



Cost-effectiveness of HCV case-finding for people who inject drugs via dried blood spot testing in specialist addiction services and prisons

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1 **Title: Cost-effectiveness of HCV case-finding for people who inject drugs via**
2 **dried blood spot testing in specialist addiction services and prisons**

3
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12
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15
16 **Abbreviations:** hepatitis C virus (HCV), people who inject drugs (PWID), dried blood
17 spot (DBS), incremental cost-effectiveness ratio (ICER), quality-adjusted life-year
18 (QALY), willingness-to-pay (WTP), hepatocellular carcinoma (HCC), liver transplant
19 (LT), pegylated interferon (pegIFN), ribavirin (RBV), sustained viral response (SVR),
20 95% confidence interval (CI), antibody (Ab)

21
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37
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39
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41
42 **Key words:** hepatitis C, testing, mathematical modelling, economic evaluation

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2
3 45 **ABSTRACT (265 words)**

4 46
5 47 **Objectives:** People who inject drugs (PWID) are at high-risk for acquiring hepatitis
6
7 48 C virus (HCV), but many are unaware of their infection. HCV dried blood spot (DBS)
8
9 49 testing increases case-finding in addiction services and prisons. We determine the
10
11 50 cost-effectiveness of increasing HCV case-finding among PWID by offering DBS
12
13 51 testing in specialist addiction services or prisons as compared to using
14
15 52 venepuncture.
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17

18 53 **Design:** Cost-utility analysis using a dynamic HCV transmission model among
19
20 54 PWID, including: disease progression, diagnosis, treatment, injecting status,
21
22 55 incarceration, and addiction services contact.
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24

25 56 **Setting:** United Kingdom
26

27 57 **Participants:** N/A
28

29 58 **Intervention:** DBS testing in specialist addiction services or prisons. Intervention
30
31 59 impact was determined by a meta-analysis of primary data
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33

34 60 **Primary and secondary outcome measures:** Costs (in UK £, £1=\$1.60 USD) and
35
36 61 utilities (quality adjusted life years, QALYs) were attached to each state and the
37
38 62 incremental cost effectiveness ratio (ICER) determined. Multivariate uncertainty and
39
40 63 one-way sensitivity analyses were performed.
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42

43 64 **Results:** For a £20,000 per QALY gained willingness-to-pay threshold, DBS testing
44
45 65 in addiction services is cost-effective (ICER of £14,600 per QALY gained). Under the
46
47 66 base-case assumption of no continuity of treatment/care when exiting/entering
48
49 67 prison, DBS testing in prisons is not cost-effective (ICER of £59,400 per QALY
50
51 68 gained). Results are robust to changes in HCV prevalence; increasing PWID
52
53 69 treatment rates to those for ex-PWID considerably reduces the ICER (£4,500 and
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55 70 £30,000 per QALY gained for addiction services and prison, respectively). If
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3 71 continuity of care is >40%, the prison DBS ICER falls below £20,000 per QALY
4
5 72 gained.

6
7 73 **Conclusions:** Despite low PWID treatment rates, increasing case-finding can be
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10 74 cost-effective in specialist addiction services, and in prisons if continuity of
11
12 75 treatment/care is ensured.

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14 76 **Trial Registration:** N/A
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18 78 **ARTICLE SUMMARY**

19 79 **Article focus**

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23 80 • We perform a cost-utility analysis of increasing HCV case-finding among
24
25 81 PWID by offering dried blood spot testing in specialist addiction services or
26
27 82 prisons.
28

29 83 **Key messages**

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32 84 • Despite low PWID treatment rates, increasing case-finding for PWID can be
33
34 85 cost-effective in specialist addiction services.
35
36 86 • In prisons, the cost-effectiveness of HCV case-finding depends on adequate
37
38 87 continuity of treatment/care between prison and the community, as many
39
40 88 treatments are discontinued due to short incarceration times.
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43 89 **Strengths and limitations of this study**

- 44
45 90 • We use a dynamic mathematical model of HCV transmission to capture the
46
47 91 potential prevention benefits of treatment, which has been shown to increase
48
49 92 cost-effectiveness of HCV treatment for PWID.
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51 93 • Key limitations are the limited empirical data on PWID health utilities,
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53 94 treatment rates, and intervention impact.
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96 INTRODUCTION

97 In developed countries, the hepatitis C virus (HCV) is spread primarily through
98 injecting drug use, with over 90% of new infections among people who inject drugs
99 (PWID) and approximately 10 million PWID infected worldwide[1 2]. However,
100 diagnosis rates are low, with only half of infected PWID in the US and UK
101 diagnosed[3 4], putting many at risk of cirrhosis, liver cancer, and death.

102

103 The majority of HCV testing performed in the US and UK is through venepuncture,
104 which is available in virtually all prisons[5 6] and addiction services (structured
105 programs providing pharmacological or nonpharmacological drug treatment in the
106 community) either on site or by referral. However, testing opportunities among PWID
107 still may be limited. This is because venous access can be poor and specialist staff
108 (who may not be available at all potential testing sites) are required to take blood,
109 which if only available in hospital phlebotomy services can increase stigma[7].

110

111 Dried blood spot (DBS) testing is non-invasive and can be performed by clinical and
112 non-clinical staff. Two UK studies[8 9] showed offering DBS testing within specialist
113 addiction services and prisons led to a 3 to 6-fold increase in HCV testing, and a
114 recent systematic review identified DBS as the best available targeted intervention
115 for increasing HCV case-finding amongst PWID[10]. Hence, DBS testing could be
116 an important component of any strategy attempting to scale-up treatment provision
117 for PWID, for both care and prevention[11].

118

119 We perform a cost-utility analysis of introducing DBS testing amongst current and
120 former PWID in specialist addiction services and prisons in the UK[8]. Unlike

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2
3 121 previous economic evaluations of HCV testing in these settings[12 13], we
4
5 122 incorporate a dynamic mathematical model to capture the potential prevention
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7 123 benefits of treatment, which can substantially increase the cost-effectiveness of HCV
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10 124 treatment for PWID[14]. Our model is also the first to explore the importance of
11
12 125 continuity of care between prison and the community.
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127 **METHODS**

128 **Mathematical model**

129 An existing dynamic, deterministic model of HCV transmission, progression and HCV
130 treatment was adapted to project the impact of introducing DBS testing in prisons
131 and addiction services[14]. See **appendix** for details and model schematics. Briefly,
132 the model stratifies by: injecting state (never PWID/PWID/ex-PWID); incarceration
133 status (never/currently/formerly); contact with addiction services (in contact/not in
134 contact); age ([15-19],[20-24],[25-29],[30-54],[55-64],[65-74],[75+]); HCV infection
135 and disease progression (never infected, spontaneously cleared, mild HCV,
136 moderate HCV, compensated cirrhosis, decompensated cirrhosis, hepatocellular
137 carcinoma, liver transplant, post-transplant). HCV disease stages are further
138 subdivided into undiagnosed or diagnosed, where those who are diagnosed can
139 either be lost to follow-up, in referral (early/late), on antiviral treatment, sustained
140 viral response (SVR), or non-SVR.

141

142 All PWID can acquire and transmit HCV, but imprisoned PWID only transmit HCV to
143 other prisoners. We define ex-PWID as those who have permanently ceased
144 injecting, and assume no ongoing transmission from non/ex-PWID. An individual's
145 risk of acquiring HCV is proportional to the setting-specific HCV prevalence

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3 146 (prison/community). The model assumes a background rate of HCV testing for all
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5 147 PWID and ex-PWID in the community/prison, and in addiction services for PWID.
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10 149 No UK data exist regarding continuity of care (treatment or referral) on prison
11
12 150 entry/exit, but experts described difficulty in ensuring continuity on release (Eamonn
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14 151 O'Moore[Offender Health, UK Department of Health], Iain Brew[HMP Leeds]
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16 152 *personal communication*). Therefore, in our base-case we assume those in
17
18 153 treatment or referral become lost to follow-up upon entering/exiting prison, but can
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20
21 154 be re-tested/re-treated.
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24 25 156 **Model fitting and base-case projections**

26
27 157 For the probabilistic uncertainty analysis, 1000 parameter sets were sampled from
28
29 158 each parameter uncertainty distribution in **tables 1-3**. For each of these parameter
30
31 159 sets, the model was calibrated to UK epidemiological data on incarceration, injecting
32
33 160 drug use, HCV prevalence, and diagnosis. This was achieved through a multi-step
34
35 161 parameter sampling and model calibration process, utilizing simplified models where
36
37 162 possible to reduce computational time and to verify the full model predictions against
38
39 163 simplified models. For details on the model calibration (including schematics and
40
41 164 equations) and initialization, see **appendix**.
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47 166 After calibration, for each of the 1000 parameter sets, the model was run with and
48
49 167 without the intervention ('intervention' and 'baseline', respectively). We model an
50
51 168 intervention of offering DBS testing in prison, compared to a baseline of current
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53 169 testing with venepuncture only. Additionally, we evaluate an intervention of offering
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55 170 DBS in specialist addiction services, compared to a baseline of current testing with
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3 171 venepuncture. The economic analysis was performed from a UK National Health
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5 172 Service perspective. Costs (in 2011 GBP, £1=\$1.55 USD) and health utilities (in
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7 173 quality-adjusted life years, QALYs) were attached to each model compartment.
8
9 174 Costs and QALYs were discounted 3.5% per annum as per NICE guidelines, with a
10
11 175 100 year time horizon (to accrue individual and population benefits). The mean
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13 176 incremental cost-effectiveness ratio (ICER) was calculated and cost-effectiveness
14
15 177 determined using the UK willingness-to-pay (WTP) threshold, estimated between
16
17 178 £20,000 and £30,000 per QALY gained[15]. Cost-effectiveness acceptability curves
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19 179 were constructed and univariate sensitivity analyses undertaken. Analysis of
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21 180 covariance (ANCOVA) methods were used to summarize the proportion of the
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23 181 variability in the incremental costs and QALYs explained by the uncertainty in input
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25 182 parameters[16].
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32 184 **Parameters**

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34 185 **Health state utilities:** Uninfected utility values were taken from UK population
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36 186 norms[17] for non-PWID, and a large cross-sectional study of injectors in
37
38 187 Scotland[18] for current PWID. We assumed equal utilities for ex-PWID and non-
39
40 188 PWID[13]. Utilities for HCV disease and treatment stages came from UK HCV trials
41
42 189 and economic evaluations[19-21] and used for ex-PWID (**table 1**). To derive PWID
43
44 190 HCV utilities, non-PWID HCV utilities were rescaled by multiplying by the ratio of the
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46 191 uninfected PWID utility to the uninfected ex-PWID utility for the youngest age group.
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48 192 All states included disutilities with age[17].
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54 194 No disutility was associated with testing in the base-case. However, some evidence
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56 195 suggests PWID may experience a disutility after positive HCV diagnosis[18 22]. We
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3 196 explored the impact of a disutility (0.09[18], see **appendix**) on diagnosis, which was
4
5 197 fully regained with treatment SVR.
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10 199 **Health state and testing costs:** Health care costs for HCV disease stages, antiviral
11
12 200 treatment (pegylated interferon-alfa and ribavirin, pegIFN+RBV), and testing were
13
14 201 taken from UK economic analyses[19 20 23 24](**table 1** and **appendix**). Data on the
15
16 202 yield (proportion tests Ab+) and prevalence in each setting were used to calculate
17
18 203 the number of non-PWID tested for each PWID/ex-PWID (see **appendix**). Costs
19
20 204 were inflated to 2011 GBP using the Health and Community Hospital Service pay
21
22 205 and prices index[25]. Additional PWID treatment delivery costs were applied[14]. We
23
24 206 assumed undiagnosed individuals do not incur HCV-related health care costs unless
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26 207 progressing to decompensated disease[12].
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32 209 **HCV disease progression parameters:** Transition rates between disease stages
33
34 210 were taken from UK economic evaluations[19-21] (**table 1**). Although estimates were
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36 211 not PWID specific, a recent meta-analysis suggests little evidence for differences in
37
38 212 progression between PWID and non-PWID[26].
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43 214 **HCV prevalence:** PWID HCV chronic prevalence was estimated from HCV antibody
44
45 215 prevalence among PWID in England (45% [41-49%, 95% confidence interval
46
47 216 (CI)][27]), with spontaneous clearance of 26% of acute infections[28] resulting in
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49 217 35% chronic infection.
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54 219 **Testing rates:** The overall baseline PWID testing rate was estimated through fitting
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56 220 the model to the current proportion of diagnosed PWID (approximately 50%[4]), and
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3 221 used to calculate setting-specific testing rates (prison, addiction services, other) (see
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5 222 **appendix**). We assume ex-PWID are tested at equal rates to PWID in prison and in
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7 223 general community settings. We assumed all diagnostic tests are 100% accurate
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9 224 due to the high sensitivity and specificity of DBS and venepuncture [29 30] and
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11 225 because those who receive an initial positive test will receive additional tests before
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13 226 treatment.
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19 228 **Referral and treatment transition rates:** The referral rate from testing services to
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21 229 secondary care (35%) was estimated from a UK study[31]. Those not referred or not
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23 230 attending referral were considered 'lost to follow-up'.
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27 232 Approximately 50% of diagnosed ex-PWID in referral are treated within 2 years[31-
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29 233 33]. Since many delay treatment, we assume that after 2 years, 10% of those in
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31 234 referral initiate treatment annually. Within prison, treatment rates are much lower
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33 235 than in the community[31 34], although a recent UK prison audit found 24% of those
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35 236 diagnosed were treated (Iain Brew[HMP Leeds], unpublished data). We therefore
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37 237 estimated half the treatment initiation rate in prison as compared to the community.
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43 239 PWID treatment rates are unknown, but thought to be similarly low to other
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45 240 countries[35 36], with an estimated <1% of PWID treated annually (Graham
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47 241 Foster[Consultant Hepatologist], *personal communication*). Hence, if we assume 1%
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49 242 of infected PWID are treated within 2 years, this equates to treating approximately
50
51 243 5.5% of those who attend referral (35% of the 50% diagnosed) within 2 years. After
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53 244 2 years, 1% of those in referral are treated annually thereafter. Testing and treatment
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55 245 rates are shown in **table 1**.
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5 247 **Intervention:** The effect of introducing DBS was modelled by assuming a 3.6-fold
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7 248 increase in testing [2.2-5.8 CI] in addiction services, and 2.6-fold increase in testing
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9 249 [0.1-34.9 CI] in prison, based on two multicentre studies (**table 2** and **appendix**).
10
11 250 Intervention costs were determined from the study methods[8] and in consultation
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13 251 with the authors (**table 2**).
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17 253 **Sensitivity analyses**

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20 254 We performed one-way sensitivity analyses on: time horizon (50/200 years),
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22 255 discount rates (3.5% costs/1.5% QALYs), PWID treatment rates (increased in each
23
24 256 setting), PWID SVR rates (reduced by 20%), PWID HCV chronic prevalence
25
26 257 (20%/50%), antiviral treatment (telaprevir/boceprevir for genotype 1 patients, see
27
28 258 **appendix**), and continuity of care for treatment/referral on entry/exit from prison
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30 259 (varied from 0% to 100%). We also explored the effect of assuming no prevention
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32 260 benefit (but allowing for reinfection), by permanently fixing the force of infection.
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39 263 **RESULTS**

40 264 41 265 **Case finding in addiction services**

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43 266 The incremental cost effectiveness ratio (ICER) of increasing case-finding in
44
45 267 addiction services, by introducing DBS testing, was an estimated £14,600 (\$22,630
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47 268 USD) per QALY gained in the base-case (**table 4**). At a £20,000 or £30,000 WTP
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49 269 threshold, the intervention is likely to be cost-effective in 69% or 93% of the
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51 270 simulations, respectively (**figure 1a**). Uncertainty in the intervention effect
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3 271 contributed to 86% and 58% of the variation in incremental costs and QALYs,
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5 272 respectively. The remaining variation in incremental QALYs was mainly due to
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7 273 uncertainty in treatment rates (22%) and health utilities (17%).
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11 275 For most sensitivity analyses, the ICER remained below a £30,000 WTP threshold
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13 276 (**figure 2a**). Reducing the time horizon to 50 years increased the estimated ICER to
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15 277 £22,900 per QALY gained because fewer prevention benefits were accrued,
16
17 278 whereas lengthening to 200 years increased cost-effectiveness. Changing the
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19 279 discount rates to 3.5% costs/1.5% QALYs or no discounting decreased the
20
21 280 estimated ICER to £5,100 or £6,700 per QALY gained, respectively. Variations in
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23 281 baseline HCV chronic prevalence had little effect (<10%). At lower prevalence (20%),
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25 282 identifying cases was more expensive but prevention impact was greater due to
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27 283 reduced reinfection risk, whereas the opposite occurred at higher prevalence (50%).
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32 285 Increasing treatment rates increased the intervention's cost-effectiveness. If 50%
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34 286 (compared to 5.5% for base-case) of PWID in referral initiated treatment within 2
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36 287 years (a treatment rate achieved by one UK service[37]) the ICER fell to £4,500 per
37
38 288 QALY gained. If SVR rates amongst PWID were 20% lower than in ex-PWID, the
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40 289 ICER increased by 14% (£16,700 per QALY gained). Using telaprevir/boceprevir for
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42 290 genotype 1 patients minimally altered the ICER. Ignoring any prevention benefit
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44 291 doubled the ICER to £29,900 per QALY gained.
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48 293 Only one sensitivity analysis substantially altered the cost-effectiveness conclusion.
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50 294 If a disutility was attached to diagnosis, the intervention resulted in negative
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52 295 incremental QALYs (due to low treatment rates) and was dominated (more
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3 296 expensive with fewer health benefits). However, even with this disutility, if treatment
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5 297 rates were increased to 50% of PWID in referral initiating treatment within 2 years,
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7 298 then the estimated ICER was £20,100 per QALY gained.
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11 300 **Case finding in prison**

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14 301 The ICER of increasing case-finding in prison, by introducing DBS testing, was
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16 302 estimated at £59,400 (\$92,070 USD) per QALY gained (21% likely to be cost-
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18 303 effective at a £30,000 WTP threshold) in the base-case (**table 4** and **figure 1b**).

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20 304 Uncertainty in the intervention effect contributed to most (>85%) of the variation in
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22 305 incremental costs and QALYs.
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27 307 The base-case conclusion was robust to most one-way sensitivity analyses (**figure**
28
29 308 **2b**) – including time horizon, discount rates, HCV prevalence, and use of new
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31 309 treatments. If 50% of PWID in referral initiated treatment within 2 years, the ICER
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33 310 halved to just below £30,000 per QALY gained.
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38 312 Introducing continuity of care (which measures the proportion of initiated
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40 313 treatments/referrals that are continued when entering/exiting prison) led to an
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42 314 increase in cost-effectiveness: from an ICER of £59,400 per QALY gained with 0%
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44 315 continuity to £10,400 per QALY gained with 100% continuity (**figure 3**). The ICER
45
46 316 fell below £20,000 when >40% continuity of care was ensured; at 40% continuity the
47
48 317 intervention was 57% and 83% likely to be cost-effective at the £20,000 and £30,000
49
50 318 WTP thresholds, respectively. The level of continuity required for prison case-finding
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52 319 to be cost-effective also depended on treatment rates. If prison treatment rates were
53
54 320 increased to equal those in the community (50%/5.5% of ex-PWID/PWID treated
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3 321 within 2 years of referral), then 35% continuity results in an ICER just below £20,000
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5 322 per QALY gained. Increasing treatment rates further so 50% of all referred prisoners
6
7 323 initiate treatment within 2 years lowers the required continuity to 20% for an ICER
8
9 324 below £20,000.
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326 **DISCUSSION**

327 **Main findings**

328 Our results indicate the introduction of dried blood spot testing for HCV case-finding
329 is likely to be cost-effective under commonly used willingness-to-pay thresholds in
330 the UK (£20,000-£30,000/QALY gained[15]) and US (\$50,000/QALY gained[38]) in
331 addiction services, but not in prison unless a minimum level of continuity of care in
332 treatment or referral between prison and the community can be ensured. Ignoring
333 the prevention benefit doubles the ICER of the intervention in addiction services. In
334 the base-case, most PWID treatments initiated in prison were interrupted due to the
335 lack of continuity of care and short PWID incarceration times (~4 months) in the UK.
336 Consequently, little prevention benefit was achieved from the prison intervention,
337 with the results approaching the 'static' model. With the low base-case PWID
338 treatment rates, the continuity required for DBS to be cost-effective was
339 approximately 35-40% of the estimated treatment/referral rates, but if
340 treatment/referral rates increased then lower levels of continuity would be cost-
341 effective. Crucially, not all treatments need to be initiated or completed in prison, as
342 only maintaining treatment or referral contact is necessary. Finally, both interventions
343 are most cost-effective at higher treatment rates.

344

345 **Strengths and Limitations**

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3 346 The key strength of this analysis is that the model is dynamic, therefore capturing the
4
5 347 prevention impact of case-finding and treatment. The main limitations are concerned
6
7 348 with parameter uncertainty and lack of model heterogeneity. First, we based our
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9 349 increase in case-finding on the DBS intervention, which though empirically founded,
10
11 350 was informed by relatively small UK studies, resulting in wide uncertainty around the
12
13 351 effect estimates.
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18 353 Second, the base-case assumed comparatively low treatment rates for PWID, partly
19
20 354 because UK data on PWID treatment numbers are not available, although similar
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22 355 rates have been reported in the US[36] and Canada[35]. This information is critical,
23
24 356 as higher treatment rates increase the intervention's cost-effectiveness. This is
25
26 357 especially important for prisons where information on treatment completion was
27
28 358 unavailable, yet these factors strongly influenced cost-effectiveness. Additionally,
29
30 359 even if treatment is interrupted, some may benefit from shortened treatment, which
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32 360 we did not incorporate. However, the rapid development of resistance observed with
33
34 361 new treatments[39] indicates treatment continuity will become an increasingly crucial
35
36 362 issue.
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42 364 Third, more data are needed to quantify PWID health utilities, which can be below
43
44 365 the general population[40]. Especially important is whether any transient or
45
46 366 permanent disutility on HCV diagnosis occurs, as current data are weak and not
47
48 367 based on prospective studies. No consensus exists regarding diagnosis utilities in
49
50 368 other diseases[41 42]. Our projections indicate if a disutility occurs then higher
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52 369 treatment rates are required for case-finding to be cost-effective.
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3 371 Fourth, the model did not incorporate other interventions or behaviours that may
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5 372 influence HCV risk or treatment uptake. For example, case-finding and treatment of
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7 373 PWID is targeted towards those on opiate substitution therapy[43] who may
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10 374 contribute fewer secondary infections[44]. However, modelling work has shown
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12 375 introducing risk heterogeneity does not substantially reduce intervention impact if
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14 376 PWID circulate between risk states[45] which is likely to occur as individuals move
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16 377 in/out of drug treatment and prison.
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21 379 Fifth, the model was parameterized to UK data, so our results are not necessarily
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23 380 applicable to other settings. However, our conclusions are robust to changes in HCV
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25 381 prevalence. Continuity of care could also be an issue in Australia, where PWID
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27 382 incarceration duration is similar to the UK[46]. However, sentences are longer in the
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29 383 US[47], so fewer treatments may be interrupted, and therefore case-finding in US
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31 384 prisons could be more cost-effective than our results indicate.
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36 386 Our modelled UK treatment and HCV health care costs are within the range of those
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38 387 presented by recent US studies[48 49], with the exception of approximately 3-fold
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40 388 higher liver transplantation costs, which would increase the cost-effectiveness of
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42 389 case-finding in the US. Finally, the higher proportion of genotype 1 (75%) in the US
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44 390 would reduce the population average SVR by approximately 15%, but we show
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46 391 case-finding is still cost-effective in addiction services with a reduction in PWID SVR
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48 392 by 20%.
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54 394 **Comparison with other studies**
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3 395 Two publications evaluated the cost-effectiveness of testing ex-PWID in prison, with
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5 396 ICERs varying from about £20,000[13] to £55,000[12] per QALY gained. Our
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7 397 results are consistent with Sutton et al.[12], which used the same discount rates as
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9
10 398 our study. However, we included the possible prevention impact of treating PWID,
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12 399 and unlike the previous studies, show how continuity of care between prison and the
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14 400 community can make case-finding cost-effective.

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18 402 Three papers evaluated testing PWID in drug services[13 24 50]. Differences in
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20 403 baseline assumptions led to varying ICERs from £28,100[24] to £17,500[13 50] per
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22 404 QALY gained. Our results for addiction services support those found in the latter
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24 405 studies[13 50]. However, the intervention examined in these studies[13 24 50] was
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26 406 one-off testing using a cohort model (with no evidence based intervention effect) and
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28 407 neglected any prevention benefit.

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33 409 Several US studies examined birth cohort screening for all people born in 1945-
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35 410 1965[49 51] or 1946-1970[48] as compared to risk based screening, reporting ICERs
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37 411 of \$38,000 per QALY gained with direct-acting antivirals[48 49] and \$5,400-16,000
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39 412 per QALY gained with pegIFN+RBV[49 51]. Critically, the cost-effectiveness varies
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41 413 substantially by HCV prevalence[51], and the estimated US prevalence is higher
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43 414 than many other developed countries. Additionally, the ICERs were generated given
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45 415 assumptions of higher treatment rates, as well as greater utility gains with SVR than
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47 416 we consider. Importantly, our intervention targets PWID with a risk of transmitting
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49 417 infection to others, whereas birth cohort screening is likely to identify infections
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51 418 among ex-injectors and non-injecting populations which will have little primary
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53 419 prevention impact.

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45 421 **Implications**
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7 422 Our cost-effectiveness work indicates increasing HCV case-finding in addiction
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9 423 services can be cost-effective. However, the cost-effectiveness of prison case-
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11 424 finding interventions depends on adequate continuity of care with the community.
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13 425 Few settings have developed comprehensive strategies to address this issue,
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15 426 though New York state recently initiated the Hepatitis C Continuity Program[52]. In
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17 427 all settings, treatment uptake is critical: higher treatment rates prevent more disease
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19 428 transmission and increase the cost-effectiveness of case-finding interventions. If a
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21 429 disutility on diagnosis occurs, higher treatment rates would be necessary to ensure
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23 430 cost-effectiveness. Further empirical data are required on treatment uptake and
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25 431 changes in utilities following diagnosis and treatment in order to compare targeted
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27 432 case-finding with cohort models.
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32 433
3334 434 **AUTHOR CONTRIBUTIONS**
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36 435 NKM contributed to the study design, model development, analysis, manuscript
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38 436 drafting and editing. MH contributed to the study design, model development,
39
40 437 analysis, and manuscript editing. AM contributed to the analysis and manuscript
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42 438 editing. SJH contributed to the model parameterization, analysis, and manuscript
43
44 439 editing. AT contributed to the model parameterization and manuscript editing. PV
45
46 440 contributed to the study design, model development, analysis, and manuscript
47
48 441 editing.
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51
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9
10 446 **Competing Interests**

11 447 NM has received an honorarium for speaking at a conference sponsored by
12
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14
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3 455
4 456 1. Nelson PK, Mathers BM, Cowle B, et al. Global epidemiology of hepatitis B and hepatitis C
5 457 in people who inject drugs: results of systematic reviews. *The Lancet* 2011;**378**:571-
6 458 83
7
8 459 2. De Angelis D, Sweeting M, Ades AE, et al. An evidence synthesis approach to estimating
9 460 Hepatitis C Prevalence in England and Wales. *Statistical Methods in Medical
10 461 Research* 2009;**18**(4):361-79 doi: 10.1177/0962280208094691[published Online
11 462 First: Epub Date]].
12 463 3. Hagan H, Campbell J, Thiede H, et al. Self-reported hepatitis C virus antibody status and
13 464 risk behavior in young injectors. *Addiction* 2006;**121**(6):710-9
14
15 465 4. Health Protection Agency Colindale. Hepatitis C in the UK 2011, July 2011.
16 466 5. Department of Health, HPA Prison Infection Prevention Team, Liver Strategy Team.
17 467 National Survey of hepatitis C services in prisons (Draft report). 2011
18 468 6. Taxman FS, Perdoni ML, Harrison LD. Drug treatment services for adult offenders: The
19 469 state of the state. *Journal of Substance Abuse Treatment* 2007;**32**:239-54
20 470 7. Harris M, Rhodes T. Venous access and care: harnessing pragmatics in harm reduction for
21 471 people who inject drugs. *Addiction* 2011;doi:10.1111/j.1360-0443.2011.03749.x
22 472 8. Hickman M, McDonald T, Ali J, et al. Increasing the uptake of hepatitis C virus testing
23 473 among injecting drug users in specialist drug treatment and prison settings by using
24 474 dried blood spots for diagnostic testing: a cluster randomized controlled trial. *Journal
25 475 of Viral Hepatitis* 2008;**15**(4):250-54
26 476 9. Craine N, Parry J, O'Toole J, et al. Improving blood-borne viral diagnosis; clinical audit of
27 477 the uptake of dried blood spot testing offered by a substance misuse service. *Journal
28 478 of Viral Hepatitis* 2009;**16**:219-22
29 479 10. Jones L, Bates G, McCoy E, et al. A systematic review of the effectiveness & cost-
30 480 effectiveness of interventions aimed at raising awareness and engaging with groups
31 481 who are at an increased risk of hepatitis B and C infection.
32 482 <http://www.nice.org.uk/nicemedia/live/11957/5946/5946.pdf>, 2012.
33 483 11. Martin NK, Vickerman P, Foster GR, et al. Can antiviral therapy for hepatitis C reduce the
34 484 prevalence of HCV among injecting drug user populations? A modelling analysis of its
35 485 prevention utility. *Journal of Hepatology* 2011;**54**:1137-44
36 486 12. Sutton AJ, Edmunds WJ, Sweeting MJ, et al. The cost-effectiveness of screening and
37 487 treatment for hepatitis C in prisons in England and Wales: a cost-utility analysis.
38 488 *Journal of Viral Hepatitis* 2008;**15**(11):797-808
39 489 13. Castelnovo E, Thompson-Coon J, Pitt M, et al. The cost-effectiveness of testing for
40 490 hepatitis C in former injecting drug users. *Health Technology Assessment*
41 491 2006;**2006**(10):32
42 492 14. Martin NK, Miners A, Vickerman P, et al. The cost-effectiveness of HCV antiviral
43 493 treatment for injecting drug user populations. *Hepatology* 2012;**55**(1):49-57
44 494 15. NICE. Guide to the methods of technology appraisal, 2008.
45 495 16. Briggs A, Claxton K, Sculpher M. *Decision Modelling for Health Economic Evaluation*.
46 496 Oxford: Oxford University Press, 2006.
47 497 17. Kind P, Hardman G, Macran S. UK Population Norms for EQ-5D: University of York, 2008.
48 498 18. McDonald S, Hutchinson SJ, Palmateer N, et al. Decrease in health-related quality of life
49 499 associated with awareness of hepatitis C virus infection among people who inject
50 500 drugs in Scotland. *Journal of Hepatology* (in press) 2012
51
52
53
54
55
56
57
58
59
60

