. In the absence of clear evidence, we also assumed that opioid and methamphetamine injectors had similar durations. If the true duration is towards the higher end of our ranges, scaling-up HCV treatment will have a greater impact on transmission. If towards the lower end, scaling-up OST and NSP will have a greater contribution on reducing transmission.[10]

Fourth, DAA SVRs for PWID in "real world" settings are yet to emerge, and so we assumed a range of 85–95%.[31,32] Given the short treatment duration and early treatment of a predominantly mild disease, it is likely that SVRs will be very high. However, it is possible that, as treatment is scaled-up among more vulnerable PWID, the SVR may reduce. In general, the impact of HCV treatment in our projections is relatively robust to variations in SVR. However, an uncertainty in SVR becomes more influential in settings with lower chronic prevalence and higher HCV treatment rates. Furthermore, we assumed that PWID who had either cleared HCV spontaneously or after successful treatment had the same risk of re-infection as the susceptible population of PWID i.e. the per capita transmission probability of re-infection was the same as for primary infection. There is some evidence to suggest that previous spontaneous clearance could result in higher rates of clearance for subsequent reinfection.[22] However, similar data surrounding spontaneous clearance of reinfections after SVR do not exist. Infrequent testing intervals can contribute bias, as some reinfections may go unnoticed.[22,33] Observational studies have reported that reinfection after SVR can be of a similar, higher, or lower rate than the background rate of infection,[34–38] indicating uncertainty in the evidence. However, if the reinfection risk was lower than the primary infection for people achieving SVR, or the spontaneous clearance is higher for reinfections, then our model projections represent conservative estimates for the number of treatments needed to reduce prevalence and incidence across the different sites.

Fifth, we recorded substantial differences in coverage of OST and NSP between sites that are incorporated into the baseline model. In subsequent intervention scenarios, we either considered no scale-up of these interventions, or assumed their scale-up to 80% coverage. This optimistic scenario may overestimate the likely impact of what could be achieved from scaling-up OST and NSP, although some of our sites demonstrate such coverage is possible. However, even if this scale-up is possible, it is unlikely that it would be achieved quickly, and so these projections may overestimate the real reduction in HCV that could be achieved from scaling-up OST and NSP.

Sixth, the model does not incorporate information on HCV case-finding and any future difficulty in diagnosing and treating PWID with chronic HCV when HCV transmission and prevalence have fallen to low levels. However, this limitation will only affect a small number of the most optimistic model projections.

Seventh, we have not modelled HIV co-infection, which varies across Europe and may impact both on linkage to services and morbidity outcomes.

Finally, we assume no change in injecting-risk behaviour following HCV treatment—apart from through exposure to OST and NSP, which is also included prior to HCV treatment. If injecting risk was reduced following treatment,[39] our assumption provides conservative projections of impact.

Implications and comparisons with other literature

Multiple studies in specific countries and across Europe have used statistical and mathematical model projections to suggest that new DAA treatments need to increase to reverse trends in end-stage liver disease.[40–44] However, to project impact on HCV transmission, a dynamic transmission model that can track both reinfection and prevention of future infections is required, alongside information on the number and proportion of individuals from key populations, like PWID treated for HCV infection. Consequently, there are fewer analyses that project impact on HCV transmission.

An earlier study revealed a two- to threefold difference in chronic HCV prevalence and four- to fivefold difference in baseline HCV treatment rates in seven cities in the UK.[45] We also found considerable heterogeneity between sites in Europe. For example, the Czech Republic and Slovenia both have baseline chronic prevalence of <30%,[25,46,47] whilst in Finland and Sweden it is over 55%. Treatment rates also varied two- to threefold. At baseline, 8/11 sites had low treatment rates (<10/1,000 PWID treated annually), whereas France had a much higher treatment rate (21/1,000 PWID treated annually). This is a consequence of the high access to HCV treatment in France compared to other countries.[41] In this study, a greater decrease in prevalence for Amsterdam is shown than was projected in other studies.[15,48] However, this could be caused by differences in modelling the decreasing epidemic to achieve the incidence estimate, and differences modelling the PWID population and transmission dynamics.

The lack of ongoing surveillance data, including PWID prevalence and HCV treatment rates among PWID, in many European settings and comparable indicators between countries is important and a public health concern. Using our model projections, it was shown that scaling-up OST and NSP combined with switching to DAAs with comparatively small increases in the number of PWID treated could generate substantial observable reductions in HCV prevalence in several sites. However, robust HCV surveillance data among PWID were not always available and chronic HCV prevalence was uncertain. To ensure that empirical evidence of the impact of HCV treatment as prevention can be generated, it is important that more attention is given to establishing robust surveillance systems to reduce the uncertainty surrounding chronic HCV prevalence among PWID. The potential and relative costs of introducing effective HCV surveillance are trivial compared to the costs of HCV treatment, and need to be encouraged across Europe.

Conflict of interest

Authors' contributions

Acknowledgements

Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jhep.2017.10.010.

References

[1] Williams R, Aspinall R, Bellis M, Camps-Walsh G, Cramp M, Dhawan A, et al. Addressing liver disease in the UK: a blueprint for attaining excellence in health care and reducing premature mortality from lifestyle issues of excess consumption of alcohol, obesity, and viral hepatitis. Lancet 2014;384:1953–1997.

[2] Nelson PK, Mathers BM, Cowie B, Hagan H, Des JD, Horyniak D, et al. Global epidemiology of hepatitis B and hepatitis C in people who inject drugs: results of systematic reviews. Lancet 2011;378:571–583.

[3] Ly KN, Xing J, Klevens RM, Jiles RB, Ward JW, Holmberg SD. The increasing burden of mortality from viral hepatitis in the United States between 1999 and 2007. Ann Intern Med 2012;156:271–278.

[4] Cowie B, Allard N, MacLachlan J. O86 European responses in focus: comparing viral hepatitis and HIV related deaths in Europe 1990–2010 in the global burden of disease study 2010. J Hepatol 2014;1:S35–S36.

[5] European Centre for Disease Prevention and ControlEuropean Monitoring Centre for Drugs and Drug Addiction. Prevention and control of infectious diseases among people who inject drugs. Stockholm: European Centre for Disease Prevention and Control; 2011.

[6] European Monitoring Centre for Drugs and Drug Addition. Hepatitis C among drug users in Europe: epidemiology, treatment and prevention. EMCDDA Insights, 23. Luxembourg: Publications Office of the European Union; 2016.

[7] Turner KM, Hutchinson S, Vickerman P, Hope V, Craine N, Palmateer N, et al. 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 2011;106:1978–1988.

[8] Van Den Berg C, Smit C, Van BG, Coutinho R, Prins M. 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 2007;102:1454–1462.

[9] Vickerman P, Martin N, Turner K, Hickman M. Can needle and syringe programmes and opiate substitution therapy achieve substantial reductions in hepatitis C virus prevalence? Model projections for different epidemic settings. Addiction 2012;107:1984–1995.

[10] Martin NK, Hickman M, Hutchinson SJ, Goldberg DJ, Vickerman P. Combination interventions to prevent HCV transmission among people who inject drugs: modeling the impact of antiviral treatment, needle and syringe programs, and opiate substitution therapy. Clin Infect Dis 2013;57:S39–S45.

[11] Martin NK, Vickerman P, Foster GR, Hutchinson SJ, Goldberg DJ, Hickman M. 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 2011;54:1137–1144.

[12] Martin NK, Vickerman P, Grebely J, Hellard M, Hutchinson SJ, Lima VD, et al. Hepatitis C virus treatment for prevention among people who inject drugs: modeling treatment scale-up in the age of direct-acting antivirals. Hepatology 2013;58:1598–1609.

[13] Wedemeyer H, Duberg AS, Buti M, Rosenberg WM, Frankova S, Esmat G, et al. Strategies to manage hepatitis C virus (HCV) disease burden. J Viral Hepat 2014;21:60–89.

[14] De Vos A, Kretzschmar M. Benefits of hepatitis C virus treatment: A balance of preventing onward transmission and re-infection. Math Biosci 2014;258:11–18.

[15] de Vos AS, van der Helm JJ, Matser A, Prins M, Kretzschmar ME. Decline in incidence of HIV and hepatitis C virus infection among injecting drug users in Amsterdam; evidence for harm reduction? Addiction 2013;108:1070–1081.