- 1
2
3 501 19. Shepherd J, Jones J, Hartwell D, et al. Interferon alfa (pegylated and non-pegylated) and
4 502 ribavirin for the treatment of mild chronic hepatitis C: a systematic review and
5 503 economic evaluation. *Health Technology Assessment* 2007;**11**(11):1-224
6 504
7 504 20. Wright M, Grieve R, Roberts J, et al. Health benefits of antiviral therapy for mild chronic
8 505 hepatitis C: randomised controlled trial and economic evaluation. *Health Technol*
9 506 *Assess* 2006;**10**(21)
10 507 21. Hartwell D, Jones J, Baxter L, et al. Peginterferon alfa and ribavirin for chronic hepatitis C
11 508 in patients eligible for shortened treatment, re-treatment, or in HCV/HIV co-
12 509 infection: a systematic review and economic evaluation. *Health Technol Assess*
13 510 2011;**15**(17):1-210
14 511 22. Dalgard O, Egeland A, Skaug K, et al. Health-related Quality of Life in Active Injecting
15 512 Drug Users With and Without Chronic Hepatitis C Virus Infection. *Hepatology*
16 513 2004;**39**(1):74-80
17 514 23. British Medical Association. *British National Formulary, number 62*: BMJ Publishing
18 515 Group, 2011.
19 516 24. Stein K, Dalziel K, Walker A, et al. Screening for Hepatitis C in injecting drug users: A cost
20 517 utility analysis. *Journal of Public Health* 2004;**26**(1):61-71
21 518 25. Personal Social Services Research Unit. *Unit Costs of Health and Social Care 2011*:
22 519 University of Kent, 2011.
23 520 26. John-Baptiste A, Krahn MD, Heathcote J, et al. The natural history of hepatitis C infection
24 521 acquired through injection drug use: Meta-analysis and meta-regression. *Journal of*
25 522 *Hepatology* 2010;**53**(2):245-51
26 523 27. Harris RJ, Ramsay M, Hope VD, et al. Hepatitis C prevalence in England remains low and
27 524 varies by ethnicity: an updated evidence synthesis. *European Journal of Public Health*
28 525 2011;**Epub ahead of print**
29 526 28. Micallef JM, Kaldor JM, Dore GJ. Spontaneous viral clearance following hepatitis C
30 527 infection: a systematic review of longitudinal studies. *J Viral Hepat* 2006;**13**:34-41
31 528 29. Judd A, Parry J, Hickman M, et al. Evaluation of a modified commercial assay in detecting
32 529 antibody to hepatitis C virus in oral fluids and dried blood spots. *J Med Virol*
33 530 2003;**71**:49 - 55
34 531 30. Colin C, Lanoir D, Touzet S, et al. Sensitivity and specificity of third-generation hepatitis C
35 532 virus antibody detection assays: an analysis of the literature. *J Viral Hepat*
36 533 2001;**8**(2):87-95
37 534 31. Irving WL, Smith S, Cater R, et al. Clinical pathways for patients with newly diagnosed
38 535 hepatitis C - What actually happens. *Journal of Viral Hepatitis* 2006;**13**(4):264-71
39 536 32. Jowett SL, Agarwal K, Smith BC, et al. Managing chronic hepatitis C acquired through
40 537 intravenous drug use. *Q J Med* 2001;**94**:153-58
41 538 33. Foster G, Goldin RD, Main J, et al. Management of chronic hepatitis C: clinical audit of
42 539 biopsy based management algorithm. *BMJ* 1997;**315**:453-8
43 540 34. Skipper C, Guy JM, Parkes J, et al. Evaluation of a prison outreach clinic for the diagnosis
44 541 and prevention of hepatitis C: implications for the national strategy. *Gut*
45 542 2003;**52**:1500 - 04
46 543 35. Grebely J, Raffa JD, Lai C, et al. Low uptake of treatment for hepatitis C virus infection in
47 544 a large community-based study of inner city residents. *J Viral Hepat* 2009;**16**(5):352-
48 545 8
49 546 36. Mehta SH, Genberg BL, Astemborski J, et al. Limited Uptake of Hepatitis C Treatment
50 547 Among Injection Drug Users. *J Comm Health* 2008;**33**(3):126-33
51
52
53
54
55
56
57
58
59
60

- 1
2
3 548 37. Wilkinson M, Crawford V, Tippet A, et al. Community-based treatment for chronic
4 549 hepatitis C in drug users: high rates of compliance with therapy despite ongoing drug
5 550 use. *Alimentary Pharmacology & Therapeutics* 2009;**29**(1):29-37
6 551
7 551 38. Grosse SD. Assessing cost-effectiveness in healthcare: history of the \$50,000 per QALY
8 552 threshold. *Expert Rev Pharmacoecon Outcomes Res* 2008;**8**(2):165-78
9 553
10 553 39. Halfon P, Locarnini S. Hepatitis C virus resistance to protease inhibitors. *Journal of*
11 554 *Hepatology* 2011;**55**(1):192-206
12 555
13 555 40. Kimber J, Copeland L, Hickman M, et al. Survival and cessation in injecting drug users:
14 556 prospective observational study of outcomes and effect of opiate substitution
15 557 treatment. *BMJ* 2010;**340**:c3172 doi: 10.1136/bmj.c3172[published Online First:
16 558 Epub Date]].
17 559
18 559 41. Mattarozzi K, Vignatelli L, Baldin E, et al. Effect of the disclosure of MS diagnosis on
19 560 anxiety, mood and quality of life of patients: a prospective study. *Int J Clin Pract*
20 561 2012;**66**(5):504-14
21 562
22 562 42. Nekhlyudov L, Kroenke C, Jung I, et al. Prospective Changes in Quality of Life After Ductal
23 563 Carcinoma-in-Situ: Results From the Nurses' Health Study. *Journal of Clinical*
24 564 *Oncology* 2006;**24**(18):2822-27
25 565
26 565 43. Hellard M, Sacks-Davis R, Gold J. Hepatitis C Treatment for Injection Drug Users: A
27 566 Review of the Available Evidence. *Clinical Infectious Diseases* 2009;**49**(4):561-73 doi:
28 567 doi:10.1086/600304[published Online First: Epub Date]].
29 568
30 568 44. Turner K, Hutchinson S, Craine N, et al. The impact of needle and syringe provision and
31 569 opiate substitution therapy on the incidence of Hepatitis C virus in injecting drug
32 570 users: pooling of UK evidence. *Addiction* 2011;**106**(11):1978-88
33 571
34 571 45. Vickerman P, Martin N, Turner K, et al. Can needle and syringe programmes and opiate
35 572 substitution therapy achieve substantial reductions in HCV prevalence? Model
36 573 projections for different epidemic settings. *Addiction* 2012;**107**:1984-95
37 574
38 574 46. Miller E, Bi P, Ryan P. Hepatitis C virus infection in South Australian prisoners:
39 575 seroprevalence, seroconversion, and risk factors. *International Journal of Infectious*
40 576 *Diseases* 2009;**13**:201-08
41 577
42 577 47. West H, Sabol W, Greenman S. Bureau of Justice Statistics Bulletin: Prisoners in 2009.
43 578 <http://bjs.ojp.usdoj.gov/content/pub/pdf/p09.pdf>, 2010.
44 579
45 579 48. McGarry LJ, Pawar VS, Parekh HH, et al. Economic model of a birth cohort screening
46 580 program for hepatitis C virus. *Hepatology* 2012;**55**(5):1344-55 doi:
47 581 10.1002/hep.25510[published Online First: Epub Date]].
48 582
49 582 49. Rein D, Smith B, Witenborn J, et al. The Cost-Effectiveness of Birth-Cohort Screening for
50 583 Hepatitis C Antibody in U.S. Primary Care Settings. *Annals of Internal Medicine*
51 584 2012;**156**(4):263-70
52 585
53 585 50. Thompson Coon J, Castelnovo E, Pitt M, et al. Case finding for hepatitis C in primary
54 586 care: a cost utility analysis. *Family Practice* 2006;**23**(4):393-406 doi:
55 587 10.1093/fampra/cml032[published Online First: Epub Date]].
56 588
57 588 51. Coffin PO, Scott JD, Golden MR, et al. Cost-effectiveness and Population Outcomes of
58 589 General Population Screening for Hepatitis C. *Clinical Infectious Diseases*
59 590 2012;**54**(1259-1271)
60 591
61 591 52. Klein SJ, Wright LN, Birkhead GS, et al. Promoting HCV Treatment Completion for Prison
62 592 Inmates: New York State's Hepatitis C Continuity Program. *Public Health Reports*
63 593 2007;**122**(Suppl 2):83-88

- 1
2
3 594 53. Health Protection Agency. Data tables of the Unlinked Anonymous Monitoring Survey of
4 595 HIV and Hepatitis in Injecting Drug Users Surveillance Update: July 2011, 2011.
5 596 54. NICE. Peginterferon alfa and ribavirin for the treatment of mild chronic hepatitis C.
6 597 Technology appraisal guidance 106: National Institute for Health and Clinical
7 598 Excellence, 2006.
9 599 55. Hadziyannis SJ, Sette H, Morgan TR, et al. Peginterferon- α 2a and Ribavirin Combination
10 600 Therapy in Chronic Hepatitis C. *Annals of Internal Medicine* 2004;**140**(5):346-55
11 601 56. McHutchison JG, Lawitz EJ, Shiffman ML, et al. Peginterferon Alfa-2b or Alfa-2a with
12 602 Ribavirin for Treatment of Hepatitis C Infection. *New England Journal of Medicine*
13 603 2009;**361**(6):580-93 doi: doi:10.1056/NEJMoa0808010[published Online First: Epub
14 604 Date]].
16 605 57. Shiffman ML, Suter F, Bacon BR, et al. Peginterferon Alfa-2a and Ribavirin for 16 or 24
17 606 Weeks in HCV Genotype 2 or 3. *N Engl J Med* 2007;**357**(2):124-34 doi:
18 607 10.1056/NEJMoa066403[published Online First: Epub Date]].
20 608 58. Bruno S, Shiffman M, Roberts SK, et al. Efficacy and Safety of Peginterferon Alfa-2D
21 609 (40KD) Plus Ribavirin in Hepatitis C Patients with Advanced Fibrosis and Cirrhosis.
22 610 *Hepatology* 2010;**51**(2):388-97
23 611 59. Sweeting MJ, De Angelis D, Ades AE, et al. Estimating the prevalence of ex-injecting drug
24 612 use in the population. *Stats Meth Med Res* 2009;**18**(4):381-95 doi:
25 613 10.1177/0962280208094704[published Online First: Epub Date]].
27 614 60. Vickerman P, Miners A, Williams J. Assessing the cost-effectiveness of interventions
28 615 linked to needle and syringe programmes for injecting drug users. In: NICE, ed.
29 616 London, 2008.
30 617 61. Cornish R, Macleod J, Strang J, et al. Risk of death during and after opiate substitution
31 618 treatment in primary care: prospective observational study in UK General Practice
32 619 Research Database. *BMJ* 2010;**341** doi: 10.1136/bmj.c5475[published Online First:
33 620 Epub Date]].
35 621 62. Sutton AJ, Gay NJ, Edmunds WJ, et al. Modelling the hepatitis B vaccination programme
36 622 in prisons. *Epidemiol Infect* 2006;**134**:231 - 42
37 623 63. Government Actuary's Department. Interim life tables 1980-82 to 2004-06: Office for
38 624 National Statistics.
39 625 64. Ministry of Justice. Population in Custody Tables August 2010, 2010.
41 626 65. Office for National Statistics. Population Estimates for UK, England and Wales, Scotland
42 627 and Northern Ireland, Mid-2010, 2010.
43 628 66. Hay G, Gannon M, MacDougall J, et al. Capture-recapture and anchored prevalence
44 629 estimation of injecting drug users in England: national and regional estimates.
45 630 *Statistical Methods in Medical Research* 2009;**18**(4):323-39
47 631 67. Prime J, White S, Liriano S, et al. Criminal careers of those born between 1953 and 1978,
48 632 England and Wales: Home Office, Statistical Bulletin, 2001.
49 633
50 634
51 635
52
53
54
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Figure Legends:

Figure 1. **Base-case cost-effectiveness acceptability curves for the dried blood spot intervention.** Results shown for the (a) addiction services and (b) prison interventions for various willingness-to-pay thresholds.

Figure 2. **Univariate sensitivity analyses on the mean incremental cost-effectiveness ratio (ICER).** Results shown for the dried blood spot intervention in (a) addiction services and (b) prison. Vertical line represents the base-case ICER, estimated at (a) £14,600 per QALY gained and (b) £59,400 per QALY gained.

Figure 3. **Incremental cost-effectiveness ratios for the prison intervention with varying continuity of care assumptions.** Base-case scenario assumed 0% continuity.

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	Mean value	Distribution	Reference
Transition probabilities per year (all probabilities converted to instantaneous rates)			
Mild to moderate	0.025	Beta($\alpha=38.0859$, $\beta=1485.3516$)	[19]
Moderate to cirrhosis	0.037	Beta($\alpha=26.905$, $\beta=700.2582$)	[19]
Cirrhosis to decompensated cirrhosis	0.039	Beta($\alpha=14.6168$, $\beta=360.1732$)	[19]
Cirrhosis/decomp. cirrhosis to HCC	0.014	Beta($\alpha=1.9326$, $\beta=136.1074$)	[19]
Decompensated cirrhosis/HCC to LT	0.03	Beta($\alpha=6.5256$, $\beta=210.9945$)	[19]
Decompensated cirrhosis to death	0.13	Beta($\alpha=147.03$, $\beta=983.97$)	[19]
HCC to death	0.43	Beta($\alpha=117.1033$, $\beta=155.23$)	[19]
LT to death	0.21	Beta($\alpha=16.2762$, $\beta=61.2294$)	[19]
Post transplant to death	0.057	Beta($\alpha=22.9017$, $\beta=378.8825$)	[19]
Health state utilities/disutilities per year			
Ex-PWID age 15-19			
Uninfected	0.94		[17]
Mild	0.77	Beta($\alpha=521.2375$, $\beta=155.6943$)	[19 20]
Moderate	0.66	Beta($\alpha=168.2461$, $\beta=86.6723$)	[19 20]
Cirrhosis	0.55	Beta($\alpha=47.1021$, $\beta=38.5381$)	[19 20]
Decompensated cirrhosis	0.45	Beta($\alpha=123.75$, $\beta=151.25$)	[19 20]
Hepatocellular carcinoma	0.45	Beta($\alpha=123.75$, $\beta=151.25$)	[19 20]
Liver transplant	0.45	Beta($\alpha=123.75$, $\beta=151.25$)	[19 20]
Post transplant	0.67	Beta($\alpha=59.2548$, $\beta=29.1852$)	[20 21]
Mild - on treatment	0.66	Beta($\alpha=115.706$, $\beta=59.6063$)	[19 20]
Moderate - on treatment	0.55	Beta($\alpha=47.1021$, $\beta=38.5381$)	[12 19 20]
Cirrhosis - on treatment	0.46	Beta($\alpha=3953$, $\beta=4641$)	[12]
Mild SVR	0.82	Beta($\alpha=65.8678$, $\beta=14.4588$)	[19 20]
Moderate SVR	0.72	Beta($\alpha=58.0608$, $\beta=22.5792$)	[12 19 20]
Cirrhosis SVR	0.61	Beta($\alpha=58.0476$, $\beta=37.1124$)	[21]
PWID age 15-19			
Uninfected	0.74	Uniform(0.67,0.8)	[18]
HCV disease states		As in ex-PWID, but reduced by PropPWID [†]	Assumed
Disutility with age			
20-24	0		[17]
25-29	0.005		[17]
30-54	0.049		[17]
55-64	0.14		[17]
65-74	0.16		[17]
75+	0.21		[17]
Costs (£ per year, except where noted)			
Mild diagnosed	169	PPI [†] ×Gamma($k=25.6995$, $\theta=5.3698$)	[19 20]
Moderate diagnosed	880	PPI [†] ×Gamma($k=88.8502$, $\theta=8.0698$)	[19 20]
Cirrhosis diagnosed	1,397	PPI [†] ×Gamma($k=24.2342$, $\theta=46.9584$)	[19 20]
Decompensated cirrhosis	11,199	PPI [†] ×Gamma($k=36.0249$, $\theta=253.1582$)	[19 20]
Hepatocellular carcinoma	9,980	PPI [†] ×Gamma($k=18.1081$, $\theta=448.8045$)	[19]
Liver transplant (per transplant)	33,561	PPI [†] ×Gamma($k=89.7536$, $\theta=304.5004$)	[19]
Cost of care in year of liver transplant	11,614	PPI [†] ×Gamma($k=13.7788$, $\theta=686.4168$)	[19]
Post transplant	1,701	PPI [†] ×Gamma($k=15.2189$, $\theta=91.0053$)	[19]
Mild SVR	318	PPI [†] ×Gamma($k=28.8141$, $\theta=8.9887$)	[19]
Moderate SVR	880	PPI [†] ×Gamma($k=88.8502$, $\theta=8.0698$)	[19]
Cirrhosis SVR	1,397	PPI [†] ×Gamma($k=24.2342$, $\theta=46.9584$)	[19]
Undiagnosed states	0		
PegIFN+RBV drug only			
24 weeks, halved/doubled for 12/48 wks	5,320	Uniform (4788, 5852)	[23]
Treatment delivery			
Ex-PWID, 12 weeks	1,912	Varied, see appendix	See appendix[19]

Ex-PWID, 24 weeks	2,057	Varied, see appendix	See appendix[19]
Ex-PWID, 48 weeks	2,326	Varied, see appendix	See appendix[19]
PWID, 12 weeks	2,193	Varied, see appendix	See appendix
PWID, 24 weeks	2,435	Varied, see appendix	See appendix
PWID, 48 weeks	2,900	Varied, see appendix	See appendix
Testing costs in all settings except prison	115.21	Uniform +/- 50%	See appendix
Testing costs in prison	144.21	Uniform +/- 60%	See appendix
PCR RNA test (if antibody positive)	73.67		[24]
Testing and treatment parameters			
Proportion PWID diagnosed (initial)	50%		[4]
Proportion PWID treated (initial)	0%		Assumption
Proportion ex-PWID diagnosed (initial)	30%	Uniform (24%, 36%)	Assumption [53]
Proportion of diagnosed ex-PWID treated (initial)	10%	Uniform (5%, 15%)	Estimated <10% diagnosed chronic infections treated
Proportion HCV genotype 1 Sustained viral response(SVR)	50%		[4 54]
Genotype 1 mild/moderate	0.45	Uniform (0.4, 0.5)	[54-56]
Genotype 2/3 mild/mod	0.8	Uniform (0.75, 0.85)	[54 57]
Genotype 1 cirrhosis	0.25	55% reduction from mild/mod	[58]
Genotype 2/3 cirrhosis	0.6	75% reduction from mild/mod	[58]
Antiviral treatment duration (weeks)			
Genotype 1 SVR	48		[54]
Genotype 1 non-SVR	12		[54]
Genotype 2/3	24		[54]
Distribution of PWID HCV tests			
GP	38.4%		§
Prison	11.5%		§
Addiction services	29.4%		§
Other	20.7%		§
Proportion who are referred and attend referral	35%	Uniform (25%, 45%)	[13 31]
Proportion in referral who initiate treatment within 2 years (excl. prison)			
Ex-PWID	50%	Uniform(40%, 60%)	[13 31-33]
PWID	5.5%	Uniform(1%, 10%)	Assumption
Treatment initiation rate after 2 years in referral (excl. prison) per year			
Ex-PWID	10%	Uniform(5%, 15%)	Assumption
PWID	3%	Uniform(1%, 5%)	Assumption
Treatment rates in prison		Half out-of- prison rates	Assumption"
Yield (proportion tests Ab+)			
GP	2.7%		§
Prison	14.7%		§
Addiction services	17.7%		§
Other	1.7%		§

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Table 1. Model parameters. †PropPWID=(uninfected PWID utility value for age 15-19)/Uninfected ex-PWID utility for age 15-19). ‡PPI=Hospital and Community Health Services Pay and Prices Index inflation factor. §Health Protection Agency (HPA) unpublished data from the 2010 Sentinel Surveillance. ||Iain Brew, HMP Leeds, unpublished data. HCC=hepatocellular carcinoma; LT=liver transplant; SVR=sustained viral response; pegIFN=pegylated interferon; RBV= ribavirin

	Mean value	Distribution	Units	Ref.
Intervention effect (proportional change in testing rate)				
Addiction services	3.6	Lognormal		[8]
	[2.3-5.8]	($\mu=1.285$, $\sigma=0.239$)	-	
Prison	2.6	Lognormal	-	[8]
	[0.2-34.9]	($\mu=0.968$, $\sigma=1.317$)		
Intervention costs (addiction services)				
Organization/coordination of training*	2,005.71		per health board	†
Training session [‡]	135		per training session	†
Attendees time [§]	1,620		per training session	†
Travel reimbursement for training leader	90.86		per training session	†
Total cost per addiction services training	3851.57		per training session	†
Mean number tested	40.3		per addiction service	[8]
Total intervention cost per test	95.57	Uniform +/-50%	per test	
Intervention costs (prison)				
Organization/coordination of training**	7020		per prison	†
Training session [‡]	135		per prison	†
Attendees time ^{††}	405		per prison	†
Travel reimbursement for training leader ^{†††}	127.20		per prison	†
Total cost per prison training	7687.20		per prison	†
Mean number tested per prison	116		per prison	[8]
Total intervention cost per test	66.27	Uniform +/- 50%	per test	

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Table 2. Intervention parameters. All cost estimates assume a staff-nurse cost per hour of £364 (median estimate for band 5 general practice nurse[25]). * 1 nurse 2 days/week for 6 months for 7 health boards. One training session per health board. †Noel Craine, *personal communication*. ‡1 nurse, half day. §12 nurses, half day. ||1200 miles (£0.53 per mile) for travel to 7 health boards. |||Assumed 1 addiction service per health board. ** 1 nurse full time for 6 prisons (1 training session per prison) ††3 nurses per prison, half day. †††1200 miles (£0.53 per mile) for 5 prisons.

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	Mean value	Sampled values				Units	Ref.
Average duration of injecting until cessation	11	6.2, 8.6, 11, 13.4, 15.8				years	[59 60]
PWID overdose rate	0.01	0.007, 0.01, 0.013				Per year	[61]
Duration in addiction services	9	7, 9, 11				months	Estimated from OST duration[61]
Incarceration duration							
PWID							
All ages	4	2.67, 4, 5.33				Months	[62]
Ex-PWID							
15-19	2.75					Months	[62]
20-24	6.26					Months	[62]
25-29	8.42					Months	[62]
30-54	9.76					Months	[62]
55-64	11.92					Months	[62]
65+	12.49					Months	[62]
Age of first injection distribution							
15-19	41%					-	Combined UK data from [44]
20-24	30%					-	Combined UK data from [44]
25-29	16%					-	Combined UK data from [44]
30-54	13%					-	Combined UK data from [44]
55+	0%					-	Combined UK data from [44]
Death rate by age							
15-19	0.0003					Per year	[63]
20-24	0.0005					Per year	[63]
25-29	0.0006					Per year	[63]
30-54	0.0019					Per year	[63]
55-64	0.0073					Per year	[63]
65-74	0.0200					Per year	[63]
75+	0.165					Per year	[63]
Proportion of England population currently imprisoned aged 15-59	0.2%						[64 65]
Proportion of population who are PWID aged 15-59	0.65%						[66]
Proportion PWID in contact with addiction services	50%						[44]
Proportion PWID diagnosed	50%						[4]
PWID HCV chronic prevalence	35%						[27]
Proportion infections leading to spontaneous clearance	0.26	Uniform (0.22, 0.29)				-	[28]
		Age distribution					Reference
		15-19	20-24	25-29	30-54	55+	
Proportion general population with a custodial sentence	1.3%	2.5%	3%	4%	-		[67]
Age distribution of prisoners	8%	20%	18%	47%	7%		[64]
Proportion PWID ever in prison	48%	46%	67%	73%	-		*
Proportion prisoners ever PWID	5%	16%	36%	44%	8%		†

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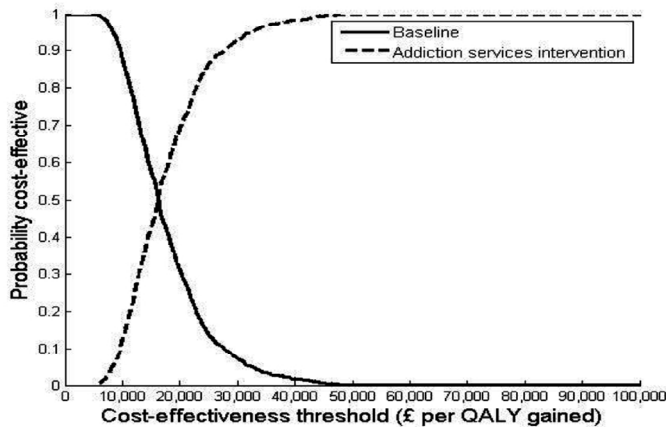
Table 23. Epidemiological/prison input parameters for model fitting *Unlinked Anonymous Monitoring Survey of PWID, Health Protection Agency, London, unpublished data. †Scottish prison data. ‡Avril Taylor, unpublished data.

Intervention location	Discounted Costs (2011 £) [95% interval]	Discounted QALYs [95% interval]	Incremental costs [95% interval]	Incremental QALYs [95% interval]	ICER (£ per QALY gained)
Addiction services					
Baseline	37,181,582 [19,384,816–67,271,249]	5,354,331 [4,867,168–5,960,766]	-	-	-
Intervention	38,099,060 [20,140,578–68,378,488]	5,354,393 [4,867,206–5,960,853]	917,478 [481,174–1,664,430]	63 [19–153]	14,632
Prison					
Baseline	37,181,582 [19,384,816–67,271,249]	5,354,331 [4,867,168–5,960,766]	-	-	-
Intervention	38,245,293 [19,852,634–68,601,970]	5,354,349 [4,867,184–5,960,823]	1,063,710 [-225,101 – 6,060,267]	18 [-12 – 75]	59,418

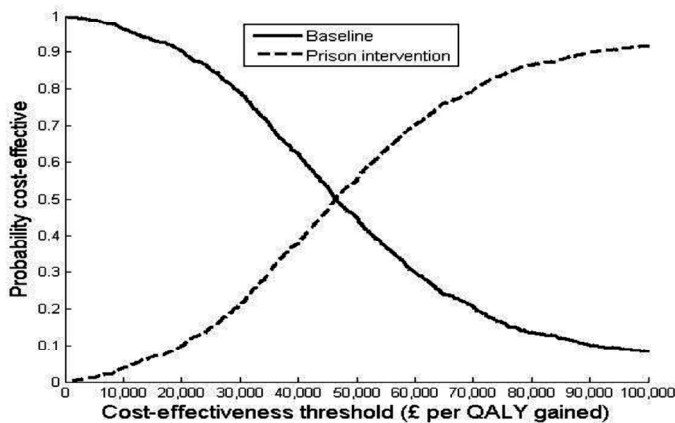
Table 4. Cost-effectiveness results from the base-case intervention analyses.

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(a)

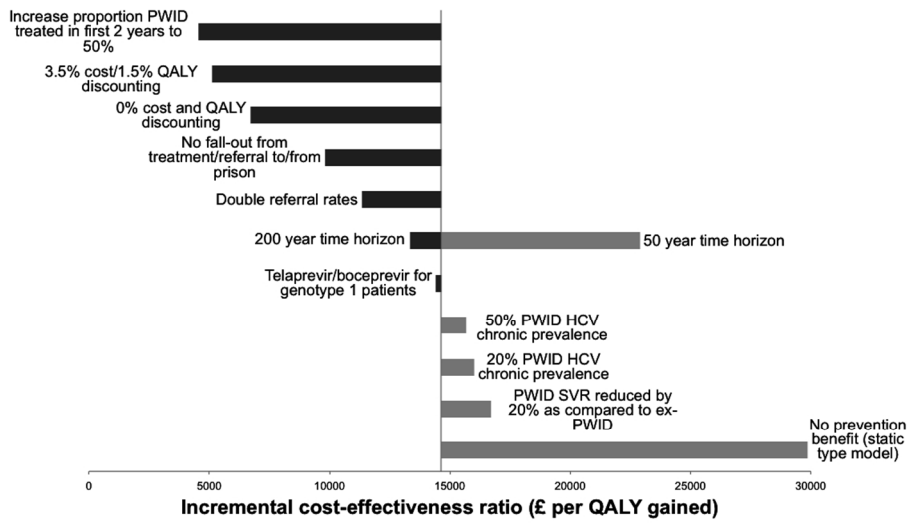


(b)

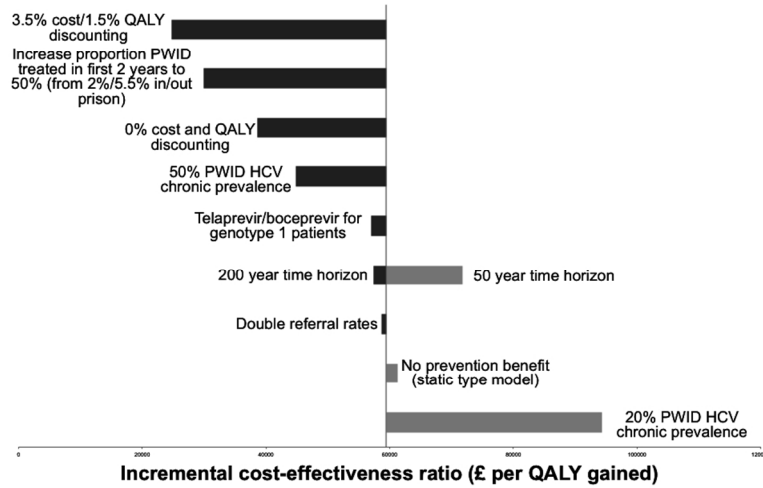
Figure 1

Base-case cost-effectiveness acceptability curves for the dried blood spot intervention. Results shown for the (a) addiction services and (b) prison interventions for various willingness-to-pay thresholds.
396x529mm (72 x 72 DPI)

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(a)



(b)

Figure 2

Univariate sensitivity analyses on the mean incremental cost-effectiveness ratio (ICER). Results shown for the dried blood spot intervention in (a) addiction services and (b) prison. Vertical line represents the base-case ICER, estimated at (a) £14,600 per QALY gained and (b) £59,400 per QALY gained.
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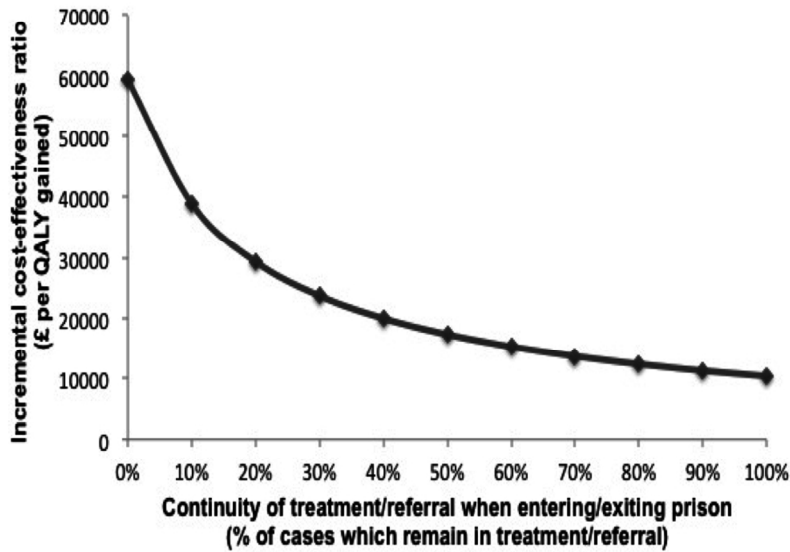


Figure 3

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Incremental cost-effectiveness ratios for the prison intervention with varying continuity of care assumptions.
 Base-case scenario assumed 0% continuity.
 396x529mm (72 x 72 DPI)

APPENDIX

Mathematical model

A dynamic, deterministic compartmental model of injecting drug use, HCV transmission, progression, treatment, and diagnosis amongst PWID was developed, to project the impact of interventions to increase HCV testing of PWID. Schematics for the model components can be found in **appendix figures 1 and 2**. The HCV transmission, antiviral treatment, and disease progression model was based on a coupled system of ordinary differential equations previously published by the authors[1]. Susceptible PWID can become acutely infected with HCV by sharing injecting equipment with other infected PWID. We model a frequency dependent force of infection, such that an individual's risk of infection is proportional to the overall prevalence of infection. This model assumes a proportion (26%) of acutely infected PWID progress to chronic infection, with the remainder resolving their acute infection after a number of months and developing an antibody (Ab) response, thus becoming Ab+/RNA-. Those that develop chronic infection (Ab+/RNA+) remain infected and, unless successfully treated, progress through the various HCV disease stages (mild, moderate, compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma (HCC), liver transplant, and post transplant). Death occurs from all stages, but elevated mortality rates were used from the decompensated cirrhosis, HCC, liver transplant, and post-transplant stages. If treated, infected PWID can achieve sustained viral response (SVR) whereby they are cured and are not at risk of progressing to a more advanced disease state, but remain at their current stage of liver progression (mild, moderate, or compensated cirrhosis), and are susceptible to reinfection. If reinfected after achieving SVR, the PWID re-enters the infected compartment of their associated HCV disease stage. If a PWID fails treatment (non-SVR), they remain infected and can progress to more severe disease stages. Successfully treated PWID can be reinfected and retreated, but those who do not achieve SVR are ineligible for retreatment. Due to reduced viral loads during treatment (even amongst those who relapse and do not achieve SVR), we assume PWID are not infectious during treatment[2, 3]. Current injectors are at risk of infection, but after permanent cessation of injecting do not have any infection risk. For simplicity, the model does not assume any behavioural heterogeneity among the PWID population

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3 (such as high/low risk), as modelling indicated introducing heterogeneity in risk does not
4 have an undue influence on prevention intervention effectiveness as long as individuals
5 circulate between high risk and intervention states[4].
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10 For this analysis, the model was adapted in the following ways. First, the model
11 compartments were subdivided to allow for a distinction between naïve uninfected (Ab-
12 /RNA-) or spontaneously cleared individuals (Ab+/RNA-), as well as the following
13 diagnosis stages for chronic infection: undiagnosed, diagnosed but lost to follow-up and
14 not in referral, diagnosed and in the first 2 years of referral, and diagnosed and in
15 referral after 2 years. For ex-PWID, an additional compartment was added to represent
16 those who were uninfected and tested (hence who would not be re-tested as they do
17 not have a continuing infection risk).
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26 In order to appropriately model incarceration, the model structure was replicated to track
27 the flow of PWID and ex-PWID between never incarcerated, currently incarcerated, and
28 formerly incarcerated states. In addition, compartments for never-PWID were added
29 (never incarcerated, currently incarcerated, formerly incarcerated) to enable model
30 calibration to general population incarceration data. This model structure was based on
31 previously published mathematical models of PWID incarceration[5, 6], and it was
32 assumed that incarceration and re-incarceration rates of ex-PWID were equal to that of
33 never-PWID.
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42 Additionally, for PWID not imprisoned (never imprisoned and formerly imprisoned) we
43 further stratified movement by contact with addiction services (in contact/not in contact).
44 We assumed only those in contact with addiction services could be tested in addiction
45 services. We also assumed that on release from prison, PWID were not immediately in
46 contact with addiction services.
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52 Finally, the model was split into 7 age compartments ([15-19],[20-24],[25-29],[30-
53 54],[55-64],[65-74],[75+]), with individuals entering the model at age 15-19 as never-
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PWID. In total, the model consists of 222 states and 7 age stratifications, leading to 222 x 7=1,554 compartments.