[16] Dore GJ, Feld JJ. Hepatitis C virus therapeutic development: in pursuit of "perfectovir". Clin Infect Dis 2015;60:1829–1836.

[17] G Everson, T Tran, W Towner, M Davis, D Wyles, R Nahass, et al. Safety and efficacy of treatment with the interferon-free ribavirin-free combination of sofosbuvir+ GS-5816 for 12 weeks in treatment naive patients with genotype 1–6 HCV infection. 49th European Association for the Study of the Liver International Liver Congress (EASL 2014). London, United Kingdom; 2014.

[18] European Association for the Study of the Liver. EASL recommendations on treatment of hepatitis C 2014. J Hepatol 2014;61:373–395.

[19] European Association for the Study of the Liver. EASL recommendations on treatment of hepatitis C 2015. J Hepatol 2015;63:199–236.

[20] Leidner AJ, Chesson HW, Xu F, Ward JW, Spradling PR, Holmberg SD. Cost-effectiveness of hepatitis C treatment for patients in early stages of liver disease. Hepatology 2015;61:1860–1869.

[21] Martin NK, Vickerman P, Dore GJ, Grebely J, Miners A, Cairns J, et al. Prioritization of HCV treatment in the direct-acting antiviral era: An economic evaluation. J Hepatol 2016;65:17–25.

[22] Vickerman P, Grebely J, Dore GJ, Sacks-Davis R, Page K, Thomas DL, et al. 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 2012;205:1342–1350.

[23] Martin NK, Vickerman P, Hickman M. Mathematical modelling of hepatitis C treatment for injecting drug users. J Theor Biol 2011;274:58–66.

[24] Zábranský T, Mravčík V, Chomynová P. Overall mortality of drug users in the Czech Republic. In: EMCDDA, editor. 1st ed. Prague/Lisbon: ResAd ResAd/EMCDDA; 2009.

[25] Zabransky T, Mravcik V, Korcisova B, Rehak V. Hepatitis C virus infection among injecting drug users in the Czech Republic–prevalence and associated factors. Eur Addict Res 2006;12:151–160.

[26] H Švůgerová. Spotřeba injekčního materiálu klienty pražských harm reduction služeb v závislosti na vzorcích užívání (Consumption of material for injection clients of Prague harm reduction services depending on use patterns): PhD Thesis, Clinic of Addictology of the 1st Faculty of Medicine and General Teaching Hospital in Prague (11–00611), Prague; 2015.

[27] Briggs A, Claxton K, Sculpher M. Decision modelling for health economic evaluation. In: Gray A, Briggs A, editors. Handbooks in Health Economic Evaluation Series. Oxford: Oxford University Press; 2006.

[28] European Centre for Disease Prevention and Control. Hepatitis C surveillance in Europe – 2013. Stockholm: European Centre for Disease Prevention and Control; 2015.

[29] Jones HE, Hickman M, Welton NJ, De Angelis D, Harris RJ, Ades A. Recapture or precapture? Fallibility of standard capture-recapture methods in the presence of referrals between sources. Am J Epidemiol 2014:kwu056.

[30] Palmateer NE, Taylor A, Goldberg DJ, Munro A, Aitken C, Shepherd SJ, et al. Rapid decline in HCV incidence among people who inject drugs associated with national scale-up in coverage of a combination of harm reduction interventions. PLoS One 2014;9:e104515.

[31] Grebely J, Mauss S, Brown A, Bronowicki J-P, Puoti M, Wyles D, et al. Efficacy and safety of ledipasvir/sofosbuvir with and without ribavirin in patients with chronic HCV genotype 1 infection receiving opioid substitution therapy: Analysis of Phase 3 ION trials. Clin Infect Dis 2016;63:1405–1411.

[32] Dore GJ, Altice F, Litwin AH, Dalgard O, Gane EJ, Shibolet O, et al. Elbasvir–grazoprevir to treat hepatitis C virus infection in persons receiving opioid agonist therapy: a randomized trial. Ann Intern Med 2016;165:625–634.