The model assumes that prisoners only share with other prisoners. Similarly, outside prison, we did not assume any difference in sharing behaviour between those who are never imprisoned or previously imprisoned, and these individuals share between each other.

The dynamic transmission aspect of the model is similar to our previously published mathematical models. Let $P_{m,n,l}^{a,i}$ represent the number of PWID, where the superscript m represents incarceration status ($m=0,1,2$ for never, currently, formerly incarcerated, respectively), the superscript n represents addiction services status ($n=out$ for out of contact and $n=in$ in contact, and noting that $n=out$ for all incarcerated states when $m=1$), subscript a represents the age group, with $a=1,2\dots7$ for each age group. The subscript l represents the HCV state, where $l=x_i$ for susceptible where i represents the different susceptible stages (never infected, spontaneously cleared), $l=y_i$ for chronic infected undiagnosed (including mild, moderate, compensated cirrhosis), $l=z_i$ for chronic infected diagnosed (including mild, moderate, compensated cirrhosis, decompensated cirrhosis, HCC, liver transplant, post-transplant and in early referral, late referral, or lost to follow-up states), $l=v_i$ for on treatment (including mild, moderate, compensated cirrhosis), $l=s_i$ for SVR (mild, moderate, compensated cirrhosis) and $l=f_i$ for treatment failure/non-SVR (mild, moderate, compensated cirrhosis). For example, $P_{0,0,x_1}^{1,1}$ represents a PWID who has never been imprisoned and is not in contact with addiction services, is in age group 1 (15-19), and is undiagnosed mild chronically infected. We assume proportionate mixing by age. Using this notation, the force of infection for a PWID who is not imprisoned ($m=0$ or 2) is:

$$\pi \frac{\sum_{\text{all } a,n,y_i,z_i,f_i} (P_{0,a,y_i}^n + P_{0,a,z_i}^n + P_{0,a,f_i}^n + P_{2,a,y_i}^n + P_{2,a,z_i}^n + P_{2,a,f_i}^n)}{\sum_{\text{all } a,n,x_i,y_i,z_i,v_i,s_i,f_i} (P_{0,a,x_i}^n + P_{0,a,y_i}^n + P_{0,a,z_i}^n + P_{0,a,v_i}^n + P_{0,a,s_i}^n + P_{0,a,f_i}^n + P_{2,a,x_i}^n + P_{2,a,y_i}^n + P_{2,a,z_i}^n + P_{2,a,v_i}^n + P_{2,a,s_i}^n + P_{2,a,f_i}^n)}$$

where π represents the infection rate, which is fit to the HCV prevalence among PWID.

While incarcerated, PWID can only transmit to other incarcerated PWID, so the force of infection for a susceptible PWID in prison ($m=1$) is:

$$\pi \frac{\sum_{\text{all } a, y_i, z_i, f_i} (P_{1,a,y_i} + P_{1,a,z_i} + P_{1,a,f_i})}{\sum_{\text{all } a, x_i, y_i, z_i, v_i, s_i, f_i} (P_{1,a,x_i} + P_{1,a,y_i} + P_{1,a,z_i} + P_{1,a,v_i} + P_{1,a,s_i} + P_{1,a,f_i})}$$

As stated before, all PWID in never infected (Ab-/RNA-), spontaneously cleared (Ab+/RNA-), and SVR states are susceptible for infection as described above.

Model Parameters

Intervention impact

The intervention impact was modelled a proportional increase in setting-specific testing rates, determined by a random effects meta-analysis of the primary data[7] for each setting (addiction services and prisons) separately. The results of the meta-analysis can be found in **appendix figure 3**.

SVR rates

Sustained viral response (SVR) rates for pegIFN+RBV were sampled by genotype, with mean values in the mild/moderate HCV disease stages of 45% for genotype 1 and 80% for genotype 2/3[8]. Patients with compensated cirrhosis exhibit proportional reductions in SVR values by about 45% and 25% for genotypes 1 and 2/3, respectively[9].

Preliminary studies indicate SVR rates are equal between PWID and ex/non-PWID[10], which we assumed in our base-case.

Calculation of testing rates

The HPA collects comprehensive yearly data of HCV testing in their sentinel surveillance, which includes a question on PWID as a risk factor. However, only a very small proportion of tests are coded with PWID status as a risk factor, and current or former PWID status is not recorded. Therefore, we were unable to use the HPA data to estimate the yearly testing rates of current and ex-PWID.

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3 To circumvent this problem, we fitted an overall PWID annual testing rate to calibrate
4 the model to the estimated proportion of PWID who are diagnosed (approximately
5 50%^[11]). This rate varied for each sampled group of parameters, but the mean annual
6 testing rate was 12% per year among undiagnosed PWID. This annual testing rate
7 ensured the proportion of diagnosed PWID remained stable (at equilibrium) without any
8 intervention.
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16 As testing of PWID takes place in different locations (prison, addiction services, other
17 settings) and the proportion of PWID in contact with these settings varies, it was
18 necessary to calculate setting-specific testing rates from the overall testing rate. This
19 was done using three pieces of information: 1) the overall testing rate, 2) the fraction of
20 tests attributable to each location, and 3) the proportion of the population in contact with
21 each location. We obtained the fraction of tests attributable to each location from the
22 HPA sentinel surveillance of hepatitis testing data, using the tests coded with an PWID
23 risk only (Mary Ramsay and Sara Collins[Health Protection Agency], *unpublished data.*).
24 Although these data underestimate the number of tests given to PWID, it is reasonable
25 to assume the HPA distribution between sites would be representative of the testing
26 administered to PWID as a whole. Finally, we ran the model to obtain steady state
27 values of the proportion of population found in each testing location based on the input
28 parameters (some of which were previously fitted, such as the proportion of PWID in
29 contact with addiction services and in prison). We assume all ex-PWID are in contact
30 with a GP. These three components were then combined to obtain setting specific
31 testing rates for each parameter set simulation. The setting specific testing rates for
32 PWID and ex-PWID were assumed equal, with the exception that the model assumes
33 ex-PWID are not in contact with addiction services, so no testing occurs from this
34 scenario for this group.
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50 51 **Testing costs**

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53 Costs associated with testing were calculated as follows. The numbers of PWID tested
54 in each setting were calculated, and associated with setting specific test costs. Two
55 additional costs were added: RNA testing (for all Ab+ tests) and non-PWID testing. The
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number of non-PWID tested in order to test one PWID was calculated from the setting-specific test yield (proportion of tests Ab+) and 'true' baseline prevalence. A setting with a low yield indicates more non-PWID are tested for every PWID; if yield equals baseline prevalence, this indicates only PWID are tested.

Contact with addiction services rates

The proportion of PWID in contact with addiction services at any given time was difficult to estimate. 92% of PWID report ever accessing a needle exchange in the HPA Unlinked Anonymous Survey, though the proportion currently accessing services is not asked[12]. However, it is estimated that 50% of PWID are currently on opiate substitution therapy[13, 14], and we therefore estimated that the same proportion is currently in contact with addiction services. Similarly, the average duration of time in contact with addiction services was estimated from data of average time PWID are on OST[15].

Model fitting

Overview of model fitting and baseline projections

A multi-step parameter sampling and model calibration/fitting method was used with simplified models to reduce computational time and allow for verification of full model predictions against the simplified models. For each fitting process (5 separate model fits in total), **appendix table 3** details the model used, input parameters, calibration data used to fit the model, and parameters estimated through model fitting. The seven-step sampling and calibration process is as follows:

- 1) Values were randomly sampled for four parameters (cessation rate, overdose rate, PWID prison release rate, and addiction services duration), yielding a total of 135 possible parameter combinations, or 'calibration scenarios'. Due to the heavy computational burden of fitting the many incarceration parameters, the model was fitted to a limited range of sampled 'calibration scenarios'.
- 2) **Fit #1:** Simplified model 1 (**appendix figure 4**) was run for each sampled calibration scenario, in order to calibrate the simplified model to the (not

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sampled) incarceration data shown in **table 3**. Inputs included the sampled scenario parameters, and non-sampled input parameters estimated from literature/sources (age-specific death rates, prison release rates for never PWID, distribution of ages of first injection, and a preliminary estimate of the entry rate of never-PWID aged 15-19 which will be refit in Fit #5). The parameters which were estimated through model calibration were the age-dependent incarceration rate, reincarceration rates, PWID incarceration rates, PWID reincarceration rates, and injecting initiation rate. Simplified model 1 neglected HCV transmission, testing, and treatment. More details can be found in the section '**Details of fit #1**' and model equations can be found the section entitled "**Model Equations: Simplified Model 1**".

- 3) **Fit #2:** Simplified model 2 (**appendix figure 5**) was run for each sampled calibration scenario, in order to calibrate the model to addiction services data. For fit #2, a simplified model of incarceration and movement in/out of addiction services was used. The inputs for these simulations were the sampled calibration scenarios and inputs from Simplified model 1, as well as the estimated incarceration parameters from Simplified model 1. The model was calibrated to data on the proportion of PWID in contact with addiction services, and the estimated parameter obtained through model fitting was the recruitment rate into addiction services. Model equations can be found in the section entitled "**Model Equations: Simplified Model 2**".
- 4) **Fit #3:** Simplified model 3 (**appendix figure 6**) was run for each sampled calibration scenario, in order to calibrate the model to the diagnosis data. For fit #3, a simple model of HCV transmission and testing among PWID was used to estimate the overall PWID testing rate by calibrating the model to the proportion of PWID who report being diagnosed for HCV. The model inputs were the sampled calibration scenarios and non-sampled inputs of age-specific death rates, distribution of injecting initiation age, and preliminary estimate of the entry rate of never-PWID aged 15-19. The model also required an input of the estimated injecting initiation rate from simplified model 1. Model equations can be found in the appendix section entitled "**Model Equations: Simplified Model 3**".

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- 5) 1000 parameter sets were sampled from each parameter uncertainty distribution in from the full range of disease progression, intervention, cost, and utility parameters (**Tables 1-3**). For each of the 1000 parameter sets, one of the 135 fitted ‘calibration scenarios’ was selected.
 - 6) **Fit #4:** For each of the 1000 parameter sets, the full model was calibrated to three separate HCV PWID chronic prevalences (35%[16], used in the base-case, as well as 20% and 50% for the sensitivity analyses) to estimate the infection rate, π_i , associated with each chronic prevalence.
 - 7) **Fit #5:** For each of the 1000 parameter sets, the full model was calibrated to a total PWID population size (fit to 1000 PWID at baseline), to estimate the entry rate of never-PWID in the 15-19 age group.

Model fitting was performed by using nonlinear least-squares methods using the MATLAB solver *lsqnonlin*.

Model Equations

Simplified model 1

For Simplified Model 1, the mathematical model tracks injecting drug use state (never/current/former PWID) and incarceration state (never/currently/formerly incarcerated). $N_{m,a}$ represents never PWID, with superscript m representing incarceration status ($m=0,1,2$ for never, currently, formerly incarcerated, respectively) and subscript a representing age group, with $a=1,2\dots7$ for each age group. Using the same subscript notation, $P_{m,a}$ represents PWID and $E_{m,a}$ represents ex-PWID. The full system of equation is as follows:

$$\begin{aligned}
 \frac{dN_{0,a}}{dt} &= \theta_a - (\rho_{0,a} + \xi_a + \gamma_a)N_{0,a} \\
 \frac{dN_{1,a}}{dt} &= \rho_{0,a}N_{0,a} + \alpha_{0,a}N_{2,a} - (\beta_{0,a} + \xi_a + \gamma_a)N_{1,a} \\
 \frac{dN_{2,a}}{dt} &= \beta_{0,a}N_{1,a} - (\alpha_{0,a} + \xi_a + \gamma_a)N_{2,a} \\
 \frac{dP_{0,a}}{dt} &= \xi_a N_{0,a} - (\rho_{1,a} + \zeta + \gamma_a + \eta)P_{0,a} \\
 \frac{dP_{1,a}}{dt} &= \xi_a N_{1,a} + \rho_{1,a}P_{0,a} + \alpha_{1,a}P_{2,a} - (\beta_{1,a} + \zeta + \gamma_a + \eta)P_{1,a} \\
 \frac{dP_{2,a}}{dt} &= \xi_a N_{2,a} + \beta_{1,a}P_{1,a} - (\alpha_{1,a} + \zeta + \gamma_a + \eta)P_{2,a} \\
 \frac{dE_{0,a}}{dt} &= \zeta P_{0,a} - (\rho_{0,a} + \gamma_a)E_{0,a} \\
 \frac{dE_{1,a}}{dt} &= \zeta P_{1,a} + \rho_{0,a}E_{0,a} + \alpha_{0,a}N_{2,a} - (\beta_{0,a} + \gamma_a)E_{1,a} \\
 \frac{dE_{2,a}}{dt} &= \zeta P_{2,a} + \beta_{0,a}E_{1,a} - (\alpha_{0,a} + \gamma_a)E_{2,a}
 \end{aligned}$$

where time is represented by the variable t . All populations experience age-specific death rates specified by rate γ_a and PWID have an additional death rate due to overdose of η . New never-PWID enter the system into the youngest age compartment at rate θ_1 ($\theta_a=0$ for $a \neq 1$). Never or former PWID are incarcerated at an age specific rate $\rho_{0,a}$, are released at a rate $\beta_{0,a}$, and are reincarcerated at a rate $\alpha_{0,a}$. Similarly, PWID are incarcerated at an age specific rate $\rho_{1,a}$, are released at a rate $\beta_{1,a}$, and are reincarcerated at a rate $\alpha_{1,a}$. Never PWID initiate injecting at an age-specific rate of ξ_a , and cessate from injecting at a rate ζ .

Simplified model 2

For Simplified Model 2, the mathematical model in Simplified Model 1 is extended to include flow in and out of addiction services for PWID who are not incarcerated. Using the same subscript notation as before, but adding a superscript with $n=in$ if the PWID is in contact with addiction services, and $n=out$ if they are not in contact, then

$E_{n,a}^i$ represents PWID. The full system of equation is as follows:

$$\begin{aligned}
\frac{dN_{0,a}}{dt} &= \theta_a - (\rho_{0,a} + \xi_a + \gamma_a)N_{0,a} \\
\frac{dN_{1,a}}{dt} &= \rho_{0,a}N_{0,a} + \alpha_{0,a}N_{2,a} - (\beta_{0,a} + \xi_a + \gamma_a)N_{1,a} \\
\frac{dN_{2,a}}{dt} &= \beta_{0,a}N_{1,a} - (\alpha_{0,a} + \xi_a + \gamma_a)N_{2,a} \\
\frac{dP_{0,a}^{out}}{dt} &= \xi_a N_{0,a} + \sigma P_{0,a}^{in} - (\rho_{1,a} + \zeta + \gamma_a + \eta + \nu)P_{0,a}^{out} \\
\frac{dP_{0,a}^{in}}{dt} &= \nu P_{0,a}^{out} - (\rho_{1,a} + \zeta + \gamma_a + \eta + \sigma)P_{0,a}^{in} \\
\frac{dP_{1,a}}{dt} &= \xi_a N_{1,a} + \rho_{1,a}(P_{0,a}^{out} + P_{0,a}^{in}) + \alpha_{1,a}(P_{2,a}^{out} + P_{2,a}^{in}) - (\beta_{1,a} + \zeta + \gamma_a + \eta)P_{1,a} \\
\frac{dP_{2,a}^{out}}{dt} &= \xi_a N_{2,a} + \beta_{1,a}P_{1,a} + \sigma N_{2,a}^{out} - (\alpha_{1,a} + \zeta + \gamma_a + \eta + \nu)P_{2,a}^{out} \\
\frac{dP_{2,a}^{in}}{dt} &= \nu N_{2,a}^{out} - (\alpha_{1,a} + \zeta + \gamma_a + \eta + \sigma)P_{2,a}^{in} \\
\frac{dE_{0,a}}{dt} &= \zeta(P_{0,a}^{out} + P_{0,a}^{in}) - (\rho_{0,a} + \gamma_a)E_{0,a} \\
\frac{dE_{1,a}}{dt} &= \zeta P_{1,a} + \rho_{0,a}E_{0,a} + \alpha_{0,a}N_{2,a} - (\beta_{0,a} + \gamma_a)E_{1,a} \\
\frac{dE_{2,a}}{dt} &= \zeta(P_{2,a}^{out} + P_{2,a}^{in}) + \beta_{0,a}E_{1,a} - (\alpha_{0,a} + \gamma_a)E_{2,a}
\end{aligned}$$

where the variables are as in Simplified Model 1, with the addition that PWID enter addiction services at a rate ν , and exit at a rate σ . The model assumes that when people initiate injecting, or are released from prison, they are not immediately in contact with addiction services (but can subsequently be recruited into contact at rate ν).

Simplified model 3

Simplified model 3 is used to fit the PWID diagnosis rate to the overall proportion of PWID diagnosed at a given time. Hence, it includes never PWID, uninfected PWID, infected undiagnosed PWID, and infected diagnosed PWID. As in the other simplified models, $N_{i,a}$ represents never PWID, with a representing age group, with $a=1,2\dots 7$ for each age group. Here, $P_{i,1,a}$ represents susceptible PWID, $P_{i,2,a}$ represents infected but undiagnosed PWID, and $P_{i,3,a}$ represents infected and diagnosed PWID. The full system of equation is as follows:

$$\begin{aligned} \frac{dN_a}{dt} &= \theta_a - (\xi_a + \gamma_a)N_a \\ \frac{dP_{a,x}}{dt} &= \xi_a N_a - \pi P_{a,x} \frac{P_{a,y} + P_{a,z}}{P_{a,x} + P_{a,y} + P_{a,z}} - (\zeta + \gamma_a + \eta)P_{a,x} \\ \frac{dP_{a,y}}{dt} &= \pi P_{a,x} \frac{P_{a,y} + P_{a,z}}{P_{a,x} + P_{a,y} + P_{a,z}} - (\kappa + \zeta + \gamma_a + \eta)P_{a,y} \\ \frac{dP_{a,z}}{dt} &= \kappa P_{a,y} - (\zeta + \gamma_a + \eta)P_{a,z} \end{aligned}$$

where the parameters are as in Simplified Model 1 with the addition that κ represents the diagnosis rate, and π is the infection rate.

Details of fit #1

In fit #1, the simplified incarceration model was calibrated to age-structured data on the proportion of the general population with a custodial sentence[17], proportion of PWIDs previously imprisoned, age distribution of current prisoners[18], proportion of prisoners ever PWID, proportion of the population currently imprisoned[19, 20], and the prevalence of PWID in the general population[16]. The epidemiological and prison parameters sampled for this fitting algorithm can be found in **table 3**.

As the prison data varied over several orders of magnitude (for example, the proportion of PWID previously incarcerated was around 60%, while the proportion of the England population currently imprisoned between the ages of 15-59 is 0.2%), a log-transformation of the calibration data was used in order to minimize relative error in the least-squares regression[21]. Furthermore, the error measure was re-weighted with more weight given to the error from the non-age structured parameters to provide a better fit to those parameters. Specifically, the error measure associated with each individual age-specific parameter of the 7 age-groups was weighted $1/7^{\text{th}}$ as much as a non-age specific parameter. **Appendix figure 7** provides an example of the data and calibrated model projections with the median values chosen for each parameter; all other fits were similar to this. The model fitted well to the data, with the notable exception of the proportion of PWID previously incarcerated in the 15-19 age group, which the model consistently underestimates. This was due to the low proportion of

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3 prisoners who admit ever-injecting in this age group, along with the low general rates of
4 ever incarceration in this age group. It was decided *a posteriori* that this deviation was
5 acceptable given the goodness of fit to the rest of the data and also because it is
6 unlikely that the data sources are consistent.
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10 11 12 **Initial conditions**

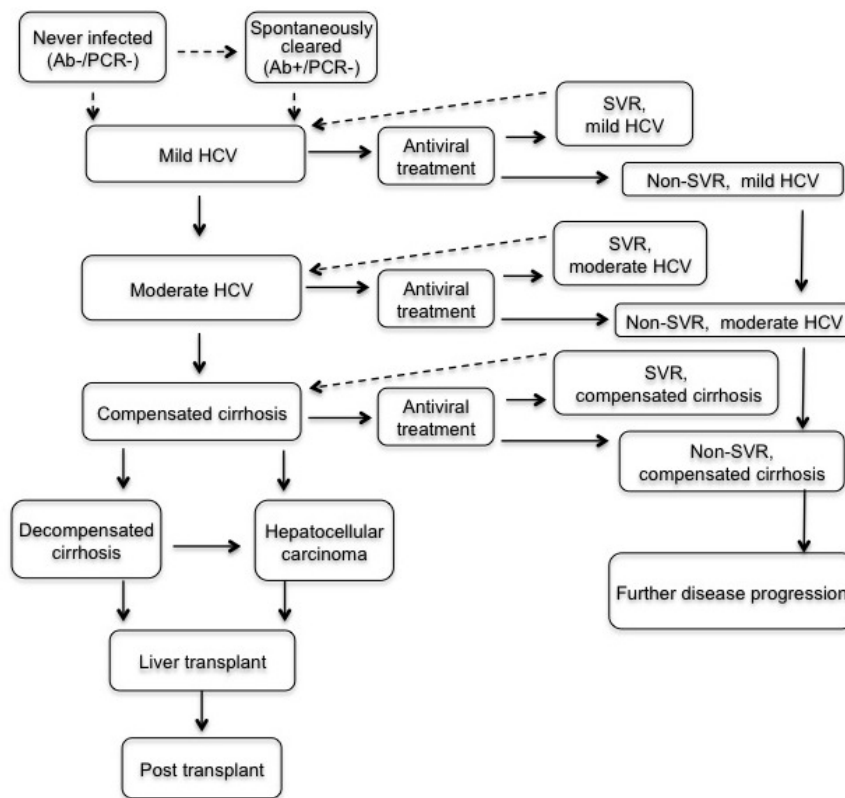
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14 The steady-state values of the full model without testing and treatment were used as
15 initial conditions for the baseline/intervention simulations, with the following alterations.
16 At baseline, the proportion of diagnosed ex-PWID was not thought to be at steady-state.
17 This was because recent testing initiatives have mainly targeted PWID; it is estimated
18 the proportion of diagnosed PWID (50%[11]) is currently likely higher than that of ex-
19 PWID (estimated at 30% based on proportion PWID diagnosed in 2000 who are likely to
20 be ex-PWID[12]). Hence, the steady-state values for infected populations were divided
21 between undiagnosed/diagnosed states for the initial conditions. As treatment rates of
22 PWID are extremely low, we assume none of the PWID population have been treated at
23 baseline, and sample the proportion of ex-PWID previously treated (mean sampled
24 value 10%[11]) from the range found in **table 1**.
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35 We calculate the initial conditions as follows. The full model without any testing and
36 treatment was run, and the number of people in all compartments was stored after the
37 system reached steady-state. This vector of initial condition values was then edited as
38 follows to account for the current proportion of diagnoses estimated in the PWID and
39 ex-PWID populations, as well as the proportion of ex-PWID already treated. As it is
40 unknown what proportion of previously diagnosed PWID are currently in referral for
41 treatment, we made the conservative assumption that all previously-diagnosed are lost-
42 to-follow-up at the beginning of the model if they have not been treated, and hence
43 need retesting in order to enter the referral and treatment pathway. We assume that no
44 PWID have been treated at baseline. Ex-PWID who have been treated are not eligible
45 for retesting and retreatment, and hence were removed from the model as they did not
46 change the cost-effectiveness of testing strategies.
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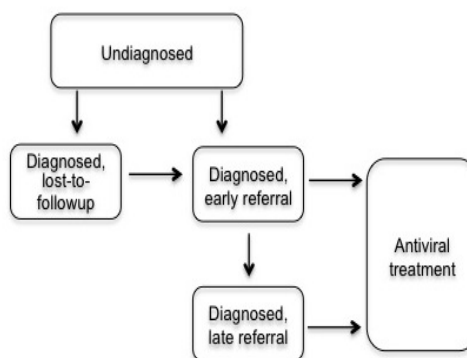
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3 Hence, half of the chronically infected PWID population were placed in the diagnosed
4 compartment of their relative disease state, with the remaining placed in the 'diagnosed
5 and lost-to-follow-up' compartment of their relative disease state. For the ex-PWID
6 population, a proportion will have been treated, and of the remaining untreated
7 proportion, 30% were considered diagnosed and were placed in the 'diagnosed and lost
8 to follow-up' compartment. As a result of this initialisation procedure, the proportion of
9 diagnosed ex-PWID was not at steady state at the start of the simulation. As stated in
10 the main text of the paper, this was deemed appropriate, as recent testing initiatives
11 have mainly targeted PWID, and therefore it is assumed that diagnosis rates among ex-
12 PWID are low. However, over time those who are PWID will become ex-PWID, and
13 therefore the proportion of diagnosed ex-PWID will increase over time.
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25 Results

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27 The incremental costs and incremental QALYs are shown on a cost-effectiveness plane
28 in **appendix figure 8**.
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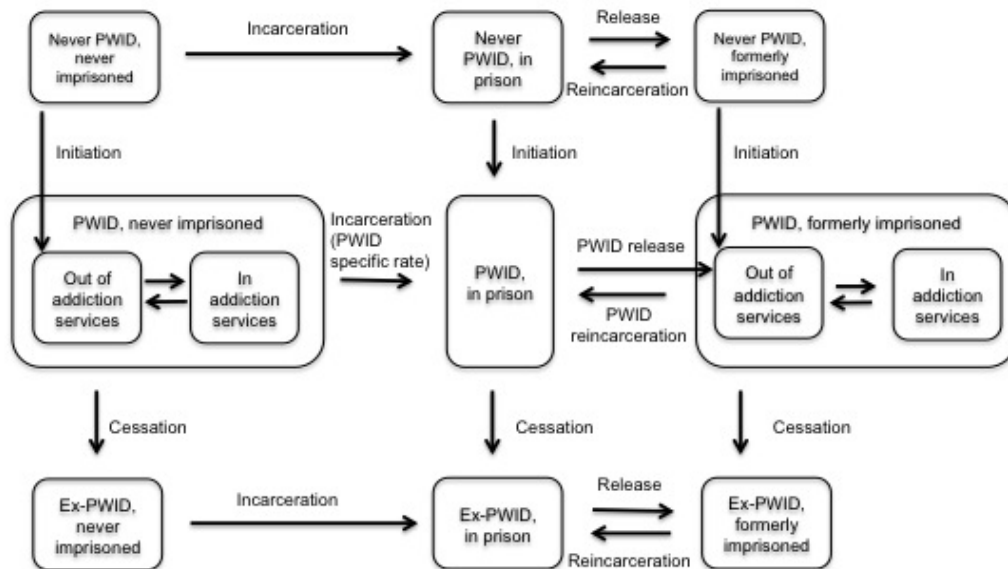


(a)



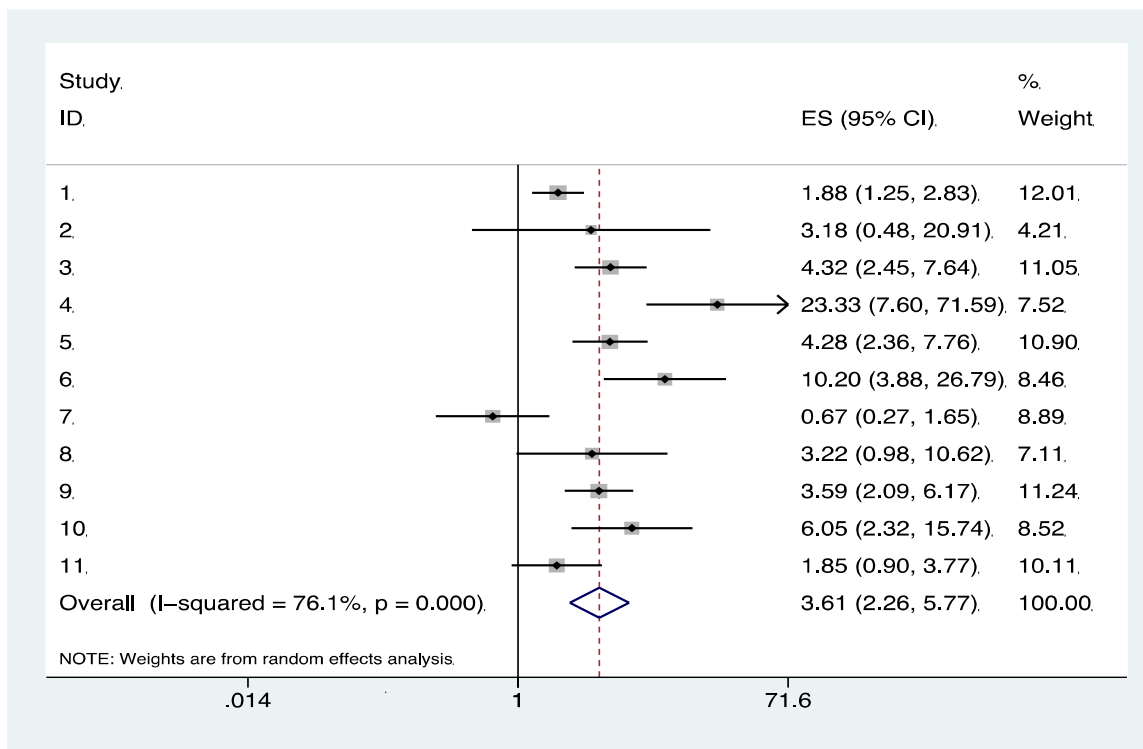
(b)

Appendix figure 1. HCV disease progression model schematics. Schematics show treatment (a) and diagnosis (b) model components. Solid black lines indicate transitions for both PWID and ex-PWID. Dashed black lines indicate PWID transitions only. For PWID, uninfecteds can be retested due to continuing risk behaviour; ex-PWID are not retested in the model.

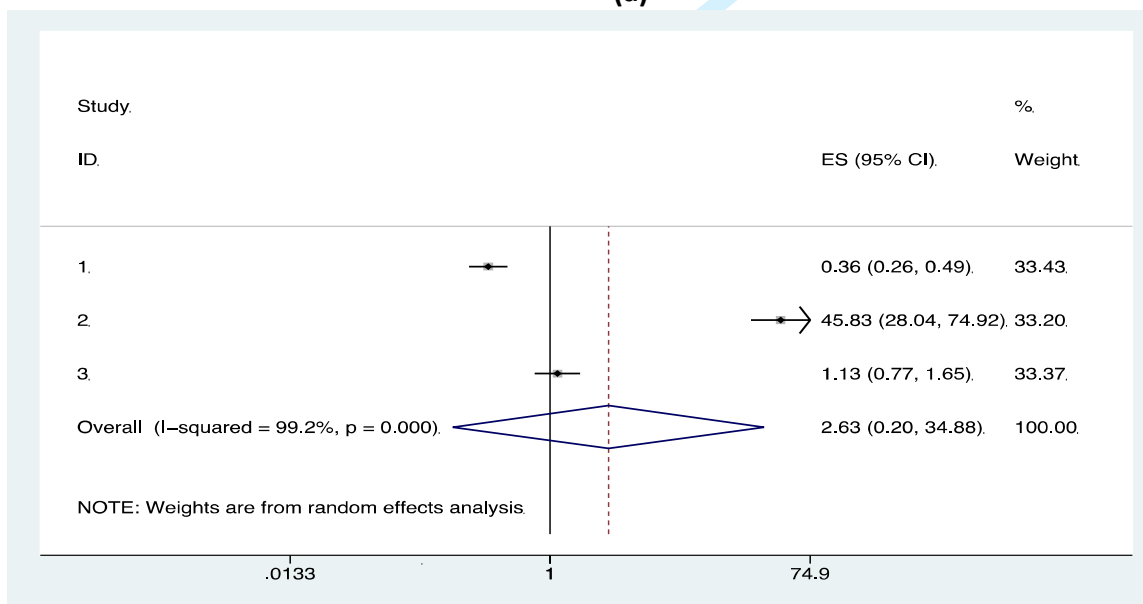


Model is stratified by age ([15-19, [20-24], [25-29], [30-54], [55-64], [65-74], [75+]), includes death from all compartments, overdose death from PWID compartments, and inflow to the youngest 'Never PWID, never imprisoned' compartment.

Appendix figure 2. General model flow schematic (each PWID and ex-PWID compartment includes HCV infection sub-compartments).

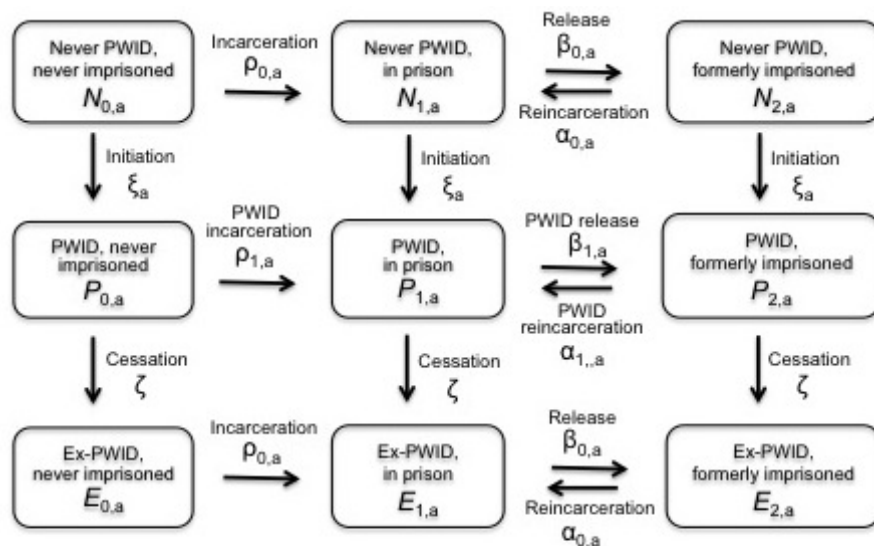


(a)



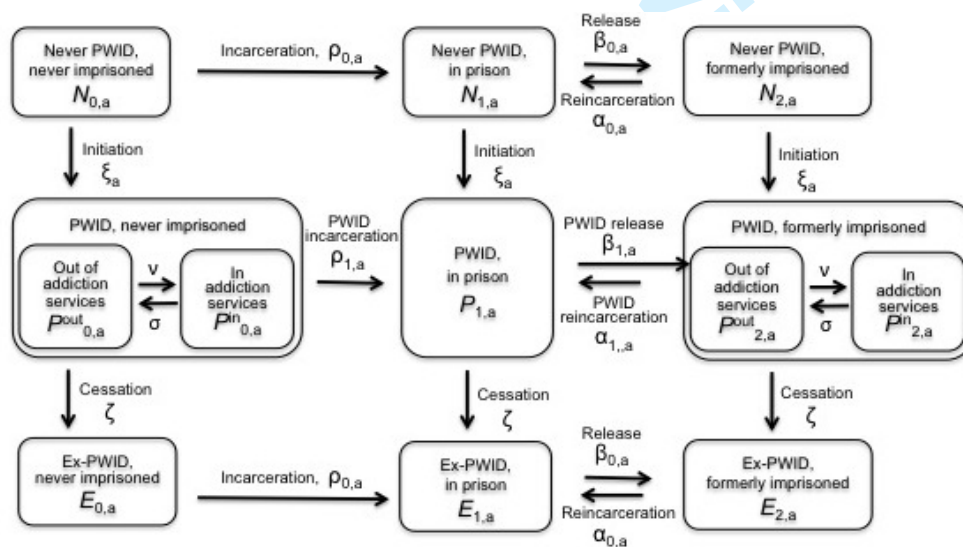
(b)

Appendix figure 3. Random effects meta-analysis results for the dried blood spot intervention effect on testing rate (proportional increase in testing rate). Results shown for (a) addiction services and (b) prison.



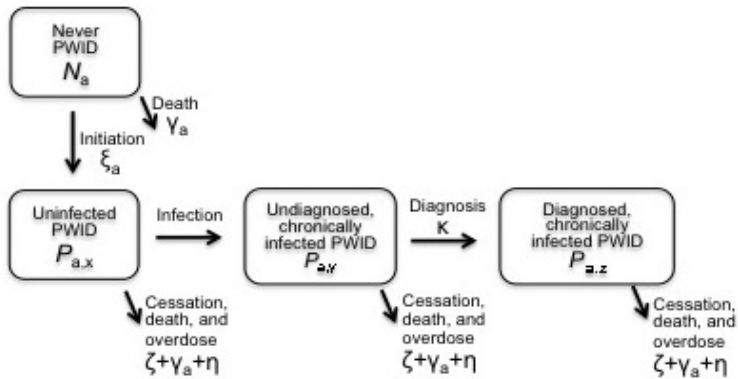
Model is stratified by age ([15-19, [20-24], [25-29], [30-54], [55-64], [65-74], [75+]), includes death from all compartments, overdose death from PWID compartments, and inflow to the youngest 'Never PWID, never imprisoned' compartment.

Appendix figure 4. Simplified model #1 schematic.



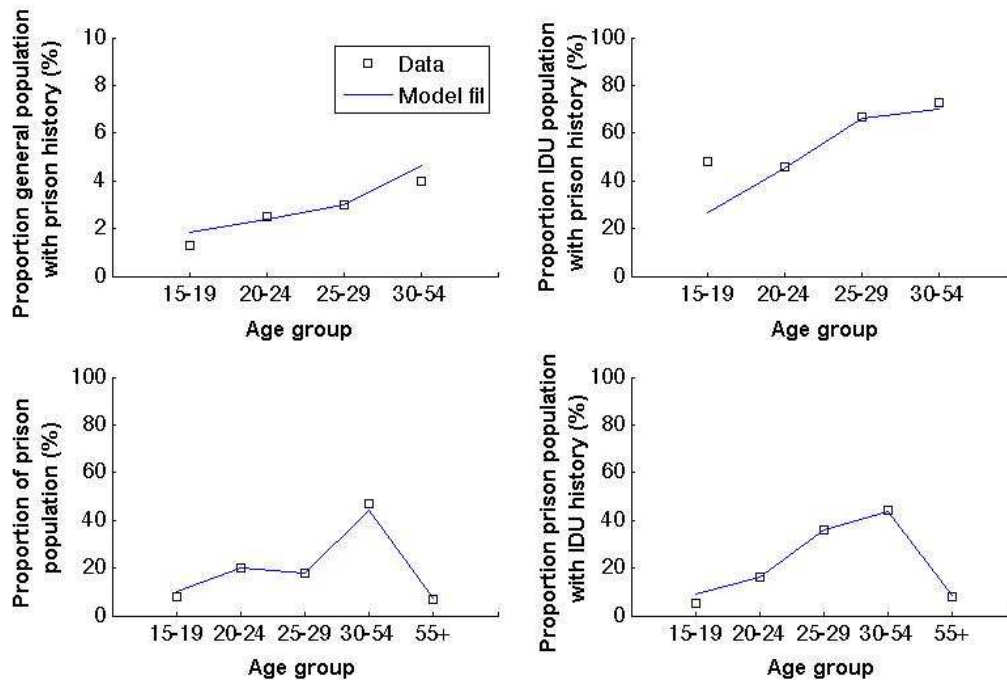
Model is stratified by age ([15-19, [20-24], [25-29], [30-54], [55-64], [65-74], [75+]), includes death from all compartments, overdose death from PWID compartments, and inflow to the youngest 'Never PWID, never imprisoned' compartment.

Appendix figure 5. Simplified model #2 schematic.



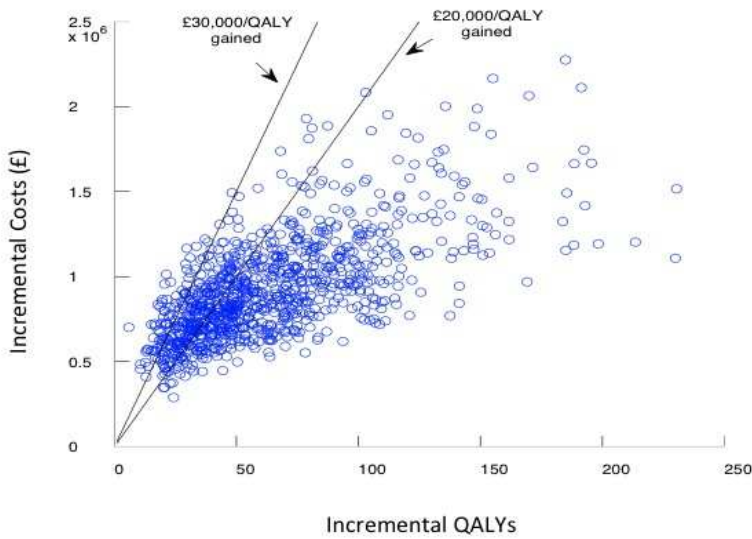
Model is stratified by age ([15-19, [20-24], [25-29], [30-54], [55-64], [65-74], [75+]) and includes inflow to the youngest [15-19] 'Never PWID' compartment.

Appendix figure 6. Simplified model #3 schematic.

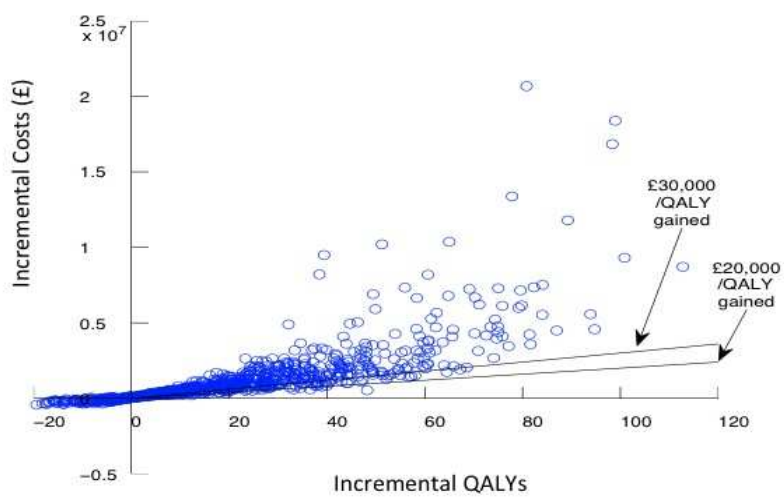


Appendix figure 7. Example of one characteristic model fit to the prison data (injecting duration 11 years, PWID incarceration duration 4 months, PWID overdose rate 1% per year). The top left shows the age-distributed proportion of general population with a custodial sentence. The bottom left shows the age-distribution within the prison population. The top right shows the proportion of PWID who have previously been incarcerated. The bottom right shows the proportion of prisoners who report ever PWID. Additionally, the model was fit to proportion of the general population imprisoned (simulated 0.21% as compared to 0.2%[19, 20]) and the proportion of population PWID (simulated 0.58% as compared to 0.65%[16])

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(b)

Appendix figure 8. Incremental costs and incremental QALYs for each of the 1000 simulation runs. Results shown for (a) addiction services and (b) prison interventions.

HCV testing costs- baseline	Mean value (in 2011 £)	Distribution /notes	Units	Ref.
Assessment	1.78	1 minute (average nurse and consultant doctor cost *)	Per test	[22]
Pre-test discussion and test	53.50	30 minutes (average nurse and consultant doctor cost *)	Per test	[22]
Post-test results	44.58	25 minutes (average nurse and consultant doctor cost *)	Per test	[22]
ELISA test	15.35		Per test	[22]
Additional assessment time (prison only)	29	Assuming 20 min. with nurse *	Per test	Estimated from timings in [22]
Total test costs in all settings except prison	115.21	Uniform +/- 50%	Per test	
Total test costs in prison setting	144.21	Uniform +/- 60% [†]	Per test	
PCR RNA test (if antibody positive)	73.67		Per year	[22]

Appendix table 1. Baseline HCV testing costs. * Assuming a consultant cost per hour of £127, and a staff-nurse cost per patient contact hour of £87 (median estimate for band 5 GP nurse, used as higher than estimate of £84 per hour for same band hospital day ward nurse) as found in the Unit Costs of Health and Social Care 2011[23]. [†]Greater uncertainty surrounding costs of testing in prison is due to uncertainty surrounding method of test offer (on prison entry, BBV/sexual health screening, or during routine health check).

HCV antiviral treatment costs	Mean value (in 2011 £)	Distribution	Ref.
PegIFN+RBV drug only			
12 weeks	2,660*	Halved from sampled cost at 24 wks	[24]
24 weeks	5,320*	Uniform (4788, 5852)	[24]
48 weeks	10,640*	Doubled from sampled cost at 24 wks	[24]
Treatment delivery			
12 weeks			
Staff	307	Varied by staff cost variation [†]	[25]
Tests	1,605	Varied by test cost variation [‡]	[25]
24 weeks			
Staff	374	Varied by staff cost variation [†]	[25]
Tests	1,683	Varied by test cost variation [‡]	[25]
48 weeks			
Staff	504	Varied by staff cost variation [†]	[25]
Tests	1,822	Varied by test cost variation [‡]	[25]
Additional treatment delivery for PWID			
PWID extra nurse time			
12 weeks	129	Varied by staff cost variation [†] and PWID staff time variation [§]	[1] "
24 weeks	159		[1] "
48 weeks	220		[1] "
PWID extra basic assessments			
12 weeks		Varied by test cost variation [‡] , staff cost variation [†] , and PWID staff time variation [§]	
Staff	58		[1] "
Tests	43		[1] "
24 weeks			
Staff	97		[1] "
Tests	71		[1] "
48 weeks			
Staff	174		[1] "
Tests	129		[1] "
PWID psychiatric visits	51	Varied by staff cost variation [†] and PWID staff time variation [§]	[1] "

Appendix table 2. HCV antiviral treatment costs. * Average peginterferon cost between alfa-2a (Pegasys) and alfa-2b (ViraferonPeg), and average ribavirin cost between Copegus and Rebetol. [†]Test value calculated by multiplying mean test cost with a test cost variation parameter, uniformly sampled between 0.8 and 1.2. [‡]Staff value calculated by multiplying mean staff cost by a staff cost variation parameter, uniformly sampled between 0.8 and 1.2. [§]PWID staff cost calculated by multiplying mean staff cost by a staff cost variation parameter and an extra PWID staff time variation parameter (both uniformly sampled between 0.8 and 1.2). "Graham Foster, Consultant Hepatologist, *personal communication*. pegIFN=pegylated interferon; RBV=ribavirin.

Model	Input parameters	Data used to fit model	Parameters estimated through model fitting
Fit #1 Simplified model 1 (Appendix figure 2)	<ul style="list-style-type: none"> • Sampled cessation rate • Sampled overdose rate • Sampled PWID prison release rate • Death rates by age • Prison release rate for never-PWID or ex-PWID by age • Injecting initiation age distribution • (Rough estimate) entry rate of never-PWID aged 15-19. 	<ul style="list-style-type: none"> • Proportion general population with a custodial sentence by age • Proportion of PWID population previously imprisoned by age • Age distribution of current prisoners • Proportion of prisoners ever-PWID by age • Proportion of the population currently imprisoned • Prevalence of PWID in general population 	<ul style="list-style-type: none"> • Incarceration rates by age • Re-incarceration rates by age • PWID incarceration rates by age • PWID re-incarceration rates by age • Injecting initiation rate
Fit #2 Simplified model 2 (Appendix figure 4)	<ul style="list-style-type: none"> • Input and output parameters from Fit #1 • Sampled addiction services duration • (Rough estimate) entry rate of never-PWID aged 15-19. 	<ul style="list-style-type: none"> • Proportion PWID in contact with addiction services 	<ul style="list-style-type: none"> • Recruitment rate into addiction services
Fit #3 Simplified model 3 (Appendix figure 5)	<ul style="list-style-type: none"> • Sampled cessation rate • Sampled overdose rate • Death rates by age • Injecting initiation age distribution • Fit injecting initiation rate (Fit #1) • (Rough estimate) entry rate of never-PWID aged 15-19. 	<ul style="list-style-type: none"> • Proportion PWID diagnosed 	<ul style="list-style-type: none"> • Overall (not setting-specific) PWID testing rate
Fit #4 Full model (figures 1 and 2 of the main text) without ex-PWID	<ul style="list-style-type: none"> • All model parameters from Fits #1-3 and sampled sets. • (Rough estimate) entry rate of never-PWID aged 15-19. 	<ul style="list-style-type: none"> • HCV PWID chronic prevalence 	<ul style="list-style-type: none"> • Infection rate, π
Fit #5 Full model	<ul style="list-style-type: none"> • All model parameters from Fits #1-4 and sampled sets. 	<ul style="list-style-type: none"> • Total population size (fit to 1000 PWID) 	<ul style="list-style-type: none"> • Entry rate of never-PWID in the 15-19 age group

Appendix table 3. Model fitting procedure summary

Telaprevir/boceprevir scenario parameters	Value	Units	Notes	Ref.
Proportional increase in SVR for genotype 1 patients	68%	-		[26, 27]
Average duration of treatment for genotype 1	37	weeks	Assume 50% have a rapid viral response (RVR) and only require 26 weeks treatment (24 weeks telaprevir, 28 weeks boceprevir). The remaining 50% require 48 weeks. In trials, 58-65% achieve RVR.	[26, 27]
Telaprevir or boceprevir drug cost only (pegIFN+RBV cost additional)	£19,600	per treatment	Mean cost between telaprevir (12 weeks, £22,398) and boceprevir (24 weeks, £16,800). Cost in addition to 37 weeks pegIFN+RBV (sampled as in table 1 of main text)	[28, 29]

Appendix table 4. Telaprevir/boceprevir sensitivity analysis parameters. pegIFN=pegylated interferon; RBV=ribavirin; RVR=rapid viral response; SVR=sustained viral response.

Health state utilities/disutilities per year	Mean	Distribution	Ref.
Ex-PWID			
Mild diagnosed [age 15-19]	0.77	Beta($\alpha=521.2375$, $\beta=155.6943$)	[25, 30]
Moderate diagnosed [age 15-19]	0.66	Beta($\alpha=168.2461$, $\beta=86.6723$)	[25, 30]
Compensated cirrhosis diagnosed [age 15-19]	0.55	Beta($\alpha=47.1021$, $\beta=38.5381$)	[25, 30]
Undiagnosed stages		Diagnosed state utility value + 0.09	[31]
Mild SVR [age 15-19]	0.82	Beta($\alpha=65.8678$, $\beta=14.4588$)	[25, 30]
Moderate SVR [age 15-19]	0.72	Beta($\alpha=58.0608$, $\beta=22.5792$)	[6, 25, 30]
Compensated cirrhosis SVR [age 15-19]	0.61	Beta($\alpha=58.0476$, $\beta=37.1124$)	[32]
PWID			
HCV disease states		As in ex-PWID, but reduced by PropPWID [†]	Assumed

Appendix table 5. Disutility on diagnosis sensitivity analysis parameters [†]PropPWID=(uninfected PWID utility value for age 15-19)/(uninfected ex-PWID utility for age 15-19). SVR=sustained viral response.

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7 [1] Martin NK, Miners A, Vickerman P, Foster G, Hutchinson S, Goldberg D, et al. The
8 cost-effectiveness of HCV antiviral treatment for injecting drug user populations.
9 *Hepatology* 2012;55:49-57.
- 10 [2] Martin NK, Vickerman P, Foster GR, Hutchinson SJ, Goldberg DJ, Hickman M. Can
11 antiviral therapy for hepatitis C reduce the prevalence of HCV among injecting drug user
12 populations? A modelling analysis of its prevention utility. *Journal of Hepatology*
13 2011;54:1137-1144.
- 14 [3] Martin NK, Vickerman P, Hickman M. Mathematical modelling of Hepatitis C
15 Treatment for Injecting Drug Users. *Journal of Theoretical Biology* 2011;274:58-66.
- 16 [4] Vickerman P, Hickman M, May M, Kretzschmar M, Wiessing L. Can hepatitis C virus
17 prevalence be used as a measure of injection-related human immunodeficiency virus risk in
18 populations of injecting drug users? An ecological analysis. *Addiction* 2009;105:311-318.
- 19 [5] Sutton AJ, Gay NJ, Edmunds WJ, Andrews NJ, Hope VD, Gilbert RL, et al. Modelling
20 the hepatitis B vaccination programme in prisons. *Epidemiol Infect* 2006;134:231 - 242.
- 21 [6] Sutton AJ, Edmunds WJ, Sweeting MJ, Gill ON. The cost-effectiveness of screening
22 and treatment for hepatitis C in prisons in England and Wales: a cost-utility analysis. *Journal*
23 *of Viral Hepatitis* 2008;15:797-808.
- 24 [7] Hickman M, McDonald T, Ali J, Nichols T, Hope V, Skidmore S, et al. Increasing the
25 uptake of hepatitis C virus testing among injecting drug users in specialist drug treatment
26 and prison settings by using dried blood spots for diagnostic testing: a cluster randomized
27 controlled trial. *Journal of Viral Hepatitis* 2008;15:250-254.
- 28 [8] NICE. Peginterferon alfa and ribavirin for the treatment of mild chronic hepatitis C:
29 National Institute for Health and Clinical Excellence; 2006.
- 30 [9] Bruno S, Shiffman M, Roberts SK, Gane EJ, Messinger D, Hadziyannis SJ, et al. Efficacy
31 and Safety of Peginterferon Alfa-2D (40KD) Plus Ribavirin in Hepatitis C Patients with
32 Advanced Fibrosis and Cirrhosis. *Hepatology* 2010;51:388-397.
- 33 [10] Hellard M, Sacks-Davis R, Gold J. Hepatitis C Treatment for Injection Drug Users: A
34 Review of the Available Evidence. *Clinical Infectious Diseases* 2009;49:561-573.
- 35 [11] Health Protection Agency Colindale. Hepatitis C in the UK 2011; July 2011.
- 36 [12] Health Protection Agency. Data tables of the Unlinked Anonymous Monitoring
37 Survey of HIV and Hepatitis in Injecting Drug Users Surveillance Update: July 2011; 2011.
- 38 [13] Turner K, Hutchinson S, Craine N, Hope V, Palmateer N, Vickerman P, et al. The
39 impact of needle and syringe provision and opiate substitution therapy on the incidence of
40 Hepatitis C virus in injecting drug users: pooling of UK evidence. *Addiction* 2011;106:1978-
41 1988.
- 42 [14] Hickman M, Hope V, Brady T, Madden P, Jones S, Honor S, et al. Hepatitis C virus
43 (HCV) prevalence, and injecting risk behaviour in multiple sites in England in 2004. *Journal of*
44 *Viral Hepatitis* 2007;14:645-652.
- 45 [15] Cornish R, Macleod J, Strang J, Vickerman P, Hickman M. Risk of death during and
46 after opiate substitution treatment in primary care: prospective observational study in UK
47 General Practice Research Database. *BMJ* 2010;341.
- 48 [16] Harris RJ, Ramsay M, Hope VD, Brant L, Hickman M, Foster GR, et al. Hepatitis C
49 prevalence in England remains low and varies by ethnicity: an updated evidence synthesis.
50 *European Journal of Public Health* 2011;Epub ahead of print.
- 51
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2
3 [17] Prime J, White S, Liriano S, K P. Criminal careers of those born between 1953 and
4 1978, England and Wales: Home Office, Statistical Bulletin; 2001.
5 [18] Ministry of Justice. Offender Management Statistics Quarterly Bulletin, April to June
6 2011, England and Wales; 2011.
7 [19] Ministry of Justice. Population in Custody Tables August 2010; 2010.
8 [20] Office for National Statistics. Population Estimates for UK, England and Wales,
9 Scotland and Northern Ireland, Mid-2010; 2010.
10 [21] Carroll RJ, Ruppert D. Transformation and Weighting in Regression: Chapman and
11 Hall; 1988.
12 [22] Stein K, Dalziel K, Walker A, Jenkins B, Round A, Royle P. Screening for Hepatitis C in
13 injecting drug users: A cost utility analysis. *Journal of Public Health* 2004;26:61-71.
14 [23] Personal Social Services Research Unit. Unit Costs of Health and Social Care 2011:
15 University of Kent; 2011.
16 [24] British Medical Association. British National Formulary, number 62: BMJ Publishing
17 Group; 2011.
18 [25] Shepherd J, Jones J, Hartwell D, Davidson P, Price A, Waugh N. Interferon alfa
19 (pegylated and non-pegylated) and ribavirin for the treatment of mild chronic hepatitis C: a
20 systematic review and economic evaluation. *Health Technology Assessment* 2007;11:1-224.
21 [26] Jacobson IM, McHutchison JG, Dusheiko G, Di Bisceglie AM, Reddy KR, Bzowej NH, et
22 al. Telaprevir for Previously Untreated Chronic Hepatitis C Virus Infection. *New England*
23 *Journal of Medicine* 2011;364:2405-2416.
24 [27] Poordad F, McCone J, Bacon BR, Bruno S, Manns MP, Sulkowski MS, et al. Boceprevir
25 for Untreated Chronic HCV Genotype 1 Infection. *New England Journal of Medicine*
26 2011;364:1195-1206.
27 [28] NELM.NHS.UK Press Release. Janssen Cilag launches telaprevir (Incivo) 375mg tablets
28 for the treatment of genotype 1 chronic hepatitis c. 2011 [cited; Available from:
29 <http://www.nelm.nhs.uk>
30 [29] NELM.NHS.UK Press Release. MD launches boceprevir (Victrelis) for the treatment of
31 chronic hepatitis C in the UK. 2011 [cited; Available from: <http://www.nelm.nhs.uk>
32 [30] Wright M, Grieve R, Roberts J, Main J, HC T. Health benefits of antiviral therapy for
33 mild chronic hepatitis C: randomised controlled trial and economic evaluation. *Health*
34 *Technol Assess* 2006;10.
35 [31] McDonald S, Hutchinson SJ, Palmateer N, Allen E, Cameron S, Goldberg D, et al.
36 Decrease in health-related quality of life associated with awareness of hepatitis C virus
37 infection among people who inject drugs in Scotland. *Journal of Hepatology* (in press) 2012.
38 [32] Hartwell D, Jones J, Baxter L, Shepherd J. Peginterferon alfa and ribavirin for chronic
39 hepatitis C in patients eligible for shortened treatment, re-treatment, or in HCV/HIV co-
40 infection: a systematic review and economic evaluation. *Health Technol Assess* 2011;15:1-
41 210.
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The CHEERS Checklist is part of the CHEERS Statement. The CHEERS Statement has been endorsed and co-published by the following journals:

- BJOG: An International Journal of Obstetrics and Gynaecology
- [BMC Medicine 2013; 11:80](#)
- [BMJ 2013;346:f1049](#)
- [Clinical Therapeutics 27 March 2013 \(Article in Press DOI: 10.1016/j.clinthera.2013.03.003\)](#)
- [Cost Effectiveness and Resource Allocation 2013 11:6.](#)
- [The European Journal of Health Economics 2013 Mar 26. \[Epub ahead of print\]](#)
- International Journal of Technology Assessment in Health Care
- [Journal of Medical Economics 2013 Mar 25. \[Epub ahead of print\]](#)
- [Pharmacoeconomics 2013 Mar 26. \[Epub ahead of print\]](#)
- [Value in Health 2013 March - April;16\(2\):e1-e5](#)

CHEERS Checklist
Items to include when reporting economic evaluations of health interventions

Section/item	Item No	Recommendation	Reported on page No/ line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as “cost-effectiveness analysis”, and describe the interventions compared.	page 1, line 1-2
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	pg 2-3, line 47-74
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	pg 4, line 110-124
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	pg 4, line 96-100. pg 5 line 130-136, 140-143
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	page 5, 128-130
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	pg 7, lines 170-173
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	pg 6, line 165-170
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	pg 7, line 173-174
Discount rate	9	Report the choice of discount rate(s) used for costs and	pg 7, line 173



1		outcomes and say why appropriate.	
2			
3	Choice of health	10 Describe what outcomes were used as the measure(s) of	
4	outcomes	benefit in the evaluation and their relevance for the type of	pg 7, line 172-173
5		analysis performed.	and 184-196
6	Measurement of	11a <i>Single study-based estimates:</i> Describe fully the design	
7	effectiveness	features of the single effectiveness study and why the single	
8		study was a sufficient source of clinical effectiveness data.	
9			
10		11b <i>Synthesis-based estimates:</i> Describe fully the methods used for	pg 10, lines
11		identification of included studies and synthesis of clinical	246-250 and
12		effectiveness data.	appendix
13	Measurement and	12 If applicable, describe the population and methods used to	
14	valuation of preference	elicit preferences for outcomes.	n/a
15	based outcomes		
16	Estimating resources	13a <i>Single study-based economic evaluation:</i> Describe approaches	
17	and costs	used to estimate resource use associated with the alternative	
18		interventions. Describe primary or secondary research methods	
19		for valuing each resource item in terms of its unit cost.	
20		Describe any adjustments made to approximate to opportunity	
21		costs.	
22		13b <i>Model-based economic evaluation:</i> Describe approaches and	
23		data sources used to estimate resource use associated with	pg 8, line 198-206
24		model health states. Describe primary or secondary research	pg 10, line 249-250
25		methods for valuing each resource item in terms of its unit	and appendix
26		cost. Describe any adjustments made to approximate to	
27		opportunity costs.	
28	Currency, price date,	14 Report the dates of the estimated resource quantities and unit	
29	and conversion	costs. Describe methods for adjusting estimated unit costs to	pg 7, lines
30		the year of reported costs if necessary. Describe methods for	171-172. pg 8,
31		converting costs into a common currency base and the	202-204
32		exchange rate.	
33	Choice of model	15 Describe and give reasons for the specific type of decision-	pg 5, lines 120-123
34		analytical model used. Providing a figure to show model	and 128-130.
35		structure is strongly recommended.	figure in appendix
36	Assumptions	16 Describe all structural or other assumptions underpinning the	
37		decision-analytical model.	pg 5, lines 128-153
38	Analytical methods	17 Describe all analytical methods supporting the evaluation. This	and appendix
39		could include methods for dealing with skewed, missing, or	
40		censored data; extrapolation methods; methods for pooling	pg 6, lines
41		data; approaches to validate or make adjustments (such as half	155-181. pg10
42		cycle corrections) to a model; and methods for handling	lines 252-259,
43		population heterogeneity and uncertainty.	appendix
44			
45	Results		
46	Study parameters	18 Report the values, ranges, references, and, if used, probability	
47		distributions for all parameters. Report reasons or sources for	Tables 1-3,
48		distributions used to represent uncertainty where appropriate.	appendix
49		Providing a table to show the input values is strongly	
50		recommended.	
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Cost-effectiveness of HCV case-finding for people who inject drugs via dried blood spot testing in specialist addiction services and prisons

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1 **Title: Cost-effectiveness of HCV case-finding for people who inject drugs via**
2 **dried blood spot testing in specialist addiction services and prisons**

3
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15
16 **Abbreviations:** hepatitis C virus (HCV), people who inject drugs (PWID), dried blood
17 spot (DBS), incremental cost-effectiveness ratio (ICER), quality-adjusted life-year
18 (QALY), willingness-to-pay (WTP), hepatocellular carcinoma (HCC), liver transplant
19 (LT), pegylated interferon (pegIFN), ribavirin (RBV), sustained viral response (SVR),
20 95% confidence interval (CI), antibody (Ab)

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37
38 **Word count:** 3118

39
40 **Figures/Tables:** 3 figures, 2 tables

41
42 **Key words:** hepatitis C, testing, mathematical modelling, economic evaluation

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3 45
4 46 **ABSTRACT (265 words)**
5 47

6 48 **Objectives:** People who inject drugs (PWID) are at high-risk for acquiring hepatitis

7
8 49 C virus (HCV), but many are unaware of their infection. HCV dried blood spot (DBS)

9
10 50 testing increases case-finding in addiction services and prisons. We determine the

11
12 51 cost-effectiveness of increasing HCV case-finding among PWID by offering DBS

13
14 52 testing in specialist addiction services or prisons as compared to using

15
16 53 venepuncture.

17
18
19 54 **Design:** Cost-utility analysis using a dynamic HCV transmission model among

20
21 55 PWID, including: disease progression, diagnosis, treatment, injecting status,

22
23 56 incarceration, and addiction services contact.

24
25 57 **Setting:** United Kingdom

26
27 58 **Participants:** N/A

28
29 59 **Intervention:** DBS testing in specialist addiction services or prisons. Intervention

30
31 60 impact was determined by a meta-analysis of primary data

32
33 61 **Primary and secondary outcome measures:** Costs (in UK £, £1=\$1.60 USD) and

34
35 62 utilities (quality adjusted life years, QALYs) were attached to each state and the

36
37 63 incremental cost effectiveness ratio (ICER) determined. Multivariate uncertainty and

38
39 64 one-way sensitivity analyses were performed.