[33] Sacks-Davis R, McBryde E, Grebely J, Hellard M, Vickerman P. Many hepatitis C reinfections that spontaneously clear may be undetected: Markov-chain Monte Carlo analysis of observational study data. J R Soc Interface 2015;12:20141197.

[34] Mehta SH, Cox A, Hoover DR, Wang X-H, Mao Q, Ray S, et al. Protection against persistence of hepatitis C. Lancet 2002;359:1478–1483.

[35] Grebely J, Prins M, Hellard M, Cox AL, Osburn WO, Lauer G, et al. Hepatitis C virus clearance, reinfection, and persistence, with insights from studies of injecting drug users: towards a vaccine. Lancet Infect Dis 2012;12:408–414.

[36] Micallef J, Macdonald V, Jauncey M, Amin J, Rawlinson W, Van Beek I, et al. High incidence of hepatitis C virus reinfection within a cohort of injecting drug users. J Viral Hepat 2007;14:413–418.

[37] Aitken CK, Lewis J, Tracy SL, Spelman T, Bowden DS, Bharadwaj M, et al. High incidence of hepatitis C virus reinfection in a cohort of injecting drug users. Hepatology 2008;48:1746–1752.

[38] Simmons B, Saleem J, Hill A, Riley RD, Cooke GS. Risk of late relapse or reinfection with hepatitis C virus after achieving a sustained virological response: a systematic review and meta-analysis. Clin Infect Dis 2016: civ948.

[39] Alavi M, Spelman T, Matthews GV, Haber PS, Day C, van Beek I, et al. Injecting risk behaviours following treatment for hepatitis C virus infection among people who inject drugs: The Australian Trial in Acute Hepatitis C. Int J Drug Policy 2015;26:976–983.

[40] Duberg AS, Blach S, Falconer K, Kaberg M, Razavi H, Aleman S. The future disease burden of hepatitis C virus infection in Sweden and the impact of different treatment strategies. Scand J Gastroenterol 2015;50: 233–244.

[41] Razavi H, Waked I, Sarrazin C, Myers R, Idilman R, Calinas F, et al. The present and future disease burden of hepatitis C virus (HCV) infection with today's treatment paradigm. J Viral Hepat 2014;21:34–59.

[42] Harris R, Thomas B, Griffiths J, Costella A, Chapman R, Ramsay M, et al. Increased uptake and new therapies are needed to avert rising hepatitis C-related end stage liver disease in England: modelling the predicted impact of treatment under different scenario. J Hepatol 2014;61: 530–537.

[43] Mullhaupt B, Bruggmann P, Bihl F, Blach S, Lavanchy D, Razavi H, et al. Modeling the health and economic burden of hepatitis C virus in Switzerland. PLoS One 2015;10:13.

[44] Innes H, Goldberg D, Dillon J, Hutchinson SJ. Strategies for the treatment of Hepatitis C in an era of interferon-free therapies: what public health outcomes do we value most? Gut 2015;64:1800–1809.

[45] Martin NK, Foster GR, Vilar J, Ryder S, Cramp ME, Gordon F, et al. HCV treatment rates and sustained viral response among people who inject drugs in seven UK sites: real world results and modelling of treatment impact. J Viral Hepat 2015;22:399–408.

[46] V Mravčík, C P., G K., N V., G L., K L., et al. Výroční zpráva o stavu ve věcech drog v České republice v roce 2013 [Annual Report on Drug Situation 2013 – Czech Republic], MRAVČÍK V.2014, Praha: Úřad vlády České republiky.

[47] Reitox National Focal Point. Report on the drug situation 2013 of the republic of Slovenia, Drev A.2013, Ljubljana.

[48] van Santen DK, de Vos AS, Matser A, Willemse SB, Lindenburg K, Kretzschmar ME, et al. Cost-effectiveness of hepatitis C treatment for people who inject drugs and the impact of the type of epidemic; extrapolating from Amsterdam, the Netherlands. PLoS One 2016;11: e0163488.

[49] Micallef JM, Kaldor JM, Dore GJ. Spontaneous viral clearance following acute hepatitis C infection: a systematic review of longitudinal studies. J Viral Hepat 2006;13:34–41.