40
41 65 **Results:** For a £20,000 per QALY gained willingness-to-pay threshold, DBS testing

42
43 66 in addiction services is cost-effective (ICER of £14,600 per QALY gained). Under the

44
45 67 base-case assumption of no continuity of treatment/care when exiting/entering

46
47 68 prison, DBS testing in prisons is not cost-effective (ICER of £59,400 per QALY

48
49 69 gained). Results are robust to changes in HCV prevalence; increasing PWID

50
51 70 treatment rates to those for ex-PWID considerably reduces the ICER (£4,500 and

52
53 71 £30,000 per QALY gained for addiction services and prison, respectively). If

1
2
3 72 continuity of care is >40%, the prison DBS ICER falls below £20,000 per QALY
4
5 73 gained.
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7 74 **Conclusions:** Despite low PWID treatment rates, increasing case-finding can be
8
9
10 75 cost-effective in specialist addiction services, and in prisons if continuity of
11
12 76 treatment/care is ensured.
13

14 77 **Trial Registration:** N/A
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18 79 **ARTICLE SUMMARY**

20 80 **Article focus**

- 21 81 • We perform a cost-utility analysis of increasing HCV case-finding among
22
23 82 PWID by offering dried blood spot testing in specialist addiction services or
24
25 83 prisons.
26
27
28

29 84 **Key messages**

- 30 85 • Despite low PWID treatment rates, increasing case-finding for PWID can be
31
32 86 cost-effective in specialist addiction services.
33
34 87 • In prisons, the cost-effectiveness of HCV case-finding depends on adequate
35
36 88 continuity of treatment/care between prison and the community, as many
37
38 89 treatments are discontinued due to short incarceration times.
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42 90 **Strengths and limitations of this study**

- 43 91 • We use a dynamic mathematical model of HCV transmission to capture the
44
45 92 potential prevention benefits of treatment, which has been shown to increase
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47 93 cost-effectiveness of HCV treatment for PWID.
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49 94 • Key limitations are the limited empirical data on PWID health utilities,
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51 95 treatment rates, and intervention impact.
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45 98 **INTRODUCTION**

6
7 99 In developed countries, the hepatitis C virus (HCV) is spread primarily through
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9
10 100 injecting drug use, with over 90% of new infections among people who inject drugs
11
12 101 (PWID) [1]. However, diagnosis rates are low, with only half of infected PWID in the
13
14 102 US and UK diagnosed[2].

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17
18 104 The majority of HCV testing performed in the US and UK is through venepuncture,
19
20 105 which is available in virtually all prisons[3] and addiction services (structured
21
22 106 programs providing pharmacological or nonpharmacological drug treatment in the
23
24 107 community) either on site or by referral. However, testing opportunities among PWID
25
26 108 still may be limited. This is because venous access can be poor and specialist staff
27
28 109 (who may not be available at all potential testing sites) are required to take blood,
29
30 110 which if only available in hospital phlebotomy services can increase stigma[4].

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32 111

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35
36 112 Dried blood spot (DBS) testing is non-invasive and can be performed by clinical and
37
38 113 non-clinical staff. Two UK studies[5 6] showed offering DBS testing within specialist
39
40 114 addiction services and prisons led to a 3 to 6-fold increase in HCV testing, and a
41
42 115 recent systematic review identified DBS as the best available targeted intervention
43
44 116 for increasing HCV case-finding amongst PWID[7]. Hence, DBS testing could be an
45
46 117 important component of any strategy attempting to scale-up treatment provision for
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48 118 PWID, for both care and prevention[8].

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54 120 We perform a cost-utility analysis of introducing DBS testing amongst current and
55
56 121 former PWID in specialist addiction services and prisons in the UK[5]. Unlike

1
2
3 122 previous economic evaluations of HCV testing in these settings[9 10], we incorporate
4
5 123 a dynamic mathematical model to capture the potential prevention benefits of
6
7 124 treatment, which can substantially increase the cost-effectiveness of HCV treatment
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10 125 for PWID[11]. A dynamic model accounts for both individual and population benefits
11
12 126 of treatment, as well as the dynamic nature of incarceration, especially among
13
14 127 PWID. Our model is the first to explore the importance of continuity of care between
15
16 128 prison and the community.
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20 21 130 **METHODS**

22 23 131 **Mathematical model**

24
25 132 An existing dynamic, deterministic model of HCV transmission, progression and HCV
26
27 133 treatment was adapted to project the impact of introducing DBS testing in prisons
28
29 134 and addiction services[11]. See **appendix** for details and model schematics. Briefly,
30
31 135 the model stratifies by: injecting state (never PWID/PWID/ex-PWID); incarceration
32
33 136 status (never/currently/formerly); contact with addiction services (in contact/not in
34
35 137 contact); age ([15-19],[20-24],[25-29],[30-54],[55-64],[65-74],[75+]); HCV infection
36
37 138 and disease progression (never infected, spontaneously cleared, mild HCV,
38
39 139 moderate HCV, compensated cirrhosis, decompensated cirrhosis, hepatocellular
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41 140 carcinoma, liver transplant, post-transplant). HCV disease stages are further
42
43 141 subdivided into undiagnosed or diagnosed, where those who are diagnosed can
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45 142 either be lost to follow-up, in referral (early/late), on antiviral treatment, sustained
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47 143 viral response (SVR), or non-SVR.
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54 145 All PWID can acquire and transmit HCV, but imprisoned PWID only transmit HCV to
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56 146 other prisoners. We define ex-PWID as those who have permanently ceased
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3 147 injecting, and assume no ongoing transmission from non/ex-PWID. An individual's
4
5 148 risk of acquiring HCV is proportional to the setting-specific HCV prevalence
6
7 149 (prison/community). The model assumes a background rate of HCV testing for all
8
9 150 PWID and ex-PWID in the community/prison, and in addiction services for PWID.
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11 151
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13 152 No UK data exist regarding continuity of care (treatment or referral) on prison
14
15 153 entry/exit, but experts described difficulty in ensuring continuity on release (Eamonn
16
17 154 O'Moore[Offender Health, UK Department of Health], Iain Brew[HMP Leeds]
18
19 155 *personal communication*). Therefore, in our base-case we assume those in
20
21 156 treatment or referral become lost to follow-up upon entering/exiting prison, but can
22
23 157 be re-tested/re-treated.
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29 159 **Model fitting and base-case projections**

30
31 160 For the probabilistic uncertainty analysis, 1000 parameter sets were sampled from
32
33 161 each parameter uncertainty distribution in **table 1 and appendix tables 1-2**. For
34
35 162 parameter set, the model was calibrated to UK epidemiological data on
36
37 163 incarceration, injecting drug use, HCV prevalence, and diagnosis. This was achieved
38
39 164 through a multi-step parameter sampling and model calibration process, utilizing
40
41 165 simplified models where possible to reduce computational time and to verify the full
42
43 166 model predictions against simplified models. For details on the model calibration
44
45 167 (including schematics and equations) and initialization, see **appendix**.
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52 169 After calibration, for each of the 1000 parameter sets, the model was run with and
53
54 170 without the intervention ('intervention' and 'baseline', respectively). We model an
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56 171 intervention of offering DBS testing in prison, compared to a baseline of current
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3 172 testing with venepuncture only. Additionally, we evaluate an intervention of offering
4
5 173 DBS in specialist addiction services, compared to a baseline of current testing with
6
7 174 venepuncture. The economic analysis was performed from a UK National Health
8
9 175 Service perspective. Costs (in 2011 GBP, £1=\$1.55 USD) and health utilities (in
10
11 176 quality-adjusted life years, QALYs) were attached to each model compartment.
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13
14 177 Costs and QALYs were discounted 3.5% per annum as per NICE guidelines, with a
15
16 178 100 year time horizon (to accrue individual and population benefits). The mean
17
18 179 incremental cost-effectiveness ratio (ICER) was calculated and cost-effectiveness
19
20
21 180 determined using the UK willingness-to-pay (WTP) threshold, estimated between
22
23 181 £20,000 and £30,000 per QALY gained[12]. Cost-effectiveness acceptability curves
24
25 182 were constructed and univariate sensitivity analyses undertaken. Analysis of
26
27 183 covariance (ANCOVA) methods were used to summarize the proportion of the
28
29 184 variability in the incremental costs and QALYs explained by the uncertainty in input
30
31 185 parameters[13].
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36 187 **Parameters**

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38 188 All parameters can be found in table 1 and **appendix tables 1-4**.

39
40 189 **Health state utilities:** Uninfected utility values were taken from UK population
41
42 norms for non-PWID, and a large cross-sectional study of injectors in Scotland[14]
43
44 for current PWID. We assumed equal utilities for ex-PWID and non-PWID[10].
45
46 192 Utilities for HCV disease and treatment stages came from UK HCV trials and
47
48 economic evaluations[15-17] and used for ex-PWID. To derive PWID HCV utilities,
49
50 193 non-PWID HCV utilities were rescaled by multiplying by the ratio of the uninfected
51
52 194 PWID utility to the uninfected ex-PWID utility for the youngest age group. All states
53
54 195 included disutilities with age.
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5 198 No disutility was associated with testing in the base-case. However, some evidence
6
7 199 suggests PWID may experience a disutility after positive HCV diagnosis[14 18]. We
8
9 200 explored the impact of a disutility (0.09[14], see **appendix**) on diagnosis, which was
10
11 201 fully regained with treatment SVR.
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16 203 **Health state and testing costs:** Health care costs for HCV disease stages, antiviral
17
18 204 treatment (pegylated interferon-alfa and ribavirin, pegIFN+RBV), and testing were
19
20 205 taken from UK economic analyses[15 16 19 20]. Data on the yield (proportion tests
21
22 206 Ab+) and prevalence in each setting were used to calculate the number of non-PWID
23
24 207 tested for each PWID/ex-PWID (see **appendix**). Costs were inflated to 2011 GBP
25
26 208 using the Health and Community Hospital Service pay and prices index[21].
27
28 209 Additional PWID treatment delivery costs were applied[11]. We assumed
29
30 210 undiagnosed individuals do not incur HCV-related health care costs unless
31
32 211 progressing to decompensated disease[9].
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38 213 **HCV disease progression parameters:** Transition rates between disease stages
39
40 214 were taken from UK economic evaluations[15-17]. Although estimates were not
41
42 215 PWID specific, a recent meta-analysis suggests little evidence for differences in
43
44 216 progression between PWID and non-PWID[22].
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49 218 **HCV prevalence:** PWID HCV chronic prevalence was estimated from HCV antibody
50
51 219 prevalence among PWID in England (45% [41-49%, 95% confidence interval
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53 220 (CI)][23]). As one-quarter of acute infections spontaneously clear [24] we assume
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3 221 three-quarters of those who are ever exposed (antibody positive) are chronically
4
5 222 infected, resulting in 35% chronic infection among PWID.
6

7 223
8

9 224 **Incarceration duration:** Incarceration duration for non-PWID and ex-PWID was
10
11 225 age-stratified, with a mean of 8 months[25]. However, PWID have shorter durations
12
13 226 in custody than non-PWID[25-27]. We used a 4 month PWID incarceration duration,
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15 227 based on an estimate for England and Wales[25]. A recent study in Scotland
16
17 228 reported a median sentence of 7.1 months in PWID[27] which given most prisoners
18
19 229 serve approximately half their sentence[28] would also equate to a duration of 4
20
21 230 months.
22
23 231

24
25 232 **Testing rates:** The overall baseline PWID testing rate (mean 12% undiagnosed
26
27 233 PWID per year) was estimated through fitting the model to the current proportion of
28
29 234 diagnosed PWID (approximately 50%[2]). Data on the proportion of tests from each
30
31 235 setting was used in combination with the model projected annual numbers of PWID
32
33 236 in contact with each setting to calculate setting-specific testing rates (6% and 13%
34
35 237 per year of undiagnosed PWID in contact with addiction services and prisons,
36
37 238 respectively, see **appendix**). We assume ex-PWID are tested at equal rates to
38
39 239 PWID in prison and in general community settings. We assumed all diagnostic tests
40
41 240 are 100% accurate due to the high sensitivity and specificity of DBS (99.6%
42
43 241 sensitivity, 100% specificity in a setting with 50% prevalence [29]) and venepuncture
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45 242 assays[30], and because those who receive an initial positive test will receive
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47 243 additional tests before treatment.
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3 245 **Referral and treatment transition rates:** The referral rate from testing services to
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5 246 secondary care (35%) was estimated from a UK study[31]. Those not referred or not
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7 247 attending referral were considered 'lost to follow-up'.
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12 249 Approximately 50% of diagnosed ex-PWID in referral are treated within 2 years[31-
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14 250 33]. Since many delay treatment, we assume that after 2 years, 10% of those in
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16 251 referral initiate treatment annually. Within prison, treatment rates are lower than in
17
18 252 the community[31 34], although a recent UK prison audit found 24% of those
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20 253 diagnosed were treated (Iain Brew[HMP Leeds], unpublished data). We therefore
21
22 254 estimated halved treatment initiation rates in prison as compared to the community.
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27 256 PWID treatment rates are unknown, but thought to be similarly low to other
28
29 257 countries[35 36], with an estimated <1% of PWID treated annually (Graham
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31 258 Foster[Consultant Hepatologist], *personal communication*). Hence, if we assume 1%
32
33 259 of infected PWID are treated within 2 years, this equates to treating approximately
34
35 260 5.5% of those who attend referral (35% of the 50% diagnosed) within 2 years. After
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37 261 2 years, 1% of those in referral are treated annually thereafter.
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43 263 **Intervention:** The effect of introducing DBS was modelled by assuming a 3.6-fold
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45 264 increase in testing [2.2-5.8 CI] in addiction services, and 2.6-fold increase in testing
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47 265 [0.1-34.9 CI] in prison, based on two multicentre studies (**table 1** and **appendix**).

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49 266 Intervention costs were determined from the study methods[5] and in consultation
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51 267 with the authors (**table 1**).

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55 269 **Sensitivity analyses**
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3 270 We performed one-way sensitivity analyses on: time horizon (50/200 years),
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5 271 discount rates (3.5% costs/1.5% QALYs), PWID treatment rates (increased in each
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7 272 setting), PWID SVR rates (reduced by 20%), PWID HCV chronic prevalence
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10 273 (20%/50%), antiviral treatment (telaprevir/boceprevir for genotype 1 patients, see
11
12 274 **appendix**), and continuity of care for treatment/referral on entry/exit from prison
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14 275 (varied from 0% to 100%). We also explored the effect of assuming no prevention
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16 276 benefit (but allowing for reinfection), by permanently fixing the force of infection.
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22 23 279 **RESULTS**

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27 28 281 **Case finding in addiction services**

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30 282 The incremental cost effectiveness ratio (ICER) of increasing case-finding in
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32 283 addiction services, by introducing DBS testing, was an estimated £14,600 (\$22,630
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34 284 USD) per QALY gained in the base-case (**table 2**). At a £20,000 or £30,000 WTP
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36 285 threshold, the intervention is likely to be cost-effective in 69% or 93% of the
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38 286 simulations, respectively (**figure 1a**). Uncertainty in the intervention effect
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40 287 contributed to 86% and 58% of the variation in incremental costs and QALYs,
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42 288 respectively. The remaining variation in incremental QALYs was mainly due to
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44 289 uncertainty in treatment rates (22%) and health utilities (17%).
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50 291 For most sensitivity analyses, the ICER remained below a £30,000 WTP threshold
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52 292 (**figure 2a**). Reducing the time horizon to 50 years increased the estimated ICER to
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54 293 £22,900 per QALY gained because fewer prevention benefits were accrued,
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56 294 whereas lengthening to 200 years increased cost-effectiveness. Changing the
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3 295 discount rates to 3.5% costs/1.5% QALYs or no discounting decreased the
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5 296 estimated ICER to £5,100 or £6,700 per QALY gained, respectively. Variations in
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7 297 baseline HCV chronic prevalence had little effect (<10%). At lower prevalence (20%),
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9 298 identifying cases was more expensive but prevention impact was greater due to
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11 299 reduced reinfection risk, whereas the opposite occurred at higher prevalence (50%).
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17 301 Increasing treatment rates increased the intervention's cost-effectiveness. If 50%
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19 302 (compared to 5.5% for base-case) of PWID in referral initiated treatment within 2
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21 303 years (a treatment rate achieved by one UK service[37]) the ICER fell to £4,500 per
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23 304 QALY gained. If SVR rates amongst PWID were 20% lower than in ex-PWID, the
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25 305 ICER increased by 14% (£16,700 per QALY gained). Using telaprevir/boceprevir for
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27 306 genotype 1 patients minimally altered the ICER. Ignoring any prevention benefit
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29 307 doubled the ICER to £29,900 per QALY gained.
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35 309 Only one sensitivity analysis substantially altered the cost-effectiveness conclusion.
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37 310 If a disutility was attached to diagnosis, the intervention resulted in negative
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39 311 incremental QALYs (due to low treatment rates) and was dominated (more
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41 312 expensive with fewer health benefits). However, even with this disutility, if treatment
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43 313 rates were increased to 50% of PWID in referral initiating treatment within 2 years,
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45 314 then the estimated ICER was £20,100 per QALY gained.
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51 316 **Case finding in prison**

52 317 The ICER of increasing case-finding in prison, by introducing DBS testing, was
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54 318 estimated at £59,400 (\$92,070 USD) per QALY gained (21% likely to be cost-
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56 319 effective at a £30,000 WTP threshold) in the base-case (**table 2** and **figure 1b**).
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3 320 Uncertainty in the intervention effect contributed to most (>85%) of the variation in
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5 321 incremental costs and QALYs.
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10 323 The base-case conclusion was robust to most one-way sensitivity analyses (**figure**
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12 324 **2b**) – including time horizon, discount rates, HCV prevalence, and use of new
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14 325 treatments. If 50% of PWID in referral initiated treatment within 2 years, the ICER
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16 326 halved to just below £30,000 per QALY gained.
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21 328 Introducing continuity of care (which measures the proportion of initiated
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23 329 treatments/referrals that are continued when entering/exiting prison) led to an
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25 330 increase in cost-effectiveness: from an ICER of £59,400 per QALY gained with 0%
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27 331 continuity to £10,400 per QALY gained with 100% continuity (**figure 3**). The ICER
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29 332 fell below £20,000 when >40% continuity of care was ensured; at 40% continuity the
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31 333 intervention was 57% and 83% likely to be cost-effective at the £20,000 and £30,000
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33 334 WTP thresholds, respectively. The level of continuity required for prison case-finding
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35 335 to be cost-effective also depended on treatment rates. If prison treatment rates were
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37 336 increased to equal those in the community (50%/5.5% of ex-PWID/PWID treated
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39 337 within 2 years of referral), then 35% continuity results in an ICER just below £20,000
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41 338 per QALY gained. Increasing treatment rates further so 50% of all referred prisoners
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43 339 initiate treatment within 2 years lowers the required continuity to 20% for an ICER
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45 340 below £20,000.
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51 342 **DISCUSSION**

52 53 54 55 343 **Main findings** 56 57 58 59 60

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3 344 Our results indicate the introduction of dried blood spot testing for HCV case-finding
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5 345 is likely to be cost-effective under commonly used willingness-to-pay thresholds in
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7 346 the UK (£20,000-£30,000/QALY gained[12]) and US (\$50,000/QALY gained[38]) in
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9 347 addiction services, but not in prison unless a minimum level of continuity of care in
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11 348 treatment or referral between prison and the community can be ensured. Ignoring
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13 349 the prevention benefit doubles the ICER of the intervention in addiction services. In
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15 350 the base-case, most PWID treatments initiated in prison were interrupted due to the
16
17 351 lack of continuity of care and short PWID incarceration times (~4 months) in the
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19 352 UK[25 27]. Consequently, little prevention benefit was achieved from the prison
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21 353 intervention, with the results approaching the 'static' model. With the low base-case
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23 354 PWID treatment rates, the continuity required for DBS to be cost-effective was
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25 355 approximately 35-40% of the estimated treatment/referral rates, but if
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27 356 treatment/referral rates increased then lower levels of continuity would be cost-
28
29 357 effective. Crucially, not all treatments need to be initiated or completed in prison, as
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31 358 only maintaining treatment or referral contact is necessary. Finally, both interventions
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33 359 are most cost-effective at higher treatment rates.
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361 **Strengths and Limitations**

362 The key strength of this analysis is that the model is dynamic, therefore capturing the
363 prevention impact of case-finding and treatment. The main limitations are concerned
364 with parameter uncertainty and lack of model heterogeneity. First, we based our
365 increase in case-finding on the DBS intervention, which though empirically founded,
366 was informed by relatively small UK studies, resulting in wide uncertainty around the
367 effect estimates.

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3 369 Second, the base-case assumed comparatively low treatment rates for PWID, partly
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5 370 because UK data on PWID treatment numbers are not available. This information is
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7 371 critical, as higher treatment rates increase cost-effectiveness. This is especially
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10 372 important for prisons where treatment completion information was unavailable, yet
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12 373 strongly influenced cost-effectiveness. Additionally, even if treatment is interrupted,
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14 374 some may benefit from shortened treatment, which we did not incorporate.

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18 376 Third, more data are needed to quantify PWID health utilities, which can be below
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20 377 the general population[39]. Especially important is whether any transient or
21
22 378 permanent disutility on HCV diagnosis occurs, as current data are weak and not
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24 379 based on prospective studies. Our projections indicate if a disutility occurs then
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26 380 higher treatment rates are required for case-finding to be cost-effective.
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31 382 Fourth, the model did not incorporate other interventions or behaviours that may
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33 383 influence HCV risk or treatment uptake. However, modelling work has shown
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35 384 introducing risk heterogeneity does not substantially reduce intervention impact if
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37 385 PWID circulate between risk states[40] which is likely to occur as individuals move
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39 386 in/out of drug treatment and prison.
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45 388 Fifth, the model was parameterized to UK data, so our results are not necessarily
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47 389 applicable to other settings. However, our conclusions are robust to changes in HCV
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49 390 prevalence. Continuity of care could also be an issue in Australia, where PWID
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51 391 incarceration duration is similar to the UK[41]. However, sentences are longer in the
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53 392 US[42], so fewer treatments may be interrupted, and therefore case-finding in US
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55 393 prisons could be more cost-effective than our results indicate.
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5 395 Our modelled UK treatment and HCV health care costs are within the range of those
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7 396 presented by recent US studies[43 44], with the exception of approximately 3-fold
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9 397 higher liver transplantation costs, which would increase the cost-effectiveness of
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11 398 case-finding in the US. Testing costs were taken from UK economic evaluations,
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13 399 however it is possible a streamlined and experienced testing service could lower
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15 400 costs associated with staff time, thus increasing cost-effectiveness.
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21 402 Sixth, we were unable to evaluate future interferon-free direct-acting antiviral
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23 403 therapies as information on treatment costs and health utilities are unavailable.
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25 404 These treatments will likely have increased SVR (90% for all genotypes), shorter
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27 405 treatment durations (12-24 weeks), lower toxicity, and simpler dosing regimes[45].
28
29 406 Therapies with shorter duration could increase the impact of testing and treatment in
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31 407 prison as more patients will be able to complete therapy prior to release, and could
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33 408 potentially be more cost-effective depending on the ratio of additional costs to
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35 409 incremental impact.
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41 411 **Comparison with other studies**

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43 412 Two publications evaluated the cost-effectiveness of testing ex-PWID in prison, with
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45 413 ICERs varying from about £20,000[10] to £55,000[9] per QALY gained. Our results
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47 414 are consistent with Sutton et al.[9], which used the same discount rates as our study.
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49 415 However, we included the possible prevention impact of treating PWID, and unlike
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51 416 the previous studies, show how continuity of care between prison and the community
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53 417 can make case-finding cost-effective.
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3 419 Three papers evaluated testing PWID in drug services[10 20 46]. Differences in
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5 420 baseline assumptions led to varying ICERs from £28,100[20] to £17,500[10 46] per
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7 421 QALY gained. Our results for addiction services support those found in the latter
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9 422 studies[10 46]. However, the intervention examined in these studies[10 20 46] was
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11 423 one-off testing using a cohort model (with no evidence based intervention effect) and
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13 424 neglected any prevention benefit.
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18 426 Several US studies examined birth cohort screening for all people born in 1945-
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20 427 1965[44 47] or 1946-1970[43] as compared to risk based screening, reporting ICERs
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22 428 of \$38,000 per QALY gained with direct-acting antivirals[43 44] and \$5,400-16,000
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24 429 per QALY gained with pegIFN+RBV[44 47]. Critically, the cost-effectiveness varies
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26 430 substantially by HCV prevalence[47], and the estimated US prevalence is higher
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28 431 than many other developed countries. Additionally, the ICERs were generated given
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30 432 assumptions of higher treatment rates, as well as greater utility gains with SVR than
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32 433 we consider. Importantly, our intervention targets PWID with a risk of transmitting
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34 434 infection to others, whereas birth cohort screening is likely to identify infections
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36 435 among ex-injectors and non-injecting populations which will have little primary
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38 436 prevention impact.
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438 **Implications**

439 Our cost-effectiveness work indicates increasing HCV case-finding in addiction
440 services can be cost-effective. However, the cost-effectiveness of prison case-
441 finding interventions depends on adequate continuity of care with the community.
442 Few settings have developed comprehensive strategies to address this issue,
443 though New York recently initiated the Hepatitis C Continuity Program[48]. In all

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3 444 settings, treatment uptake is critical: higher treatment rates prevent more disease
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5 445 transmission and increase the cost-effectiveness of case-finding interventions. If a
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7 446 disutility on diagnosis occurs, higher treatment rates would be necessary to ensure
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9 447 cost-effectiveness. Further empirical data are required on treatment uptake and
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11 448 changes in utilities following diagnosis and treatment in order to compare targeted
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13 449 case-finding with cohort models.
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17 451 **AUTHOR CONTRIBUTIONS**

20 452 NKM contributed to the study design, model development, analysis, manuscript
21
22 453 drafting and editing. MH contributed to the study design, model development,
23
24 454 analysis, and manuscript editing. AM contributed to the analysis and manuscript
25
26 455 editing. SJH contributed to the model parameterization, analysis, and manuscript
27
28 456 editing. AT contributed to the model parameterization and manuscript editing. PV
29
30 457 contributed to the study design, model development, analysis, and manuscript
31
32 458 editing.
33
34

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42
43

44 463 **Competing Interests**

45
46 464 NM has received an honorarium for speaking at a conference sponsored by
47
48 465 Janssen. SH has received honoraria for speaking at conferences sponsored by
49
50 466 MSD, Janssen, Gilead, and Roche. MH, AM, AT, PV have no competing interests.
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For peer review only

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- 4 473
- 5 474 1. Nelson PK, Mathers BM, Cowle B, et al. Global epidemiology of hepatitis B and hepatitis C
- 6 475 in people who inject drugs: results of systematic reviews. *The Lancet* 2011;**378**:571-
- 7 476 83
- 8
- 9 477 2. Health Protection Agency Colindale. Hepatitis C in the UK 2011, July 2011.
- 10 478 3. Department of Health, HPA Prison Infection Prevention Team, Liver Strategy Team.
- 11 479 National Survey of hepatitis C services in prisons (Draft report). 2011
- 12 480 4. Harris M, Rhodes T. Venous access and care: harnessing pragmatics in harm reduction for
- 13 481 people who inject drugs. *Addiction* 2011;**doi:10.1111/j.1360-0443.2011.03749.x**
- 14 482 5. Hickman M, McDonald T, Ali J, et al. Increasing the uptake of hepatitis C virus testing
- 15 483 among injecting drug users in specialist drug treatment and prison settings by using
- 16 484 dried blood spots for diagnostic testing: a cluster randomized controlled trial. *Journal*
- 17 485 *of Viral Hepatitis* 2008;**15**(4):250-54
- 18
- 19 486 6. Craine N, Parry J, O'Toole J, et al. Improving blood-borne viral diagnosis; clinical audit of
- 20 487 the uptake of dried blood spot testing offered by a substance misuse service. *Journal*
- 21 488 *of Viral Hepatitis* 2009;**16**:219-22
- 22
- 23 489 7. Jones L, Bates G, McCoy E, et al. A systematic review of the effectiveness & cost-
- 24 490 effectiveness of interventions aimed at raising awareness and engaging with groups
- 25 491 who are at an increased risk of hepatitis B and C infection.
- 26 492 <http://www.nice.org.uk/nicemedia/live/11957/5946/5946.pdf>, 2012.
- 27
- 28 493 8. Martin NK, Vickerman P, Foster GR, et al. Can antiviral therapy for hepatitis C reduce the
- 29 494 prevalence of HCV among injecting drug user populations? A modelling analysis of its
- 30 495 prevention utility. *Journal of Hepatology* 2011;**54**:1137-44
- 31
- 32 496 9. Sutton AJ, Edmunds WJ, Sweeting MJ, et al. The cost-effectiveness of screening and
- 33 497 treatment for hepatitis C in prisons in England and Wales: a cost-utility analysis.
- 34 498 *Journal of Viral Hepatitis* 2008;**15**(11):797-808
- 35 499 10. Castelnovo E, Thompson-Coon J, Pitt M, et al. The cost-effectiveness of testing for
- 36 500 hepatitis C in former injecting drug users. *Health Technology Assessment*
- 37 501 2006;**2006**(10):32
- 38
- 39 502 11. Martin NK, Miners A, Vickerman P, et al. The cost-effectiveness of HCV antiviral
- 40 503 treatment for injecting drug user populations. *Hepatology* 2012;**55**(1):49-57
- 41 504 12. NICE. Guide to the methods of technology appraisal, 2008.
- 42 505 13. Briggs A, Claxton K, Sculpher M. *Decision Modelling for Health Economic Evaluation*.
- 43 506 Oxford: Oxford University Press, 2006.
- 44 507 14. McDonald S, Hutchinson SJ, Palmateer N, et al. Decrease in health-related quality of life
- 45 508 associated with awareness of hepatitis C virus infection among people who inject
- 46 509 drugs in Scotland. *Journal of Hepatology* 2013;**58**:460-6
- 47
- 48 510 15. Shepherd J, Jones J, Hartwell D, et al. Interferon alfa (pegylated and non-pegylated) and
- 49 511 ribavirin for the treatment of mild chronic hepatitis C: a systematic review and
- 50 512 economic evaluation. *Health Technology Assessment* 2007;**11**(11):1-224
- 51 513 16. Wright M, Grieve R, Roberts J, et al. Health benefits of antiviral therapy for mild chronic
- 52 514 hepatitis C: randomised controlled trial and economic evaluation. *Health Technol*
- 53 515 *Assess* 2006;**10**(21)
- 54
- 55 516 17. Hartwell D, Jones J, Baxter L, et al. Peginterferon alfa and ribavirin for chronic hepatitis C
- 56 517 in patients eligible for shortened treatment, re-treatment, or in HCV/HIV co-
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51
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54
55
56
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- 518 infection: a systematic review and economic evaluation. *Health Technol Assess*
519 2011;**15**(17):1-210
- 520 18. Dalgard O, Egeland A, Skaug K, et al. Health-related Quality of Life in Active Injecting
521 Drug Users With and Without Chronic Hepatitis C Virus Infection. *Hepatology*
522 2004;**39**(1):74-80
- 523 19. British Medical Association. *British National Formulary, number 62*: BMJ Publishing
524 Group, 2011.
- 525 20. Stein K, Dalziel K, Walker A, et al. Screening for Hepatitis C in injecting drug users: A cost
526 utility analysis. *Journal of Public Health* 2004;**26**(1):61-71
- 527 21. Personal Social Services Research Unit. *Unit Costs of Health and Social Care 2011*:
528 University of Kent, 2011.
- 529 22. John-Baptiste A, Krahn MD, Heathcote J, et al. The natural history of hepatitis C infection
530 acquired through injection drug use: Meta-analysis and meta-regression. *Journal of*
531 *Hepatology* 2010;**53**(2):245-51
- 532 23. Harris RJ, Ramsay M, Hope VD, et al. Hepatitis C prevalence in England remains low and
533 varies by ethnicity: an updated evidence synthesis. *European Journal of Public Health*
534 2011;**Epub ahead of print**
- 535 24. Micallef JM, Kaldor JM, Dore GJ. Spontaneous viral clearance following hepatitis C
536 infection: a systematic review of longitudinal studies. *J Viral Hepat* 2006;**13**:34-41
- 537 25. Sutton AJ, Gay NJ, Edmunds WJ, et al. Modelling the hepatitis B vaccination programme
538 in prisons. *Epidemiol Infect* 2006;**134**:231 - 42
- 539 26. Bird AG, Gore SM, Cameron S, et al. Anonymous HIV surveillance with risk factor
540 elicitation at Scotland's largest prison, Barlinnie. *AIDS* 1995;**9**:801-08
- 541 27. Taylor A, Munro A, Allen E, et al. Low incidence of hepatitis C virus among prisoners in
542 Scotland. *Addiction* 2013;**108**(7):1296-304 doi: 10.1111/add.12107[published Online
543 First: Epub Date]].
- 544 28. Ministry of Justice. *Offender Management Statistics Quarterly Bulletin, April to June*
545 2011, England and Wales, 2011.
- 546 29. Judd A, Parry J, Hickman M, et al. Evaluation of a modified commercial assay in detecting
547 antibody to hepatitis C virus in oral fluids and dried blood spots. *J Med Virol*
548 2003;**71**:49 - 55
- 549 30. Colin C, Lanoir D, Touzet S, et al. Sensitivity and specificity of third-generation hepatitis C
550 virus antibody detection assays: an analysis of the literature. *J Viral Hepat*
551 2001;**8**(2):87-95
- 552 31. Irving WL, Smith S, Cater R, et al. Clinical pathways for patients with newly diagnosed
553 hepatitis C - What actually happens. *Journal of Viral Hepatitis* 2006;**13**(4):264-71
- 554 32. Jowett SL, Agarwal K, Smith BC, et al. Managing chronic hepatitis C acquired through
555 intravenous drug use. *Q J Med* 2001;**94**:153-58
- 556 33. Foster G, Goldin RD, Main J, et al. Management of chronic hepatitis C: clinical audit of
557 biopsy based management algorithm. *BMJ* 1997;**315**:453-8
- 558 34. Skipper C, Guy JM, Parkes J, et al. Evaluation of a prison outreach clinic for the diagnosis
559 and prevention of hepatitis C: implications for the national strategy. *Gut*
560 2003;**52**:1500 - 04
- 561 35. Grebely J, Raffa JD, Lai C, et al. Low uptake of treatment for hepatitis C virus infection in
562 a large community-based study of inner city residents. *J Viral Hepat* 2009;**16**(5):352-
563 8

- 1
2
3 564 36. Mehta SH, Genberg BL, Astemborski J, et al. Limited Uptake of Hepatitis C Treatment
4 565 Among Injection Drug Users. *J Comm Health* 2008;**33**(3):126-33
5 566 37. Wilkinson M, Crawford V, Tippet A, et al. Community-based treatment for chronic
6 567 hepatitis C in drug users: high rates of compliance with therapy despite ongoing drug
7 568 use. *Alimentary Pharmacology & Therapeutics* 2009;**29**(1):29-37
8 569 38. Grosse SD. Assessing cost-effectiveness in healthcare: history of the \$50,000 per QALY
9 570 threshold. *Expert Rev Pharmacoecon Outcomes Res* 2008;**8**(2):165-78
10 571 39. Kimber J, Copeland L, Hickman M, et al. Survival and cessation in injecting drug users:
11 572 prospective observational study of outcomes and effect of opiate substitution
12 573 treatment. *BMJ* 2010;**340**:c3172 doi: 10.1136/bmj.c3172[published Online First:
13 574 Epub Date]].
14 575 40. Vickerman P, Martin N, Turner K, et al. Can needle and syringe programmes and opiate
15 576 substitution therapy achieve substantial reductions in HCV prevalence? Model
16 577 projections for different epidemic settings. *Addiction* 2012;**107**:1984-95
17 578 41. Miller E, Bi P, Ryan P. Hepatitis C virus infection in South Australian prisoners:
18 579 seroprevalence, seroconversion, and risk factors. *International Journal of Infectious*
19 580 *Diseases* 2009;**13**:201-08
20 581 42. West H, Sabol W, Greenman S. Bureau of Justice Statistics Bulletin: Prisoners in 2009.
21 582 <http://bjs.ojp.usdoj.gov/content/pub/pdf/p09.pdf>, 2010.
22 583 43. McGarry LJ, Pawar VS, Parekh HH, et al. Economic model of a birth cohort screening
23 584 program for hepatitis C virus. *Hepatology* 2012;**55**(5):1344-55 doi:
24 585 10.1002/hep.25510[published Online First: Epub Date]].
25 586 44. Rein D, Smith B, Witenborn J, et al. The Cost-Effectiveness of Birth-Cohort Screening for
26 587 Hepatitis C Antibody in U.S. Primary Care Settings. *Annals of Internal Medicine*
27 588 2012;**156**(4):263-70
28 589 45. Dore GJ. The changing therapeutic landscape for hepatitis C. *Med J Aust* 2012;**196**:629-
29 590 32
30 591 46. Thompson Coon J, Castelnuovo E, Pitt M, et al. Case finding for hepatitis C in primary
31 592 care: a cost utility analysis. *Family Practice* 2006;**23**(4):393-406 doi:
32 593 10.1093/fampra/cml032[published Online First: Epub Date]].
33 594 47. Coffin PO, Scott JD, Golden MR, et al. Cost-effectiveness and Population Outcomes of
34 595 General Population Screening for Hepatitis C. *Clinical Infectious Diseases*
35 596 2012;**54**(12):1259-1271
36 597 48. Klein SJ, Wright LN, Birkhead GS, et al. Promoting HCV Treatment Completion for Prison
37 598 Inmates: New York State's Hepatitis C Continuity Program. *Public Health Reports*
38 599 2007;**122**(Suppl 2):83-88
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Figure Legends:

Figure 1. **Base-case cost-effectiveness acceptability curves for the dried blood spot intervention.** Results shown for the (a) addiction services and (b) prison interventions for various willingness-to-pay thresholds.

Figure 2. **Univariate sensitivity analyses on the mean incremental cost-effectiveness ratio (ICER).** Results shown for the dried blood spot intervention in (a) addiction services and (b) prison. Vertical line represents the base-case ICER, estimated at (a) £14,600 per QALY gained and (b) £59,400 per QALY gained.

Figure 3. **Incremental cost-effectiveness ratios for the prison intervention with varying continuity of care assumptions.** Base-case scenario assumed 0% continuity.

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	Mean value	Distribution	Units	Ref.
Intervention effect (proportional change in testing rate)				
Addiction services	3.6 [2.3-5.8]	Lognormal ($\mu=1.285$, $\sigma=0.239$)	-	[5]
Prison	2.6 [0.2-34.9]	Lognormal ($\mu=0.968$, $\sigma=1.317$)	-	[5]
Intervention costs (addiction services)				
Organization/coordination of training [*]	2,005.71		per health board	†
Training session [†]	135		per training session	†
Attendees time [§]	1,620		per training session	†
Travel reimbursement for training leader	90.86		per training session	†
Total cost per addiction services training	3851.57		per training session	†
Mean number tested	40.3		per addiction service	[5]
Total intervention cost per test	95.57	Uniform +/-50%	per test	
Intervention costs (prison)				
Organization/coordination of training ^{**}	7020		per prison	†
Training session [†]	135		per prison	†
Attendees time ^{††}	405		per prison	†
Travel reimbursement for training leader ^{**}	127.20		per prison	†
Total cost per prison training	7687.20		per prison	†
Mean number tested per prison	116		per prison	[5]
Total intervention cost per test	66.27	Uniform +/- 50%	per test	

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Table 1. Intervention parameters. All cost estimates assume a staff-nurse cost per hour of £30.5 (median estimate for band 5 general practice nurse[21]). * 1 nurse 2 days/week for 6 months for 7 health boards. One training session per health board. †Noel Craine, *personal communication*. ‡1 nurse, half day. §12 nurses, half day. ||1200 miles (£0.53 per mile) for travel to 7 health boards. ††Assumed 1 addiction service per health board. ** 1 nurse full time for 5 prisons (1 training session per prison) ††3 nurses per prison, half day. †††1200 miles (£0.53 per mile) for 5 prisons.

Intervention location	Discounted Costs (2011 £) [95% interval]	Discounted QALYs [95% interval]	Incremental costs [95% interval]	Incremental QALYs [95% interval]	ICER (£ per QALY gained)
Addiction services					
Baseline	37,181,582 [19,384,816–67,271,249]	5,354,331 [4,867,168–5,960,766]	-	-	-
Intervention	38,099,060 [20,140,578–68,378,488]	5,354,393 [4,867,206–5,960,853]	917,478 [481,174–1,664,430]	63 [19–153]	14,632
Prison					
Baseline	37,181,582 [19,384,816–67,271,249]	5,354,331 [4,867,168–5,960,766]	-	-	-
Intervention	38,245,293 [19,852,634–68,601,970]	5,354,349 [4,867,184–5,960,823]	1,063,710 [-225,101 – 6,060,267]	18 [-12 – 75]	59,418

Table 2. Cost-effectiveness results from the base-case intervention analyses.

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For peer review only

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7 **Title: Cost-effectiveness of HCV case-finding for people who inject drugs via**
8 **dried blood spot testing in specialist addiction services and prisons**

9
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21
22 **Abbreviations:** hepatitis C virus (HCV), people who inject drugs (PWID), dried blood
23 spot (DBS), incremental cost-effectiveness ratio (ICER), quality-adjusted life-year
24 (QALY), willingness-to-pay (WTP), hepatocellular carcinoma (HCC), liver transplant
25 (LT), pegylated interferon (pegIFN), ribavirin (RBV), sustained viral response (SVR),
26 95% confidence interval (CI), antibody (Ab)

27
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7 45
8 **ABSTRACT (265 words)**
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10 48 **Objectives:** People who inject drugs (PWID) are at high-risk for acquiring hepatitis
11 49 C virus (HCV), but many are unaware of their infection. HCV dried blood spot (DBS)
12 50 testing increases case-finding in addiction services and prisons. We determine the
13 51 cost-effectiveness of increasing HCV case-finding among PWID by offering DBS
14 52 testing in specialist addiction services or prisons as compared to using
15 53 venepuncture.

16 54 **Design:** Cost-utility analysis using a dynamic HCV transmission model among
17 55 PWID, including: disease progression, diagnosis, treatment, injecting status,
18 56 incarceration, and addition services contact.

19 57 **Setting:** United Kingdom

20 58 **Participants:** N/A

21 59 **Intervention:** DBS testing in specialist addiction services or prisons. Intervention
22 60 impact was determined by a meta-analysis of primary data

23 61 **Primary and secondary outcome measures:** Costs (in UK £, £1=\$1.60 USD) and
24 62 utilities (quality adjusted life years, QALYs) were attached to each state and the
25 63 incremental cost effectiveness ratio (ICER) determined. Multivariate uncertainty and
26 64 one-way sensitivity analyses were performed.

27 65 **Results:** For a £20,000 per QALY gained willingness-to-pay threshold, DBS testing
28 66 in addiction services is cost-effective (ICER of £14,600 per QALY gained). Under the
29 67 base-case assumption of no continuity of treatment/care when exiting/entering
30 68 prison, DBS testing in prisons is not cost-effective (ICER of £59,400 per QALY
31 69 gained). Results are robust to changes in HCV prevalence; increasing PWID
32 70 treatment rates to those for ex-PWID considerably reduces the ICER (£4,500 and
33 71 £30,000 per QALY gained for addiction services and prison, respectively). If

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7 72 continuity of care is >40%, the prison DBS ICER falls below £20,000 per QALY
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9 73 gained.

10 74 **Conclusions:** Despite low PWID treatment rates, increasing case-finding can be
11
12 75 cost-effective in specialist addiction services, and in prisons if continuity of
13
14 76 treatment/care is ensured.

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16 77 **Trial Registration:** N/A
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19 20 79 **ARTICLE SUMMARY**

21 22 80 **Article focus**

- 23
24 81 • We perform a cost-utility analysis of increasing HCV case-finding among
25
26 82 PWID by offering dried blood spot testing in specialist addiction services or
27
28 83 prisons.

29 30 84 **Key messages**

- 31
32 85 • Despite low PWID treatment rates, increasing case-finding for PWID can be
33
34 86 cost-effective in specialist addiction services.
- 35
36 87 • In prisons, the cost-effectiveness of HCV case-finding depends on adequate
37
38 88 continuity of treatment/care between prison and the community, as many
39
40 89 treatments are discontinued due to short incarceration times.

41 42 90 **Strengths and limitations of this study**

- 43
44 91 • We use a dynamic mathematical model of HCV transmission to capture the
45
46 92 potential prevention benefits of treatment, which has been shown to increase
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48 93 cost-effectiveness of HCV treatment for PWID.
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50 94 • Key limitations are the limited empirical data on PWID health utilities,
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52 95 treatment rates, and intervention impact.

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7 978 98 **INTRODUCTION**

99 In developed countries, the hepatitis C virus (HCV) is spread primarily through
100 injecting drug use, with over 90% of new infections among people who inject drugs
101 (PWID) ~~and approximately 10 million PWID infected worldwide~~[1]. However,
102 diagnosis rates are low, with only half of infected PWID in the US and UK
103 diagnosed[2], ~~putting many at risk of cirrhosis, liver cancer, and death.~~

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22 105 The majority of HCV testing performed in the US and UK is through venepuncture,
23 106 which is available in virtually all prisons[3] and addiction services (structured
24 107 programs providing pharmacological or nonpharmacological drug treatment in the
25 108 community) either on site or by referral. However, testing opportunities among PWID
26 109 still may be limited. This is because venous access can be poor and specialist staff
27 110 (who may not be available at all potential testing sites) are required to take blood,
28 111 which if only available in hospital phlebotomy services can increase stigma[4].

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37 113 Dried blood spot (DBS) testing is non-invasive and can be performed by clinical and
38 114 non-clinical staff. Two UK studies[5 6] showed offering DBS testing within specialist
39 115 addiction services and prisons led to a 3 to 6-fold increase in HCV testing, and a
40 116 recent systematic review identified DBS as the best available targeted intervention
41 117 for increasing HCV case-finding amongst PWID[7]. Hence, DBS testing could be an
42 118 important component of any strategy attempting to scale-up treatment provision for
43 119 PWID, for both care and prevention[8].

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7 121 We perform a cost-utility analysis of introducing DBS testing amongst current and
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9 122 former PWID in specialist addiction services and prisons in the UK[5]. Unlike
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11 123 previous economic evaluations of HCV testing in these settings[9 10], we incorporate
12
13 124 a dynamic mathematical model to capture the potential prevention benefits of
14
15 125 treatment, which can substantially increase the cost-effectiveness of HCV treatment
16
17 126 for PWID[11]. A dynamic model accounts for both individual and population benefits
18
19 127 of treatment, as well as the dynamic nature of incarceration, especially among
20
21 128 PWID. Our model is ~~also~~ the first to explore the importance of continuity of care
22
23 129 between prison and the community.
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26 131 **METHODS**

27 28 132 **Mathematical model**

29
30 133 An existing dynamic, deterministic model of HCV transmission, progression and HCV
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32 134 treatment was adapted to project the impact of introducing DBS testing in prisons
33
34 135 and addiction services[11]. See **appendix** for details and model schematics. Briefly,
35
36 136 the model stratifies by: injecting state (never PWID/PWID/ex-PWID); incarceration
37
38 137 status (never/currently/formerly); contact with addiction services (in contact/not in
39
40 138 contact); age ([15-19],[20-24],[25-29],[30-54],[55-64],[65-74],[75+]); HCV infection
41
42 139 and disease progression (never infected, spontaneously cleared, mild HCV,
43
44 140 moderate HCV, compensated cirrhosis, decompensated cirrhosis, hepatocellular
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46 141 carcinoma, liver transplant, post-transplant). HCV disease stages are further
47
48 142 subdivided into undiagnosed or diagnosed, where those who are diagnosed can
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50 143 either be lost to follow-up, in referral (early/late), on antiviral treatment, sustained
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52 144 viral response (SVR), or non-SVR.
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7 146 All PWID can acquire and transmit HCV, but imprisoned PWID only transmit HCV to
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9 147 other prisoners. We define ex-PWID as those who have permanently ceased
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11 148 injecting, and assume no ongoing transmission from non/ex-PWID. An individual's
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13 149 risk of acquiring HCV is proportional to the setting-specific HCV prevalence
14
15 150 (prison/community). The model assumes a background rate of HCV testing for all
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17 151 PWID and ex-PWID in the community/prison, and in addiction services for PWID.
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20 153 No UK data exist regarding continuity of care (treatment or referral) on prison
21
22 154 entry/exit, but experts described difficulty in ensuring continuity on release (Eamonn
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24 155 O'Moore[Offender Health, UK Department of Health], Iain Brew[HMP Leeds]
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26 156 *personal communication*). Therefore, in our base-case we assume those in
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28 157 treatment or referral become lost to follow-up upon entering/exiting prison, but can
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30 158 be re-tested/re-treated.
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33 160 **Model fitting and base-case projections**

35 161 For the probabilistic uncertainty analysis, 1000 parameter sets were sampled from
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37 162 each parameter uncertainty distribution in **tables 1 and appendix tables 1–23**. For
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39 163 ~~each of these~~ parameter sets, the model was calibrated to UK epidemiological data
40
41 164 on incarceration, injecting drug use, HCV prevalence, and diagnosis. This was
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43 165 achieved through a multi-step parameter sampling and model calibration process,
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45 166 utilizing simplified models where possible to reduce computational time and to verify
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47 167 the full model predictions against simplified models. For details on the model
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49 168 calibration (including schematics and equations) and initialization, see **appendix**.
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7 170 After calibration, for each of the 1000 parameter sets, the model was run with and
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9 171 without the intervention ('intervention' and 'baseline', respectively). We model an
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11 172 intervention of offering DBS testing in prison, compared to a baseline of current
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13 173 testing with venepuncture only. Additionally, we evaluate an intervention of offering
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15 174 DBS in specialist addiction services, compared to a baseline of current testing with
16
17 175 venepuncture. The economic analysis was performed from a UK National Health
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19 176 Service perspective. Costs (in 2011 GBP, £1=\$1.55 USD) and health utilities (in
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21 177 quality-adjusted life years, QALYs) were attached to each model compartment.
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23 178 Costs and QALYs were discounted 3.5% per annum as per NICE guidelines, with a
24
25 179 100 year time horizon (to accrue individual and population benefits). The mean
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27 180 incremental cost-effectiveness ratio (ICER) was calculated and cost-effectiveness
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29 181 determined using the UK willingness-to-pay (WTP) threshold, estimated between
30
31 182 £20,000 and £30,000 per QALY gained[12]. Cost-effectiveness acceptability curves
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33 183 were constructed and univariate sensitivity analyses undertaken. Analysis of
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35 184 covariance (ANCOVA) methods were used to summarize the proportion of the
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37 185 variability in the incremental costs and QALYs explained by the uncertainty in input
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39 186 parameters[13].
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41 188 **Parameters**

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43 189 All parameters can be found in table 1 and appendix tables 1-4.

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45 190 **Health state utilities:** Uninfected utility values were taken from UK population
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47 191 norms for non-PWID, and a large cross-sectional study of injectors in Scotland[14]
48
49 192 for current PWID. We assumed equal utilities for ex-PWID and non-PWID[10].
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51 193 Utilities for HCV disease and treatment stages came from UK HCV trials and
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53 194 economic evaluations[15-17] and used for ex-PWID ~~(table 1)~~. To derive PWID HCV
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7 195 utilities, non-PWID HCV utilities were rescaled by multiplying by the ratio of the
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9 196 uninfected PWID utility to the uninfected ex-PWID utility for the youngest age group.
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11 197 All states included disutilities with age.

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14 199 No disutility was associated with testing in the base-case. However, some evidence
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16 200 suggests PWID may experience a disutility after positive HCV diagnosis[14 18]. We
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18 201 explored the impact of a disutility (0.09[14], see **appendix**) on diagnosis, which was
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20 202 fully regained with treatment SVR.

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24 204 **Health state and testing costs:** Health care costs for HCV disease stages, antiviral
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26 205 treatment (pegylated interferon-alfa and ribavirin, pegIFN+RBV), and testing were
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28 206 taken from UK economic analyses[15 16 19 20], ~~(table 1 and appendix)~~. Data on
29
30 207 the yield (proportion tests Ab+) and prevalence in each setting were used to
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32 208 calculate the number of non-PWID tested for each PWID/ex-PWID (see **appendix**).
33
34 209 Costs were inflated to 2011 GBP using the Health and Community Hospital Service
35
36 210 pay and prices index[21]. Additional PWID treatment delivery costs were
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38 211 applied[11]. We assumed undiagnosed individuals do not incur HCV-related health
39
40 212 care costs unless progressing to decompensated disease[9].

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43 214 **HCV disease progression parameters:** Transition rates between disease stages
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45 215 were taken from UK economic evaluations[15-17], ~~(table 1)~~. Although estimates
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47 216 were not PWID specific, a recent meta-analysis suggests little evidence for
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49 217 differences in progression between PWID and non-PWID[22].

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7 219 **HCV prevalence:** PWID HCV chronic prevalence was estimated from HCV antibody
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9 220 prevalence among PWID in England (45% [41-49%, 95% confidence interval
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11 221 (CI)][23]). ~~As one-quarter of acute infections spontaneously clear, with spontaneous~~
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13 222 ~~clearance of 26% of acute infections[24] we assume three-quarters of those who are~~
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15 223 ~~ever exposed (antibody positive) are chronically infected,~~ resulting in 35% chronic
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17 224 infection among PWID.

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20 226 **Incarceration duration:** Incarceration duration for non-PWID and ex-PWID was
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22 227 age-stratified, with a mean of 8 months[25]. However, PWID have shorter durations
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24 228 in custody than non-PWID[25-27]. We used a 4 month PWID incarceration duration,
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26 229 based on an estimate for England and Wales[25]. A recent study in Scotland
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28 230 reported a median sentence of 7.1 months in PWID[27] which given most prisoners
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30 231 serve approximately half their sentence[28] would also equate to a duration of 4
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32 232 months.

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34 233
35 234 **Testing rates:** The overall baseline PWID testing rate (mean 12% undiagnosed
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37 235 PWID per year) was estimated through fitting the model to the current proportion of
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39 236 diagnosed PWID (approximately 50%[2]). ~~and used Data on the proportion of tests~~
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41 237 ~~from each setting was used in combination with the model projected annual numbers~~
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43 238 ~~of PWID in contact with each setting~~ to calculate setting-specific testing rates (6%
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45 239 and 13% per year of undiagnosed PWID in contact with addiction services and
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47 240 prisons, respectively (prison, addiction services, other), (see **appendix**). We
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49 241 assume ex-PWID are tested at equal rates to PWID in prison and in general
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51 242 community settings. We assumed all diagnostic tests are 100% accurate due to the
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53 243 high sensitivity and specificity of DBS (99.6% sensitivity, 100% specificity in a setting

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7 244 | ~~with 50% prevalence~~ [29]) and venepuncture ~~assays~~[30], ~~[29-30]~~ and because those
8 245 | who receive an initial positive test will receive additional tests before treatment.

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12 247 | **Referral and treatment transition rates:** The referral rate from testing services to
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14 248 | secondary care (35%) was estimated from a UK study[31]. Those not referred or not
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16 249 | attending referral were considered 'lost to follow-up'.

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20 251 | Approximately 50% of diagnosed ex-PWID in referral are treated within 2 years[31-

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22 252 | 33]. Since many delay treatment, we assume that after 2 years, 10% of those in

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24 253 | referral initiate treatment annually. Within prison, treatment rates are ~~much~~ lower

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26 254 | than in the community[31 34], although a recent UK prison audit found 24% of those

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28 255 | diagnosed were treated (Iain Brew[HMP Leeds], unpublished data). We therefore

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30 256 | estimated ~~half the~~ halved treatment initiation rates in prison as compared to the

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32 257 | community.

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36 259 | PWID treatment rates are unknown, but thought to be similarly low to other

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38 260 | countries[35 36], with an estimated <1% of PWID treated annually (Graham

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40 261 | Foster[Consultant Hepatologist], *personal communication*). Hence, if we assume 1%

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42 262 | of infected PWID are treated within 2 years, this equates to treating approximately

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44 263 | 5.5% of those who attend referral (35% of the 50% diagnosed) within 2 years. After

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46 264 | 2 years, 1% of those in referral are treated annually thereafter. ~~Testing and treatment~~

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48 265 | ~~rates are shown in table 1.~~

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52 267 | **Intervention:** The effect of introducing DBS was modelled by assuming a 3.6-fold

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54 268 | increase in testing [2.2-5.8 CI] in addiction services, and 2.6-fold increase in testing

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7 269 | [0.1-34.9 CI] in prison, based on two multicentre studies (**table 12** and **appendix**).
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9 270 | Intervention costs were determined from the study methods[5] and in consultation
10
11 271 | with the authors (**table 12**).
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13 272

14 273 **Sensitivity analyses**

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16 274 | We performed one-way sensitivity analyses on: time horizon (50/200 years),
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18 275 | discount rates (3.5% costs/1.5% QALYs), PWID treatment rates (increased in each
19
20 276 | setting), PWID SVR rates (reduced by 20%), PWID HCV chronic prevalence
21
22 277 | (20%/50%), antiviral treatment (telaprevir/boceprevir for genotype 1 patients, see
23
24 278 | **appendix**), and continuity of care for treatment/referral on entry/exit from prison
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26 279 | (varied from 0% to 100%). We also explored the effect of assuming no prevention
27
28 280 | benefit (but allowing for reinfection), by permanently fixing the force of infection.
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33 283 **RESULTS**

34 284

37 285 **Case finding in addiction services**

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39 286 | The incremental cost effectiveness ratio (ICER) of increasing case-finding in
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41 287 | addiction services, by introducing DBS testing, was an estimated £14,600 (\$22,630
42
43 288 | USD) per QALY gained in the base-case (**table 24**). At a £20,000 or £30,000 WTP
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45 289 | threshold, the intervention is likely to be cost-effective in 69% or 93% of the
46
47 290 | simulations, respectively (**figure 1a**). Uncertainty in the intervention effect
48
49 291 | contributed to 86% and 58% of the variation in incremental costs and QALYs,
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51 292 | respectively. The remaining variation in incremental QALYs was mainly due to
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53 293 | uncertainty in treatment rates (22%) and health utilities (17%).
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For most sensitivity analyses, the ICER remained below a £30,000 WTP threshold (figure 2a). Reducing the time horizon to 50 years increased the estimated ICER to £22,900 per QALY gained because fewer prevention benefits were accrued, whereas lengthening to 200 years increased cost-effectiveness. Changing the discount rates to 3.5% costs/1.5% QALYs or no discounting decreased the estimated ICER to £5,100 or £6,700 per QALY gained, respectively. Variations in baseline HCV chronic prevalence had little effect (<10%). At lower prevalence (20%), identifying cases was more expensive but prevention impact was greater due to reduced reinfection risk, whereas the opposite occurred at higher prevalence (50%).

Increasing treatment rates increased the intervention's cost-effectiveness. If 50% (compared to 5.5% for base-case) of PWID in referral initiated treatment within 2 years (a treatment rate achieved by one UK service[37]) the ICER fell to £4,500 per QALY gained. If SVR rates amongst PWID were 20% lower than in ex-PWID, the ICER increased by 14% (£16,700 per QALY gained). Using telaprevir/boceprevir for genotype 1 patients minimally altered the ICER. Ignoring any prevention benefit doubled the ICER to £29,900 per QALY gained.

Only one sensitivity analysis substantially altered the cost-effectiveness conclusion. If a disutility was attached to diagnosis, the intervention resulted in negative incremental QALYs (due to low treatment rates) and was dominated (more expensive with fewer health benefits). However, even with this disutility, if treatment rates were increased to 50% of PWID in referral initiating treatment within 2 years, then the estimated ICER was £20,100 per QALY gained.

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7 3198 320 **Case finding in prison**9
10 321 The ICER of increasing case-finding in prison, by introducing DBS testing, was

11 322 estimated at £59,400 (\$92,070 USD) per QALY gained (21% likely to be cost-

12 323 effective at a £30,000 WTP threshold) in the base-case (**table 24** and **figure 1b**).

13 324 Uncertainty in the intervention effect contributed to most (>85%) of the variation in

14 325 incremental costs and QALYs.

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16 32617 327 The base-case conclusion was robust to most one-way sensitivity analyses (**figure**18 328 **2b**) – including time horizon, discount rates, HCV prevalence, and use of new

19 329 treatments. If 50% of PWID in referral initiated treatment within 2 years, the ICER

20 330 halved to just below £30,000 per QALY gained.

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22 332 Introducing continuity of care (which measures the proportion of initiated

23 333 treatments/referrals that are continued when entering/exiting prison) led to an

24 334 increase in cost-effectiveness: from an ICER of £59,400 per QALY gained with 0%

25 335 continuity to £10,400 per QALY gained with 100% continuity (**figure 3**). The ICER

26 336 fell below £20,000 when >40% continuity of care was ensured; at 40% continuity the

27 337 intervention was 57% and 83% likely to be cost-effective at the £20,000 and £30,000

28 338 WTP thresholds, respectively. The level of continuity required for prison case-finding

29 339 to be cost-effective also depended on treatment rates. If prison treatment rates were

30 340 increased to equal those in the community (50%/5.5% of ex-PWID/PWID treated

31 341 within 2 years of referral), then 35% continuity results in an ICER just below £20,000

32 342 per QALY gained. Increasing treatment rates further so 50% of all referred prisoners

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7 343 initiate treatment within 2 years lowers the required continuity to 20% for an ICER
8 344 below £20,000.

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11 12 346 **DISCUSSION**

13 14 15 347 **Main findings**

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17 348 Our results indicate the introduction of dried blood spot testing for HCV case-finding
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19 349 is likely to be cost-effective under commonly used willingness-to-pay thresholds in
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21 350 the UK (£20,000-£30,000/QALY gained[12]) and US (\$50,000/QALY gained[38]) in
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23 351 addiction services, but not in prison unless a minimum level of continuity of care in
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25 352 treatment or referral between prison and the community can be ensured. Ignoring
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27 353 the prevention benefit doubles the ICER of the intervention in addiction services. In
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29 354 the base-case, most PWID treatments initiated in prison were interrupted due to the
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31 355 lack of continuity of care and short PWID incarceration times (~4 months) in the
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33 356 UK[25 27]. Consequently, little prevention benefit was achieved from the prison
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35 357 intervention, with the results approaching the 'static' model. With the low base-case
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37 358 PWID treatment rates, the continuity required for DBS to be cost-effective was
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39 359 approximately 35-40% of the estimated treatment/referral rates, but if
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41 360 treatment/referral rates increased then lower levels of continuity would be cost-
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43 361 effective. Crucially, not all treatments need to be initiated or completed in prison, as
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45 362 only maintaining treatment or referral contact is necessary. Finally, both interventions
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47 363 are most cost-effective at higher treatment rates.

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49 50 365 **Strengths and Limitations**

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52 366 The key strength of this analysis is that the model is dynamic, therefore capturing the
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54 367 prevention impact of case-finding and treatment. The main limitations are concerned

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7 368 with parameter uncertainty and lack of model heterogeneity. First, we based our
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9 369 increase in case-finding on the DBS intervention, which though empirically founded,
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11 370 was informed by relatively small UK studies, resulting in wide uncertainty around the
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13 371 effect estimates.

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16 373 Second, the base-case assumed comparatively low treatment rates for PWID, partly
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18 374 because UK data on PWID treatment numbers are not available, ~~although similar~~
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20 375 ~~rates have been reported in the US[36] and Canada[35].~~ This information is critical,
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22 376 as higher treatment rates increase ~~the intervention's~~ cost-effectiveness. This is
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24 377 especially important for prisons where ~~information on~~ treatment completion
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26 378 ~~information~~ was unavailable, yet ~~these factors~~ strongly influenced cost-effectiveness.

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28 379 Additionally, even if treatment is interrupted, some may benefit from shortened
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30 380 treatment, which we did not incorporate. ~~However, the rapid development of~~
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32 381 ~~resistance observed with new treatments[39] indicates treatment continuity will~~
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34 382 ~~become an increasingly crucial issue.~~

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37 384 Third, more data are needed to quantify PWID health utilities, which can be below
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39 385 the general population[39]. Especially important is whether any transient or
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41 386 permanent disutility on HCV diagnosis occurs, as current data are weak and not
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43 387 based on prospective studies. ~~No consensus exists regarding diagnosis utilities in~~
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45 388 ~~other diseases[41-42].~~ Our projections indicate if a disutility occurs then higher
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47 389 treatment rates are required for case-finding to be cost-effective.

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51 391 Fourth, the model did not incorporate other interventions or behaviours that may
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53 392 influence HCV risk or treatment uptake. ~~For example, case-finding and treatment of~~
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7 393 ~~PWID is targeted towards those on opiate substitution therapy[43] who may~~
8 ~~contribute fewer secondary infections[44].~~ However, modelling work has shown
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10 395 introducing risk heterogeneity does not substantially reduce intervention impact if
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12 396 PWID circulate between risk states[40] which is likely to occur as individuals move
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14 397 in/out of drug treatment and prison.
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18 399 Fifth, the model was parameterized to UK data, so our results are not necessarily
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20 400 applicable to other settings. However, our conclusions are robust to changes in HCV
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22 401 prevalence. Continuity of care could also be an issue in Australia, where PWID
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24 402 incarceration duration is similar to the UK[41]. However, sentences are longer in the
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26 403 US[42], so fewer treatments may be interrupted, and therefore case-finding in US
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28 404 prisons could be more cost-effective than our results indicate.
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32 406 Our modelled UK treatment and HCV health care costs are within the range of those
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34 407 presented by recent US studies[43 44], with the exception of approximately 3-fold
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36 408 higher liver transplantation costs, which would increase the cost-effectiveness of
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38 409 case-finding in the US. ~~Testing costs were taken from UK economic evaluations,~~
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40 410 ~~however it is possible a streamlined and experienced testing service could lower~~
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42 411 ~~costs associated with staff time, thus increasing cost-effectiveness.~~
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46 413 ~~Sixth, we were unable to evaluate future interferon-free direct-acting antiviral~~
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48 414 ~~therapies as information on treatment costs and health utilities are unavailable.~~
49
50 415 ~~These treatments will likely have increased SVR (90% for all genotypes), shorter~~
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52 416 ~~treatment durations (12-24 weeks), lower toxicity, and simpler dosing regimes[45].~~
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54 417 ~~Therapies with shorter duration could increase the impact of testing and treatment in~~

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7 418 prison as more patients will be able to complete therapy prior to release, and could
8 419 potentially be more cost-effective depending on the ratio of additional costs to
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10 420 incremental impact.
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16 423 **Comparison with other studies**

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18 424 Two publications evaluated the cost-effectiveness of testing ex-PWID in prison, with
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20 425 ICERs varying from about £20,000[10] to £55,000[9] per QALY gained. Our results
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22 426 are consistent with Sutton et al.[9], which used the same discount rates as our study.
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24 427 However, we included the possible prevention impact of treating PWID, and unlike
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26 428 the previous studies, show how continuity of care between prison and the community
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28 429 can make case-finding cost-effective.
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32 431 Three papers evaluated testing PWID in drug services[10 20 46]. Differences in
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34 432 baseline assumptions led to varying ICERs from £28,100[20] to £17,500[10 46] per
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36 433 QALY gained. Our results for addiction services support those found in the latter
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38 434 studies[10 46]. However, the intervention examined in these studies[10 20 46] was
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40 435 one-off testing using a cohort model (with no evidence based intervention effect) and
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42 436 neglected any prevention benefit.
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44 437
45 438 Several US studies examined birth cohort screening for all people born in 1945-
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47 439 1965[44 47] or 1946-1970[43] as compared to risk based screening, reporting ICERs
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49 440 of \$38,000 per QALY gained with direct-acting antivirals[43 44] and \$5,400-16,000
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51 441 per QALY gained with pegIFN+RBV[44 47]. Critically, the cost-effectiveness varies
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53 442 substantially by HCV prevalence[47], and the estimated US prevalence is higher
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7 443 than many other developed countries. Additionally, the ICERs were generated given
8 444 assumptions of higher treatment rates, as well as greater utility gains with SVR than
9 445 we consider. Importantly, our intervention targets PWID with a risk of transmitting
10 446 infection to others, whereas birth cohort screening is likely to identify infections
11 447 among ex-injectors and non-injecting populations which will have little primary
12 448 prevention impact.
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20 450 **Implications**

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22 451 Our cost-effectiveness work indicates increasing HCV case-finding in addiction
23 452 services can be cost-effective. However, the cost-effectiveness of prison case-
24 453 finding interventions depends on adequate continuity of care with the community.
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26 454 Few settings have developed comprehensive strategies to address this issue,
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28 455 though New York ~~state~~ recently initiated the Hepatitis C Continuity Program[48]. In
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30 456 all settings, treatment uptake is critical: higher treatment rates prevent more disease
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32 457 transmission and increase the cost-effectiveness of case-finding interventions. If a
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34 458 disutility on diagnosis occurs, higher treatment rates would be necessary to ensure
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36 459 cost-effectiveness. Further empirical data are required on treatment uptake and
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38 460 changes in utilities following diagnosis and treatment in order to compare targeted
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40 461 case-finding with cohort models.
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45 463 **AUTHOR CONTRIBUTIONS**

46
47 464 NKM contributed to the study design, model development, analysis, manuscript
48 465 drafting and editing. MH contributed to the study design, model development,
49 466 analysis, and manuscript editing. AM contributed to the analysis and manuscript
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51 467 editing. SJH contributed to the model parameterization, analysis, and manuscript
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7 468 editing. AT contributed to the model parameterization and manuscript editing. PV
8
9 469 contributed to the study design, model development, analysis, and manuscript
10
11 470 editing.

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20 475 **Competing Interests**

21
22 476 NM has received an honorarium for speaking at a conference sponsored by
23
24 477 Janssen. SH has received honoraria for speaking at conferences sponsored by
25
26 478 MSD, Janssen, Gilead, and Roche. MH, AM, AT, PV have no competing interests.

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7 484
8 485
9 486 1. Nelson PK, Mathers BM, Cowle B, et al. Global epidemiology of hepatitis B and hepatitis C
10 487 in people who inject drugs: results of systematic reviews. *The Lancet* 2011;**378**:571-
11 488 83
12 489 2. Health Protection Agency Colindale. Hepatitis C in the UK 2011, July 2011.
13 490 3. Department of Health, HPA Prison Infection Prevention Team, Liver Strategy Team.
14 491 National Survey of hepatitis C services in prisons (Draft report). 2011
15 492 4. Harris M, Rhodes T. Venous access and care: harnessing pragmatics in harm reduction for
16 493 people who inject drugs. *Addiction* 2011;doi:10.1111/j.1360-0443.2011.03749.x
17 494 5. Hickman M, McDonald T, Ali J, et al. Increasing the uptake of hepatitis C virus testing
18 495 among injecting drug users in specialist drug treatment and prison settings by using
19 496 dried blood spots for diagnostic testing: a cluster randomized controlled trial. *Journal*
20 497 *of Viral Hepatitis* 2008;**15**(4):250-54
21 498 6. Craine N, Parry J, O'Toole J, et al. Improving blood-borne viral diagnosis; clinical audit of
22 499 the uptake of dried blood spot testing offered by a substance misuse service. *Journal*
23 500 *of Viral Hepatitis* 2009;**16**:219-22
24 501 7. Jones L, Bates G, McCoy E, et al. A systematic review of the effectiveness & cost-
25 502 effectiveness of interventions aimed at raising awareness and engaging with groups
26 503 who are at an increased risk of hepatitis B and C infection.
27 504 <http://www.nice.org.uk/nicemedia/live/11957/5946/5946.pdf>, 2012.
28 505 8. Martin NK, Vickerman P, Foster GR, et al. Can antiviral therapy for hepatitis C reduce the
29 506 prevalence of HCV among injecting drug user populations? A modelling analysis of its
30 507 prevention utility. *Journal of Hepatology* 2011;**54**:1137-44
31 508 9. Sutton AJ, Edmunds WJ, Sweeting MJ, et al. The cost-effectiveness of screening and
32 509 treatment for hepatitis C in prisons in England and Wales: a cost-utility analysis.
33 510 *Journal of Viral Hepatitis* 2008;**15**(11):797-808
34 511 10. Castelnuovo E, Thompson-Coon J, Pitt M, et al. The cost-effectiveness of testing for
35 512 hepatitis C in former injecting drug users. *Health Technology Assessment*
36 513 2006;**2006**(10):32
37 514 11. Martin NK, Miners A, Vickerman P, et al. The cost-effectiveness of HCV antiviral
38 515 treatment for injecting drug user populations. *Hepatology* 2012;**55**(1):49-57
39 516 12. NICE. Guide to the methods of technology appraisal, 2008.
40 517 13. Briggs A, Claxton K, Sculpher M. *Decision Modelling for Health Economic Evaluation*.
41 518 Oxford: Oxford University Press, 2006.
42 519 14. McDonald S, Hutchinson SJ, Palmateer N, et al. Decrease in health-related quality of life
43 520 associated with awareness of hepatitis C virus infection among people who inject
44 521 drugs in Scotland. *Journal of Hepatology* 2013;**58**:460-6
45 522 15. Shepherd J, Jones J, Hartwell D, et al. Interferon alfa (pegylated and non-pegylated) and
46 523 ribavirin for the treatment of mild chronic hepatitis C: a systematic review and
47 524 economic evaluation. *Health Technology Assessment* 2007;**11**(11):1-224
48 525 16. Wright M, Grieve R, Roberts J, et al. Health benefits of antiviral therapy for mild chronic
49 526 hepatitis C: randomised controlled trial and economic evaluation. *Health Technol*
50 527 *Assess* 2006;**10**(21)
51 528 17. Hartwell D, Jones J, Baxter L, et al. Peginterferon alfa and ribavirin for chronic hepatitis C
52 529 in patients eligible for shortened treatment, re-treatment, or in HCV/HIV co-

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- infection: a systematic review and economic evaluation. *Health Technol Assess* 2011;**15**(17):1-210
18. Dalgard O, Egeland A, Skaug K, et al. Health-related Quality of Life in Active Injecting Drug Users With and Without Chronic Hepatitis C Virus Infection. *Hepatology* 2004;**39**(1):74-80
19. British Medical Association. *British National Formulary, number 62*: BMJ Publishing Group, 2011.
20. Stein K, Dalziel K, Walker A, et al. Screening for Hepatitis C in injecting drug users: A cost utility analysis. *Journal of Public Health* 2004;**26**(1):61-71
21. Personal Social Services Research Unit. *Unit Costs of Health and Social Care 2011*: University of Kent, 2011.
22. John-Baptiste A, Krahn MD, Heathcote J, et al. The natural history of hepatitis C infection acquired through injection drug use: Meta-analysis and meta-regression. *Journal of Hepatology* 2010;**53**(2):245-51
23. Harris RJ, Ramsay M, Hope VD, et al. Hepatitis C prevalence in England remains low and varies by ethnicity: an updated evidence synthesis. *European Journal of Public Health* 2011;**Epub ahead of print**
24. Micallef JM, Kaldor JM, Dore GJ. Spontaneous viral clearance following hepatitis C infection: a systematic review of longitudinal studies. *J Viral Hepat* 2006;**13**:34-41
25. Sutton AJ, Gay NJ, Edmunds WJ, et al. Modelling the hepatitis B vaccination programme in prisons. *Epidemiol Infect* 2006;**134**:231 - 42
26. Bird AG, Gore SM, Cameron S, et al. Anonymous HIV surveillance with risk factor elicitation at Scotland's largest prison, Barlinnie. *AIDS* 1995;**9**:801-08
27. Taylor A, Munro A, Allen E, et al. Low incidence of hepatitis C virus among prisoners in Scotland. *Addiction* 2013;**108**(7):1296-304 doi: 10.1111/add.12107[published Online First: Epub Date].
28. Ministry of Justice. *Offender Management Statistics Quarterly Bulletin, April to June 2011, England and Wales, 2011*.
29. Judd A, Parry J, Hickman M, et al. Evaluation of a modified commercial assay in detecting antibody to hepatitis C virus in oral fluids and dried blood spots. *J Med Virol* 2003;**71**:49 - 55
30. Colin C, Lanoir D, Touzet S, et al. Sensitivity and specificity of third-generation hepatitis C virus antibody detection assays: an analysis of the literature. *J Viral Hepat* 2001;**8**(2):87-95
31. Irving WL, Smith S, Cater R, et al. Clinical pathways for patients with newly diagnosed hepatitis C - What actually happens. *Journal of Viral Hepatitis* 2006;**13**(4):264-71
32. Jowett SL, Agarwal K, Smith BC, et al. Managing chronic hepatitis C acquired through intravenous drug use. *Q J Med* 2001;**94**:153-58
33. Foster G, Goldin RD, Main J, et al. Management of chronic hepatitis C: clinical audit of biopsy based management algorithm. *BMJ* 1997;**315**:453-8
34. Skipper C, Guy JM, Parkes J, et al. Evaluation of a prison outreach clinic for the diagnosis and prevention of hepatitis C: implications for the national strategy. *Gut* 2003;**52**:1500 - 04
35. Grebely J, Raffa JD, Lai C, et al. Low uptake of treatment for hepatitis C virus infection in a large community-based study of inner city residents. *J Viral Hepat* 2009;**16**(5):352-8

- 1
2
3
4
5
6
7 576 36. Mehta SH, Genberg BL, Astemborski J, et al. Limited Uptake of Hepatitis C Treatment
8 577 Among Injection Drug Users. *J Comm Health* 2008;**33**(3):126-33
9 578 37. Wilkinson M, Crawford V, Tippet A, et al. Community-based treatment for chronic
10 579 hepatitis C in drug users: high rates of compliance with therapy despite ongoing drug
11 580 use. *Alimentary Pharmacology & Therapeutics* 2009;**29**(1):29-37
12 581 38. Grosse SD. Assessing cost-effectiveness in healthcare: history of the \$50,000 per QALY
13 582 threshold. *Expert Rev Pharmacoecon Outcomes Res* 2008;**8**(2):165-78
14 583 39. Kimber J, Copeland L, Hickman M, et al. Survival and cessation in injecting drug users:
15 584 prospective observational study of outcomes and effect of opiate substitution
16 585 treatment. *BMJ* 2010;**340**:c3172 doi: 10.1136/bmj.c3172[published Online First:
17 586 Epub Date]].
18 587 40. Vickerman P, Martin N, Turner K, et al. Can needle and syringe programmes and opiate
19 588 substitution therapy achieve substantial reductions in HCV prevalence? Model
20 589 projections for different epidemic settings. *Addiction* 2012;**107**:1984-95
21 590 41. Miller E, Bi P, Ryan P. Hepatitis C virus infection in South Australian prisoners:
22 591 seroprevalence, seroconversion, and risk factors. *International Journal of Infectious*
23 592 *Diseases* 2009;**13**:201-08
24 593 42. West H, Sabol W, Greenman S. Bureau of Justice Statistics Bulletin: Prisoners in 2009.
25 594 <http://bjs.ojp.usdoj.gov/content/pub/pdf/p09.pdf>, 2010.
26 595 43. McGarry LJ, Pawar VS, Parekh HH, et al. Economic model of a birth cohort screening
27 596 program for hepatitis C virus. *Hepatology* 2012;**55**(5):1344-55 doi:
28 597 10.1002/hep.25510[published Online First: Epub Date]].
29 598 44. Rein D, Smith B, Witenborn J, et al. The Cost-Effectiveness of Birth-Cohort Screening for
30 599 Hepatitis C Antibody in U.S. Primary Care Settings. *Annals of Internal Medicine*
31 600 2012;**156**(4):263-70
32 601 45. Dore GJ. The changing therapeutic landscape for hepatitis C. *Med J Aust* 2012;**196**:629-
33 602 32
34 603 46. Thompson Coon J, Castelnuovo E, Pitt M, et al. Case finding for hepatitis C in primary
35 604 care: a cost utility analysis. *Family Practice* 2006;**23**(4):393-406 doi:
36 605 10.1093/fampra/cml032[published Online First: Epub Date]].
37 606 47. Coffin PO, Scott JD, Golden MR, et al. Cost-effectiveness and Population Outcomes of
38 607 General Population Screening for Hepatitis C. *Clinical Infectious Diseases*
39 608 2012;**54**(1259-1271)
40 609 48. Klein SJ, Wright LN, Birkhead GS, et al. Promoting HCV Treatment Completion for Prison
41 610 Inmates: New York State's Hepatitis C Continuity Program. *Public Health Reports*
42 611 2007;**122**(Suppl 2):83-88
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9 **Figure Legends:**
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11 619 **Figure 1. Base-case cost-effectiveness acceptability curves for the dried blood**
12 620 **spot intervention.** Results shown for the (a) addiction services and (b) prison
13 621 interventions for various willingness-to-pay thresholds.
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15 623 **Figure 2. Univariate sensitivity analyses on the mean incremental cost-**
16 624 **effectiveness ratio (ICER).** Results shown for the dried blood spot intervention in
17 625 (a) addiction services and (b) prison. Vertical line represents the base-case ICER,
18 626 estimated at (a) £14,600 per QALY gained and (b) £59,400 per QALY gained.
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21 629 **Figure 3. Incremental cost-effectiveness ratios for the prison intervention with**
22 630 **varying continuity of care assumptions.** Base-case scenario assumed 0%
23 631 continuity.
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	Mean value	Distribution	Reference
Transition probabilities per year (all probabilities converted to instantaneous rates)			
Mild to moderate	0.025	Beta($\alpha=38.0859, \beta=1485.3516$)	[19]
Moderate to cirrhosis	0.037	Beta($\alpha=26.905, \beta=700.2582$)	[19]
Cirrhosis to decompensated cirrhosis	0.039	Beta($\alpha=14.6168, \beta=360.1732$)	[19]
Cirrhosis/decomp. cirrhosis to HCC	0.014	Beta($\alpha=1.9326, \beta=136.1074$)	[19]
Decompensated cirrhosis/HCC to LT	0.03	Beta($\alpha=6.5256, \beta=210.9945$)	[19]
Decompensated cirrhosis to death	0.13	Beta($\alpha=147.03, \beta=983.97$)	[19]
HCC to death	0.43	Beta($\alpha=117.1033, \beta=155.23$)	[19]
LT to death	0.21	Beta($\alpha=16.2762, \beta=61.2294$)	[19]
Post transplant to death	0.057	Beta($\alpha=22.9017, \beta=378.8825$)	[19]
Health state utilities/disutilities per year			
Ex-PWID age 15-19			
Uninfected	0.94		[17]
Mild	0.77	Beta($\alpha=521.2375, \beta=155.6943$)	[19-20]
Moderate	0.66	Beta($\alpha=168.2461, \beta=86.6723$)	[19-20]
Cirrhosis	0.55	Beta($\alpha=47.1021, \beta=38.5381$)	[19-20]
Decompensated cirrhosis	0.45	Beta($\alpha=123.75, \beta=151.25$)	[19-20]
Hepatocellular carcinoma	0.45	Beta($\alpha=123.75, \beta=151.25$)	[19-20]
Liver transplant	0.45	Beta($\alpha=123.75, \beta=151.25$)	[19-20]
Post transplant	0.67	Beta($\alpha=59.2548, \beta=29.1852$)	[20-21]
Mild - on treatment	0.66	Beta($\alpha=115.706, \beta=59.6063$)	[19-20]
Moderate - on treatment	0.55	Beta($\alpha=47.1021, \beta=38.5381$)	[12-19-20]
Cirrhosis - on treatment	0.46	Beta($\alpha=3953, \beta=4641$)	[12]
Mild SVR	0.82	Beta($\alpha=65.8678, \beta=14.4588$)	[19-20]
Moderate SVR	0.72	Beta($\alpha=58.0608, \beta=22.5792$)	[12-19-20]
Cirrhosis SVR	0.64	Beta($\alpha=58.0476, \beta=37.1124$)	[21]
PWID age 15-19			
Uninfected	0.74	Uniform(0.67,0.8)	[18]
HCV disease states		As in ex-PWID, but reduced by PropPWID [†]	Assumed
Disutility with age			
20-24	0		[17]
25-29	0.005		[17]
30-54	0.049		[17]
55-64	0.14		[17]
65-74	0.16		[17]
75+	0.21		[17]
Costs (£ per year, except where noted)			
Mild diagnosed	169	PPI [†] × Gamma($k=25.6995, \theta=5.3698$)	[19-20]
Moderate diagnosed	880	PPI [†] × Gamma($k=88.8502, \theta=8.0698$)	[19-20]
Cirrhosis diagnosed	1,397	PPI [†] × Gamma($k=24.2342, \theta=46.9584$)	[19-20]
Decompensated cirrhosis	11,199	PPI [†] × Gamma($k=36.0249, \theta=253.1582$)	[19-20]
Hepatocellular carcinoma	9,980	PPI [†] × Gamma($k=18.1081, \theta=448.8045$)	[19]
Liver transplant (per transplant)	33,561	PPI [†] × Gamma($k=89.7536, \theta=304.5004$)	[19]
Cost of care in year of liver transplant	11,614	PPI [†] × Gamma($k=13.7788, \theta=686.4168$)	[19]
Post transplant	1,701	PPI [†] × Gamma($k=15.2189, \theta=91.0053$)	[19]
Mild SVR	318	PPI [†] × Gamma($k=28.8141, \theta=8.9887$)	[19]
Moderate SVR	880	PPI [†] × Gamma($k=88.8502, \theta=8.0698$)	[19]
Cirrhosis SVR	1,397	PPI [†] × Gamma($k=24.2342, \theta=46.9584$)	[19]
Undiagnosed states	0		
PegIFN+RBV drug only			
24 weeks, halved/doubled for 12/48 wks	5,320	Uniform (4788, 5852)	[23]
Treatment delivery			

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7	—Ex-PWID, 12 weeks	1,912	Varied, see appendix	See appendix[19]
8	—Ex-PWID, 24 weeks	2,057	Varied, see appendix	See appendix[19]
9	—Ex-PWID, 48 weeks	2,326	Varied, see appendix	See appendix[19]
10	—PWID, 12 weeks	2,193	Varied, see appendix	See appendix
11	—PWID, 24 weeks	2,435	Varied, see appendix	See appendix
12	—PWID, 48 weeks	2,900	Varied, see appendix	See appendix
13	Testing costs in all settings except prison	115.24	Uniform +/- 50%	See appendix
14	Testing costs in prison	144.21	Uniform +/- 60%	See appendix
15	PCR-RNA test (if antibody positive)	73.67		[24]
16	Testing and treatment parameters			
17	Proportion PWID diagnosed (initial)	50%		[4]
18	Proportion PWID treated (initial)	0%		Assumption
19	Proportion ex-PWID diagnosed (initial)	30%	Uniform (24%, 36%)	Assumption [58]
20	Proportion of diagnosed ex-PWID treated (initial)	40%	Uniform (5%, 15%)	Estimated <10% diagnosed chronic infections [4]
21	Proportion HCV genotype 1	50%		[4-59]
22	Sustained viral response(SVR)			
23	—Genotype 1 mild/moderate	0.45	Uniform (0.4, 0.5)	[59-62]
24	—Genotype 2/3 mild/mod	0.8	Uniform (0.75, 0.85)	[59-62-63]
25	—Genotype 1 cirrhosis	0.25	55% reduction from mild/mod	[64]
26	—Genotype 2/3 cirrhosis	0.6	75% reduction from mild/mod	[64]
27	Antiviral treatment duration (weeks)			
28	—Genotype 1 SVR	48		[59]
29	—Genotype 1 non-SVR	12		[59]
30	—Genotype 2/3	24		[59]
31	Distribution of PWID-HCV tests			
32	GP	38.4%		§
33	Prison	11.5%		§
34	Addiction services	29.4%		§
35	Other	20.7%		§
36	Proportion who are referred and attend referral	35%	Uniform (25%, 45%)	[13-35]
37	Proportion in referral who initiate treatment within 2 years (excl. prison)			
38	Ex-PWID	50%	Uniform(40%, 60%)	[13-35-37]
39	PWID	5.5%	Uniform(1%, 10%)	Assumption
40	Treatment initiation rate after 2 years in referral (excl. prison) per year			
41	Ex-PWID	10%	Uniform(5%, 15%)	Assumption
42	PWID	3%	Uniform(1%, 5%)	Assumption
43	Treatment rates in prison	Half out-of-prison rates		Assumption [†]
44	Yield (proportion tests Ab+)			
45	GP	2.7%		§
46	Prison	14.7%		§
47	Addiction services	17.7%		§
48	Other	1.7%		§

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 46 637 **Table 1. Model parameters.** [†]PropPWID=(uninfected PWID utility value for age 15-19)/(uninfected ex-PWID utility for age 15-19). [‡]PPI=Hospital and Community Health
 47 638 Services Pay and Prices Index inflation factor. [§]Health Protection Agency (HPA)
 48 639 unpublished data from the 2010 Sentinel Surveillance. [¶]Iain Brew, HMP Leeds,
 49 640 unpublished data. HCC= hepatocellular carcinoma; LT=liver transplant;
 50 641 SVR=sustained viral response; pegIFN=pegylated interferon; RBV= ribavirin
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	Mean value	Distribution	Units	Ref.
Intervention effect (proportional change in testing rate)				
Addiction services	3.6	Lognormal		[5]
	[2.3-5.8]	($\mu=1.285, \sigma=0.239$)	-	
Prison	2.6	Lognormal	-	[5]
	[0.2-34.9]	($\mu=0.968, \sigma=1.317$)		
Intervention costs (addiction services)				
Organization/coordination of training [†]	2,005.71		per health board	†
Training session [†]	135		per training session	†
Attendees time [§]	1,620		per training session	†
Travel reimbursement for training leader	90.86		per training session	†
Total cost per addiction services training	3851.57		per training session	†
Mean number tested	40.3		per addiction service	[5]
Total intervention cost per test	95.57	Uniform +/-50%	per test	
Intervention costs (prison)				
Organization/coordination of training ^{**}	7020		per prison	†
Training session [†]	135		per prison	†
Attendees time ^{††}	405		per prison	†
Travel reimbursement for training leader ^{††}	127.20		per prison	†
Total cost per prison training	7687.20		per prison	†
Mean number tested per prison	116		per prison	[5]
Total intervention cost per test	66.27	Uniform +/- 50%	per test	

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Table 12. Intervention parameters. All cost estimates assume a staff-nurse cost per hour of £30 (median estimate for band 5 general practice nurse[21]). [†]1 nurse 2 days/week for 6 months for 7 health boards. One training session per health board. [†]Noel Craine, *personal communication*. [‡]1 nurse, half day. [§]12 nurses, half day. ^{||}1200 miles (£0.53 per mile) for travel to 7 health boards. ^{||}Assumed 1 addiction service per health board. ^{**}1 nurse full time for 5 prisons (1 training session per prison) ^{††}3 nurses per prison, half day. ^{††}1200 miles (£0.53 per mile) for 5 prisons.

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	Mean value	Sampled values	Units	Ref.			
Average duration of injecting until cessation	11	6.2, 8.6, 11, 13.4, 15.8	years	[65-66]			
PWID overdose rate	0.01	0.007, 0.01, 0.013	Per year	[67]			
Duration in addiction services	9	7, 9, 11	months	Estimated from OST duration [67]			
Incarceration duration							
— PWID							
— All ages	4	2.67, 4, 5.33	Months	[29-31]			
— Ex-PWID							
— 15-19	2.75		Months	[29]			
— 20-24	6.26		Months	[29]			
— 25-29	8.42		Months	[29]			
— 30-54	9.76		Months	[29]			
— 55-64	11.92		Months	[29]			
— 65+	12.49		Months	[29]			
Age of first injection distribution							
— 15-19	41%		-	Combined UK data from [48]			
— 20-24	30%		-	Combined UK data from [48]			
— 25-29	16%		-	Combined UK data from [48]			
— 30-54	13%		-	Combined UK data from [48]			
— 55+	0%		-	Combined UK data from [48]			
Death rate by age							
— 15-19	0.0003		Per year	[68]			
— 20-24	0.0005		Per year	[68]			
— 25-29	0.0006		Per year	[68]			
— 30-54	0.0019		Per year	[68]			
— 55-64	0.0073		Per year	[68]			
— 65-74	0.0200		Per year	[68]			
— 75+	0.165		Per year	[68]			
Proportion of England population currently imprisoned aged 15-59	0.2%			[69-70]			
Proportion of population who are PWID aged 15-59	0.65%			[71]			
Proportion PWID in contact with addiction services	50%			[48]			
Proportion PWID diagnosed	50%			[4]			
PWID HCV chronic prevalence	35%			[27]			
Proportion infections leading to spontaneous clearance	0.26	Uniform (0.22, 0.29)	-	[28]			
		Age distribution		Reference			
		15-19	20-24	25-29	30-54	55+	
Proportion general population with a custodial sentence	1.3%	2.5%	3%	4%	-		[72]
Age distribution of prisoners	8%	20%	18%	47%	7%		[69]
Proportion PWID ever in prison	48%	46%	67%	73%	-		*
Proportion prisoners ever PWID	5%	16%	36%	44%	8%		[31]†

Table 53. Epidemiological/prison input parameters for model fitting *Unlinked Anonymous Monitoring Survey of PWID, Health Protection Agency, London, unpublished data. †Scottish prison data. ‡Avril Taylor, unpublished data.

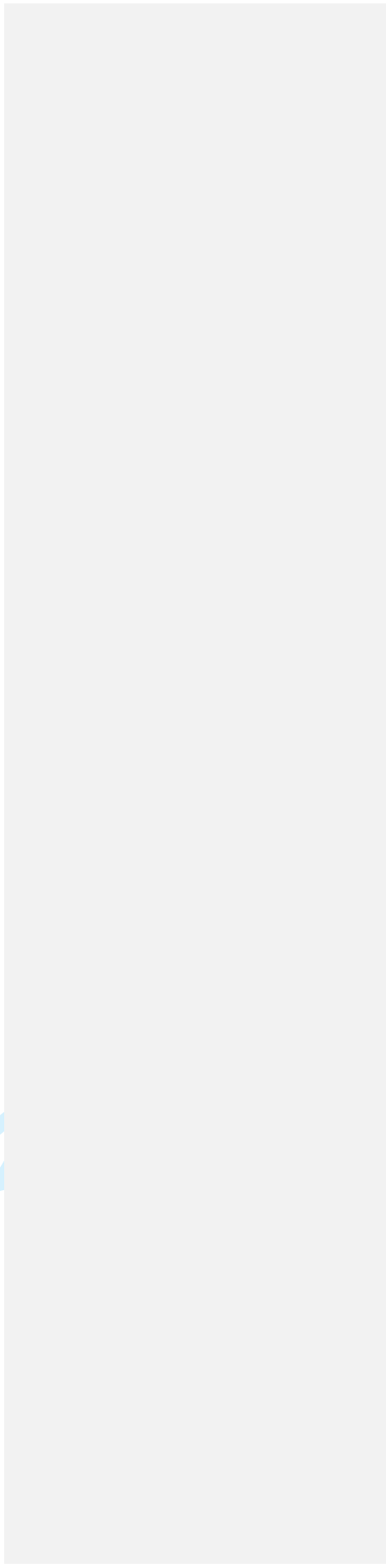
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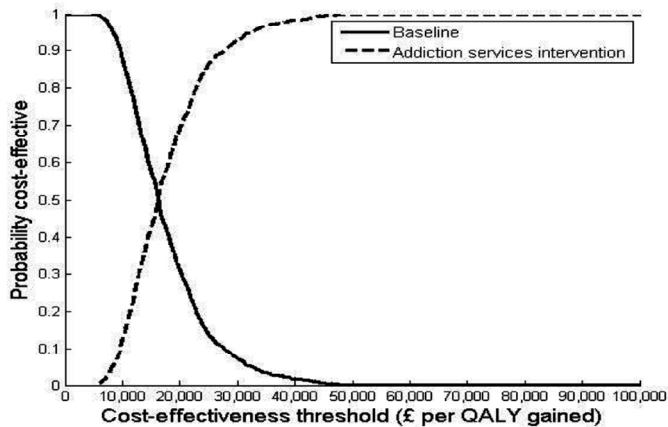
Intervention location	Discounted Costs (2011 £) [95% interval]	Discounted QALYs [95% interval]	Incremental costs [95% interval]	Incremental QALYs [95% interval]	ICER (£ per QALY gained)
Addiction services					
Baseline	37,181,582 [19,384,816–67,271,249]	5,354,331 [4,867,168–5,960,766]	-	-	-
Intervention	38,099,060 [20,140,578–68,378,488]	5,354,393 [4,867,206–5,960,853]	917,478 [481,174–1,664,430]	63 [19–153]	14,632
Prison					
Baseline	37,181,582 [19,384,816–67,271,249]	5,354,331 [4,867,168–5,960,766]	-	-	-
Intervention	38,245,293 [19,852,634–68,601,970]	5,354,349 [4,867,184–5,960,823]	1,063,710 [-225,101 – 6,060,267]	18 [-12 – 75]	59,418

| Table 24. Cost-effectiveness results from the base-case intervention analyses.

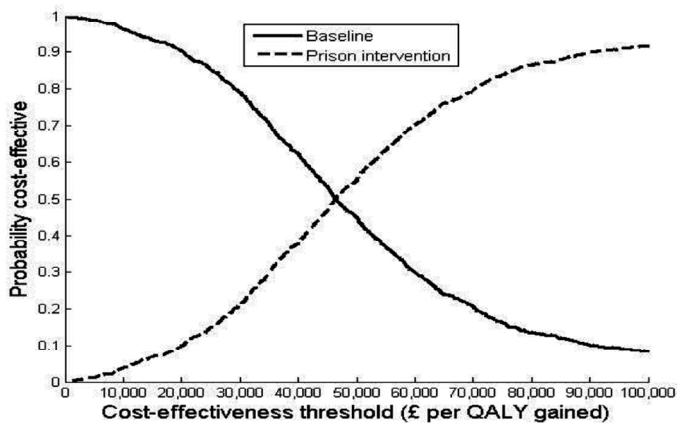
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(a)

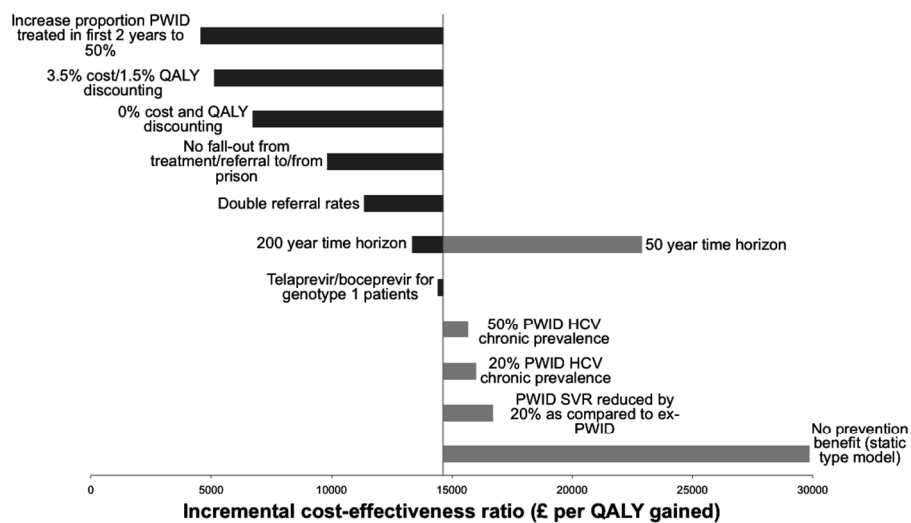


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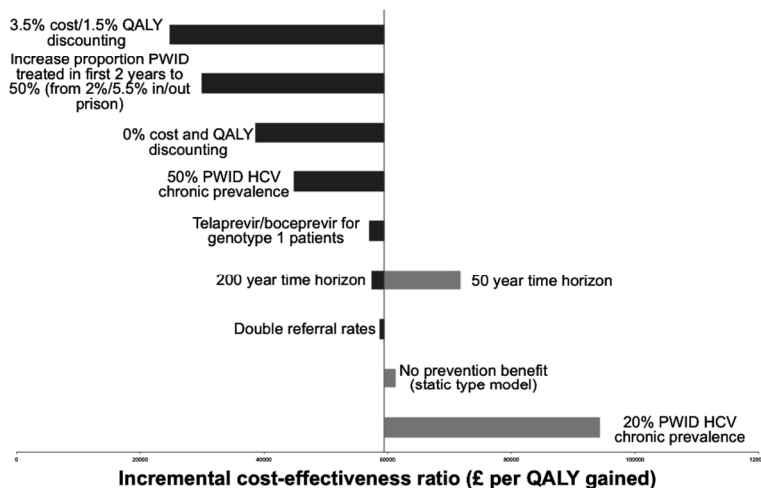
Figure 1

Base-case cost-effectiveness acceptability curves for the dried blood spot intervention. Results shown for the (a) addiction services and (b) prison interventions for various willingness-to-pay thresholds.

396x529mm (72 x 72 DPI)



(a)



(b)

Figure 2

Univariate sensitivity analyses on the mean incremental cost-effectiveness ratio (ICER). Results shown for the dried blood spot intervention in (a) addiction services and (b) prison. Vertical line represents the base-case ICER, estimated at (a) £14,600 per QALY gained and (b) £59,400 per QALY gained.
396x529mm (72 x 72 DPI)

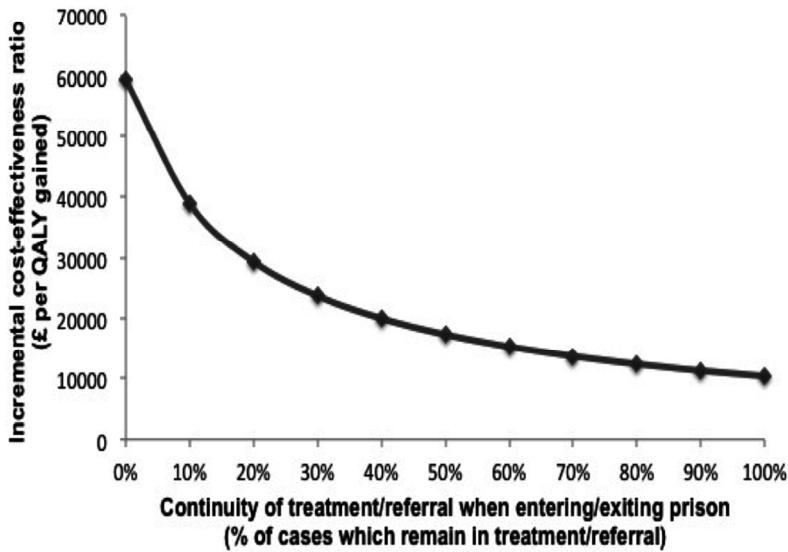


Figure 3

Incremental cost-effectiveness ratios for the prison intervention with varying continuity of care assumptions.
 Base-case scenario assumed 0% continuity.
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APPENDIX

Mathematical model

A dynamic, deterministic compartmental model of injecting drug use, HCV transmission, progression, treatment, and diagnosis amongst PWID was developed, to project the impact of interventions to increase HCV testing of PWID. Schematics for the model components can be found in **appendix figures 1 and 2**. The HCV transmission, antiviral treatment, and disease progression model was based on a coupled system of ordinary differential equations previously published by the authors[1]. Susceptible PWID can become acutely infected with HCV by sharing injecting equipment with other infected PWID. We model a frequency dependent force of infection, such that an individual's risk of infection is proportional to the overall prevalence of infection. This model assumes a proportion (26.74%) of acutely infected PWID progress to chronic infection, with the remainder (26%, [2]) resolving their acute infection after a number of months and developing an antibody (Ab) response, thus becoming Ab+/RNA-. Those that develop chronic infection (Ab+/RNA+) remain infected and, unless successfully treated, progress through the various HCV disease stages (mild, moderate, compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma (HCC), liver transplant, and post transplant). Death occurs from all stages, but elevated mortality rates were used from the decompensated cirrhosis, HCC, liver transplant, and post-transplant stages[3]. If treated, infected PWID can achieve sustained viral response (SVR) whereby they are cured and are not at risk of progressing to a more advanced disease state, but remain at their current stage of liver progression (mild, moderate, or compensated cirrhosis), and are susceptible to reinfection. If reinfected after achieving SVR, the PWID re-enters the infected compartment of their associated HCV disease stage. If a PWID fails treatment (non-SVR), they remain infected and can progress to more severe disease stages. Successfully treated PWID can be reinfected and retreated, but those who do not achieve SVR are ineligible for retreatment. Due to reduced viral loads during treatment (even amongst those who relapse and do not achieve SVR), we assume PWID are not infectious during treatment[4, 5]. Current injectors are at risk of infection, but after permanent cessation of injecting do not have any infection risk. For simplicity, the model does not assume any behavioural

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9 heterogeneity among the PWID population (such as high/low risk), as modelling
10 indicated introducing heterogeneity in risk does not have an undue influence on
11 prevention intervention effectiveness as long as individuals circulate between high risk
12 and intervention states[6].
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16 For this analysis, the model was adapted in the following ways. First, the model
17 compartments were subdivided to allow for a distinction between naïve uninfected (Ab-
18 /RNA-) or spontaneously cleared individuals (Ab+/RNA-), as well as the following
19 diagnosis stages for chronic infection: undiagnosed, diagnosed but lost to follow-up and
20 not in referral, diagnosed and in the first 2 years of referral, and diagnosed and in
21 referral after 2 years. For ex-PWID, an additional compartment was added to represent
22 those who were uninfected and tested (hence who would not be re-tested as they do
23 not have a continuing infection risk).
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29 In order to appropriately model incarceration, the model structure was replicated to track
30 the flow of PWID and ex-PWID between never incarcerated, currently incarcerated, and
31 formerly incarcerated states. In addition, compartments for never-PWID were added
32 (never incarcerated, currently incarcerated, formerly incarcerated) to enable model
33 calibration to general population incarceration data. This model structure was based on
34 previously published mathematical models of PWID incarceration[7, 8], and it was
35 assumed that incarceration and re-incarceration rates of ex-PWID were equal to that of
36 never-PWID.
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41 Additionally, for PWID not imprisoned (never imprisoned and formerly imprisoned) we
42 further stratified movement by contact with addiction services (in contact/not in contact).
43 We assumed only those in contact with addiction services could be tested in addiction
44 services. We also assumed that on release from prison, PWID were not immediately in
45 contact with addiction services.
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50 Finally, the model was split into 7 age compartments ([15-19],[20-24],[25-29],[30-
51 54],[55-64],[65-74],[75+]), with individuals entering the model at age 15-19 as never-
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PWID. In total, the model consists of 222 states and 7 age stratifications, leading to 222 x 7=1,554 compartments.

The model assumes that prisoners only share with other prisoners. Similarly, outside prison, we did not assume any difference in sharing behaviour between those who are never imprisoned or previously imprisoned, and these individuals share between each other.

The dynamic transmission aspect of the model is similar to our previously published mathematical models. Let $P_{n,c,l}^{m,a}$ represent the number of PWID, where the superscript m represents incarceration status ($m=0,1,2$ for never, currently, formerly incarcerated, respectively), the superscript n represents addiction services status ($n=out$ for out of contact and $n=in$ in contact, and noting that $n=out$ for all incarcerated states when $m=1$), subscript a represents the age group, with $a=1,2,\dots,7$ for each age group. The subscript l represents the HCV state, where $l=x_i$ for susceptible where i represents the different susceptible stages (never infected, spontaneously cleared), $l=y_i$ for chronic infected undiagnosed (including mild, moderate, compensated cirrhosis), $l=z_i$ for chronic infected diagnosed (including mild, moderate, compensated cirrhosis, decompensated cirrhosis, HCC, liver transplant, post-transplant and in early referral, late referral, or lost to follow-up states), $l=v_i$ for on treatment (including mild, moderate, compensated cirrhosis), $l=s_i$ for SVR (mild, moderate, compensated cirrhosis) and $l=f_i$ for treatment failure/non-SVR (mild, moderate, compensated cirrhosis). For example, $P_{0,1,x_1}^{0,1}$ represents a PWID who has never been imprisoned and is not in contact with addiction services, is in age group 1 (15-19), and is undiagnosed mild chronically infected. We assume proportionate mixing by age. Using this notation, the force of infection for a PWID who is not imprisoned ($m=0$ or 2) is:

$$\pi \frac{\sum_{\text{all } a,n,y_i,z_i,f_i} (P_{0,a,y_i}^n + P_{0,a,z_i}^n + P_{0,a,f_i}^n + P_{2,a,y_i}^n + P_{2,a,z_i}^n + P_{2,a,f_i}^n)}{\sum_{\text{all } a,n,x_i,y_i,z_i,v_i,s_i,f_i} (P_{0,a,x_i}^n + P_{0,a,y_i}^n + P_{0,a,z_i}^n + P_{0,a,v_i}^n + P_{0,a,s_i}^n + P_{0,a,f_i}^n + P_{2,a,x_i}^n + P_{2,a,y_i}^n + P_{2,a,z_i}^n + P_{2,a,v_i}^n + P_{2,a,s_i}^n + P_{2,a,f_i}^n)}$$

where π represents the infection rate, which is fit to the HCV prevalence among PWID.

While incarcerated, PWID can only transmit to other incarcerated PWID, so the force of infection for a susceptible PWID in prison ($m=1$) is:

$$\pi \frac{\sum_{\text{all } a, y_i, z_i, f_i} (P_{1,a,y_i} + P_{1,a,z_i} + P_{1,a,f_i})}{\sum_{\text{all } a, x_i, y_i, z_i, v_i, s_i, f_i} (P_{1,a,x_i} + P_{1,a,y_i} + P_{1,a,z_i} + P_{1,a,v_i} + P_{1,a,s_i} + P_{1,a,f_i})}$$

As stated before, all PWID in never infected (Ab-/RNA-), spontaneously cleared (Ab+/RNA-), and SVR states are susceptible for infection as described above.

Model Parameters

Intervention impact

The intervention impact was modelled a proportional increase in setting-specific testing rates, determined by a random effects meta-analysis of the primary data[9] for each setting (addiction services and prisons) separately. The results of the meta-analysis can be found in **appendix figure 3**.

SVR rates

Sustained viral response (SVR) rates for pegIFN+RBV were sampled by genotype, with mean values in the mild/moderate HCV disease stages of 45% for genotype 1 and 80% for genotype 2/3[10]. Patients with compensated cirrhosis exhibit proportional reductions in SVR values by about 45% and 25% for genotypes 1 and 2/3, respectively[11]. Preliminary studies indicate SVR rates are equal between PWID and ex/non-PWID[12, 13], which we assumed in our base-case.

Calculation of testing rates

The HPA collects comprehensive yearly data of HCV testing in their sentinel surveillance, which includes a question on PWID as a risk factor. However, only a very small proportion of tests are coded with PWID status as a risk factor, and current or former PWID status is not recorded. Therefore, we were unable to use the HPA data to estimate the yearly testing rates of current and ex-PWID.

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9 To circumvent this problem, we fitted an overall PWID annual testing rate to calibrate
10 the model to the estimated proportion of PWID who are diagnosed (approximately
11 50%[14]). This rate varied for each sampled group of parameters, but the mean annual
12 testing rate was 12% per year among undiagnosed PWID. This annual testing rate
13 ensured the proportion of diagnosed PWID remained stable (at equilibrium) without any
14 intervention.
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19 As testing of PWID takes place in different locations (prison, addiction services, other
20 settings) and the proportion of PWID in contact with these settings varies, it was
21 necessary to calculate setting-specific testing rates from the overall testing rate. This
22 was done using three pieces of information: 1) the overall testing rate, 2) the fraction of
23 tests attributable to each location, and 3) the proportion of the population in contact with
24 each location. We obtained the fraction of tests attributable to each location from the
25 HPA sentinel surveillance of hepatitis testing data, using the tests coded with an PWID
26 risk only (Mary Ramsay and Sara Collins[Health Protection Agency], *unpublished data.*).
27 Although these data underestimate the number of tests given to PWID, it is reasonable
28 to assume the HPA distribution between sites would be representative of the testing
29 administered to PWID as a whole. Finally, we ran the model to obtain steady state
30 values of the proportion of population found in each testing location based on the input
31 parameters (some of which were previously fitted, such as the proportion of PWID in
32 contact with addiction services and in prison). We assume all ex-PWID are in contact
33 with a GP. These three components were then combined to obtain setting specific
34 testing rates for each parameter set simulation. The setting specific testing rates for
35 PWID and ex-PWID were assumed equal, with the exception that the model assumes
36 ex-PWID are not in contact with addiction services, so no testing occurs from this
37 scenario for this group.
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47 **Testing costs**

48 Costs associated with testing were calculated as follows. The numbers of PWID tested
49 in each setting were calculated, and associated with setting specific test costs. Two
50 additional costs were added: RNA testing (for all Ab+ tests) and non-PWID testing. The
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9 number of non-PWID tested in order to test one PWID was calculated from the setting-
10 specific test yield (proportion of tests Ab+) and 'true' baseline prevalence. A setting with
11 a low yield indicates more non-PWID are tested for every PWID; if yield equals baseline
12 prevalence, this indicates only PWID are tested.
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15 **Contact with addiction services rates**

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17 The proportion of PWID in contact with addiction services at any given time was difficult
18 to estimate. 92% of PWID report ever accessing a needle exchange in the HPA
19 Unlinked Anonymous Survey, though the proportion currently accessing services is not
20 asked[15]. However, it is estimated that 50% of PWID are currently on opiate
21 substitution therapy[16, 17], and we therefore estimated that the same proportion is
22 currently in contact with addiction services. Similarly, the average duration of time in
23 contact with addiction services was estimated from data of average time PWID are on
24 OST[18].
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30 **Model fitting**

31 **Overview of model fitting and baseline projections**

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33 A multi-step parameter sampling and model calibration/fitting method was used with
34 simplified models to reduce computational time and allow for verification of full model
35 predictions against the simplified models. For each fitting process (5 separate model fits
36 in total), **appendix table 3-5** details the model used, input parameters, calibration data
37 used to fit the model, and parameters estimated through model fitting. The seven-step
38 sampling and calibration process is as follows:
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- 43 1) Values were randomly sampled for four parameters (cessation rate, overdose
44 rate, PWID prison release rate, and addiction services duration), yielding a total
45 of 135 possible parameter combinations, or 'calibration scenarios'. Due to the
46 heavy computational burden of fitting the many incarceration parameters, the
47 model was fitted to a limited range of sampled 'calibration scenarios'.
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- 50 2) **Fit #1:** Simplified model 1 (**appendix figure 4**) was run for each sampled
51 calibration scenario, in order to calibrate the simplified model to the (not
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9 | sampled) incarceration data shown in [appendix table 23](#). Inputs included the
10 | sampled scenario parameters, and non-sampled input parameters estimated
11 | from literature/sources (age-specific death rates, prison release rates for never
12 | PWID, distribution of ages of first injection, and a preliminary estimate of the
13 | entry rate of never-PWID aged 15-19 which will be refit in Fit #5). The
14 | parameters which were estimated through model calibration were the age-
15 | dependent incarceration rate, reincarceration rates, PWID incarceration rates,
16 | PWID reincarceration rates, and injecting initiation rate. Simplified model 1
17 | neglected HCV transmission, testing, and treatment. More details can be found
18 | in the section 'Details of fit #1' and model equations can be found the section
19 | entitled "**Model Equations: Simplified Model 1**".

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- 3) **Fit #2:** Simplified model 2 ([appendix figure 5](#)) was run for each sampled calibration scenario, in order to calibrate the model to addiction services data. For fit #2, a simplified model of incarceration and movement in/out of addiction services was used. The inputs for these simulations were the sampled calibration scenarios and inputs from Simplified model 1, as well as the estimated incarceration parameters from Simplified model 1. The model was calibrated to data on the proportion of PWID in contact with addiction services, and the estimated parameter obtained through model fitting was the recruitment rate into addiction services. Model equations can be found in the section entitled "**Model Equations: Simplified Model 2**".
- 4) **Fit #3:** Simplified model 3 ([appendix figure 6](#)) was run for each sampled calibration scenario, in order to calibrate the model to the diagnosis data. For fit #3, a simple model of HCV transmission and testing among PWID was used to estimate the overall PWID testing rate by calibrating the model to the proportion of PWID who report being diagnosed for HCV. The model inputs were the sampled calibration scenarios and non-sampled inputs of age-specific death rates, distribution of injecting initiation age, and preliminary estimate of the entry rate of never-PWID aged 15-19. The model also required an input of the estimated injecting initiation rate from simplified model 1. Model equations can be found in the appendix section entitled "**Model Equations: Simplified Model 3**".

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9 5) 1000 parameter sets were sampled from each parameter uncertainty distribution
10 in from the full range of disease progression, intervention, cost, and utility
11 parameters (Tables 1, Appendix tables 1-43). For each of the 1000 parameter
12 sets, one of the 135 fitted 'calibration scenarios' was selected.
13
14 6) **Fit #4:** For each of the 1000 parameter sets, the full model was calibrated to
15 three separate HCV PWID chronic prevalences (35%[19], used in the base-case,
16 as well as 20% and 50% for the sensitivity analyses) to estimate the infection
17 rate, π , associated with each chronic prevalence.
18
19 7) **Fit #5:** For each of the 1000 parameter sets, the full model was calibrated to a
20 total PWID population size (fit to 1000 PWID at baseline), to estimate the entry
21 rate of never-PWID in the 15-19 age group.
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25
26 Model fitting was performed by using nonlinear least-squares methods using the
27 MATLAB solver *lsqnonlin*.
28

30 Model Equations

32 Simplified model 1

33 For Simplified Model 1, the mathematical model tracks injecting drug use state
34 (never/current/former PWID) and incarceration state (never/currently/formerly
35 incarcerated). $N_{n,a}$ represents never PWID, with superscript m representing
36 incarceration status ($m=0,1,2$ for never, currently, formerly incarcerated, respectively)
37 and subscript a representing age group, with $a=1,2\dots7$ for each age group. Using the
38 same subscript notation, $P_{n,a}$ represents PWID and $E_{n,a}$ represents ex-PWID. The full
39 system of equation is as follows:
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$$\begin{aligned}
 \frac{dN_{0,a}}{dt} &= \theta_a - (\rho_{0,a} + \xi_a + \gamma_a)N_{0,a} \\
 \frac{dN_{1,a}}{dt} &= \rho_{0,a}N_{0,a} + \alpha_{0,a}N_{2,a} - (\beta_{0,a} + \xi_a + \gamma_a)N_{1,a} \\
 \frac{dN_{2,a}}{dt} &= \beta_{0,a}N_{1,a} - (\alpha_{0,a} + \xi_a + \gamma_a)N_{2,a} \\
 \frac{dP_{0,a}}{dt} &= \xi_a N_{0,a} - (\rho_{1,a} + \zeta + \gamma_a + \eta)P_{0,a} \\
 \frac{dP_{1,a}}{dt} &= \xi_a N_{1,a} + \rho_{1,a}P_{0,a} + \alpha_{1,a}P_{2,a} - (\beta_{1,a} + \zeta + \gamma_a + \eta)P_{1,a} \\
 \frac{dP_{2,a}}{dt} &= \xi_a N_{2,a} + \beta_{1,a}P_{1,a} - (\alpha_{1,a} + \zeta + \gamma_a + \eta)P_{2,a} \\
 \frac{dE_{0,a}}{dt} &= \zeta P_{0,a} - (\rho_{0,a} + \gamma_a)E_{0,a} \\
 \frac{dE_{1,a}}{dt} &= \zeta P_{1,a} + \rho_{0,a}E_{0,a} + \alpha_{0,a}N_{2,a} - (\beta_{0,a} + \gamma_a)E_{1,a} \\
 \frac{dE_{2,a}}{dt} &= \zeta P_{2,a} + \beta_{0,a}E_{1,a} - (\alpha_{0,a} + \gamma_a)E_{2,a}
 \end{aligned}$$

where time is represented by the variable t . All populations experience age-specific death rates specified by rate γ_a and PWID have an additional death rate due to overdose of η . New never-PWID enter the system into the youngest age compartment at rate θ_1 ($\theta_a = 0$ for $a \neq 1$). Never or former PWID are incarcerated at an age specific rate $\rho_{0,a}$, are released at a rate $\beta_{0,a}$, and are reincarcerated at a rate $\alpha_{0,a}$. Similarly, PWID are incarcerated at an age specific rate $\rho_{1,a}$, are released at a rate $\beta_{1,a}$, and are reincarcerated at a rate $\alpha_{1,a}$. Never PWID initiate injecting at an age-specific rate of ξ_a , and cessate from injecting at a rate ζ .

Simplified model 2

For Simplified Model 2, the mathematical model in Simplified Model 1 is extended to include flow in and out of addiction services for PWID who are not incarcerated. Using the same subscript notation as before, but adding a superscript with $n=in$ if the PWID is in contact with addiction services, and $n=out$ if they are not in contact, then

$P_{n,i,a}^{in}$ represents PWID. The full system of equation is as follows:

$$\begin{aligned}
\frac{dN_{0,a}}{dt} &= \theta_a - (\rho_{0,a} + \xi_a + \gamma_a)N_{0,a} \\
\frac{dN_{1,a}}{dt} &= \rho_{0,a}N_{0,a} + \alpha_{0,a}N_{2,a} - (\beta_{0,a} + \xi_a + \gamma_a)N_{1,a} \\
\frac{dN_{2,a}}{dt} &= \beta_{0,a}N_{1,a} - (\alpha_{0,a} + \xi_a + \gamma_a)N_{2,a} \\
\frac{dP_{0,a}^{out}}{dt} &= \xi_a N_{0,a} + \sigma P_{0,a}^{in} - (\rho_{1,a} + \zeta + \gamma_a + \eta + \nu)P_{0,a}^{out} \\
\frac{dP_{0,a}^{in}}{dt} &= \nu P_{0,a}^{out} - (\rho_{1,a} + \zeta + \gamma_a + \eta + \sigma)P_{0,a}^{in} \\
\frac{dP_{1,a}}{dt} &= \xi_a N_{1,a} + \rho_{1,a}(P_{0,a}^{out} + P_{0,a}^{in}) + \alpha_{1,a}(P_{2,a}^{out} + P_{2,a}^{in}) - (\beta_{1,a} + \zeta + \gamma_a + \eta)P_{1,a} \\
\frac{dP_{2,a}^{out}}{dt} &= \xi_a N_{2,a} + \beta_{1,a}P_{1,a} + \sigma N_{2,a}^{out} - (\alpha_{1,a} + \zeta + \gamma_a + \eta + \nu)P_{2,a}^{out} \\
\frac{dP_{2,a}^{in}}{dt} &= \nu N_{2,a}^{out} - (\alpha_{1,a} + \zeta + \gamma_a + \eta + \sigma)P_{2,a}^{in} \\
\frac{dE_{0,a}}{dt} &= \zeta(P_{0,a}^{out} + P_{0,a}^{in}) - (\rho_{0,a} + \gamma_a)E_{0,a} \\
\frac{dE_{1,a}}{dt} &= \zeta P_{1,a} + \rho_{0,a}E_{0,a} + \alpha_{0,a}N_{2,a} - (\beta_{0,a} + \gamma_a)E_{1,a} \\
\frac{dE_{2,a}}{dt} &= \zeta(P_{2,a}^{out} + P_{2,a}^{in}) + \beta_{0,a}E_{1,a} - (\alpha_{0,a} + \gamma_a)E_{2,a}
\end{aligned}$$

where the variables are as in Simplified Model 1, with the addition that PWID enter addiction services at a rate ν , and exit at a rate σ . The model assumes that when people initiate injecting, or are released from prison, they are not immediately in contact with addiction services (but can subsequently be recruited into contact at rate ν).

Simplified model 3

Simplified model 3 is used to fit the PWID diagnosis rate to the overall proportion of PWID diagnosed at a given time. Hence, it includes never PWID, uninfected PWID, infected undiagnosed PWID, and infected diagnosed PWID. As in the other simplified models, $N_{a,t}$ represents never PWID, with a representing age group, with $a=1,2,\dots,7$ for each age group. Here, $P_{a,t,\tau}$ represents susceptible PWID, $P_{a,t,\nu}$ represents infected but undiagnosed PWID, and $P_{a,t,\varepsilon}$ represents infected and diagnosed PWID. The full system of equation is as follows:

$$\begin{aligned} \frac{dN_a}{dt} &= \theta_a - (\xi_a + \gamma_a)N_a \\ \frac{dP_{a,x}}{dt} &= \xi_a N_a - \pi P_{a,x} \frac{P_{a,y} + P_{a,z}}{P_{a,x} + P_{a,y} + P_{a,z}} - (\zeta + \gamma_a + \eta)P_{a,x} \\ \frac{dP_{a,y}}{dt} &= \pi P_{a,x} \frac{P_{a,y} + P_{a,z}}{P_{a,x} + P_{a,y} + P_{a,z}} - (\kappa + \zeta + \gamma_a + \eta)P_{a,y} \\ \frac{dP_{a,z}}{dt} &= \kappa P_{a,y} - (\zeta + \gamma_a + \eta)P_{a,z} \end{aligned}$$

where the parameters are as in Simplified Model 1 with the addition that κ represents the diagnosis rate, and π is the infection rate.

Details of fit #1

In fit #1, the simplified incarceration model was calibrated to age-structured data on the proportion of the general population with a custodial sentence[20], proportion of PWIDs previously imprisoned, age distribution of current prisoners[21], proportion of prisoners ever PWID, proportion of the population currently imprisoned[22, 23], and the prevalence of PWID in the general population[19]. The epidemiological and prison parameters sampled for this fitting algorithm can be found in [appendix table 23](#).

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As the prison data varied over several orders of magnitude (for example, the proportion of PWID previously incarcerated was around 60%, while the proportion of the England population currently imprisoned between the ages of 15-59 is 0.2%), a log-transformation of the calibration data was used in order to minimize relative error in the least-squares regression[24]. Furthermore, the error measure was re-weighted with more weight given to the error from the non-age structured parameters to provide a better fit to those parameters. Specifically, the error measure associated with each individual age-specific parameter of the 7 age-groups was weighted $1/7^{\text{th}}$ as much as a non-age specific parameter. **Appendix figure 7** provides an example of the data and calibrated model projections with the median values chosen for each parameter; all other fits were similar to this. The model fitted well to the data, with the notable exception of the proportion of PWID previously incarcerated in the 15-19 age group, which the model consistently underestimates. This was due to the low proportion of

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9 prisoners who admit ever-injecting in this age group, along with the low general rates of
10 ever incarceration in this age group. It was decided *a posteriori* that this deviation was
11 acceptable given the goodness of fit to the rest of the data and also because it is
12 unlikely that the data sources are consistent.
13

14 15 16 **Initial conditions**

17 The steady-state values of the full model without testing and treatment were used as
18 initial conditions for the baseline/intervention simulations, with the following alterations.
19 At baseline, the proportion of diagnosed ex-PWID was not thought to be at steady-state.
20 This was because recent testing initiatives have mainly targeted PWID; it is estimated
21 the proportion of diagnosed PWID (50%^[14]) is currently likely higher than that of ex-
22 PWID (estimated at 30% based on proportion PWID diagnosed in 2000 who are likely to
23 be ex-PWID^[15]). Hence, the steady-state values for infected populations were divided
24 between undiagnosed/diagnosed states for the initial conditions. As treatment rates of
25 PWID are extremely low, we assume none of the PWID population have been treated at
26 baseline, and sample the proportion of ex-PWID previously treated (mean sampled
27 value 10%^[14]) from the range found in **appendix table 1**.
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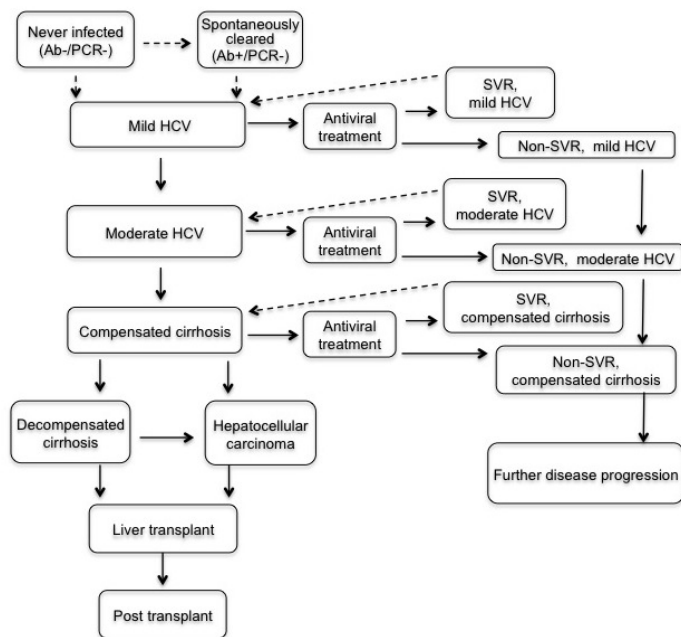
33 We calculate the initial conditions as follows. The full model without any testing and
34 treatment was run, and the number of people in all compartments was stored after the
35 system reached steady-state. This vector of initial condition values was then edited as
36 follows to account for the current proportion of diagnoses estimated in the PWID and
37 ex-PWID populations, as well as the proportion of ex-PWID already treated. As it is
38 unknown what proportion of previously diagnosed PWID are currently in referral for
39 treatment, we made the conservative assumption that all previously-diagnosed are lost-
40 to-follow-up at the beginning of the model if they have not been treated, and hence
41 need retesting in order to enter the referral and treatment pathway. We assume that no
42 PWID have been treated at baseline. Ex-PWID who have been treated are not eligible
43 for retesting and retreatment, and hence were removed from the model as they did not
44 change the cost-effectiveness of testing strategies.
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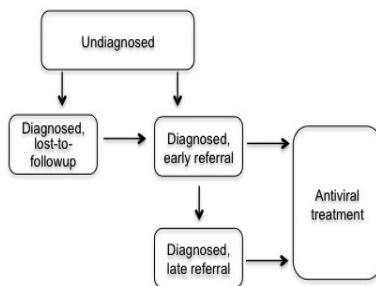
Hence, half of the chronically infected PWID population were placed in the diagnosed compartment of their relative disease state, with the remaining placed in the 'diagnosed and lost-to-follow-up' compartment of their relative disease state. For the ex-PWID population, a proportion will have been treated, and of the remaining untreated proportion, 30% were considered diagnosed and were placed in the 'diagnosed and lost to follow-up' compartment. As a result of this initialisation procedure, the proportion of diagnosed ex-PWID was not at steady state at the start of the simulation. As stated in the main text of the paper, this was deemed appropriate, as recent testing initiatives have mainly targeted PWID, and therefore it is assumed that diagnosis rates among ex-PWID are low. However, over time those who are PWID will become ex-PWID, and therefore the proportion of diagnosed ex-PWID will increase over time.

Results

The incremental costs and incremental QALYs are shown on a cost-effectiveness plane in **appendix figure 8**.



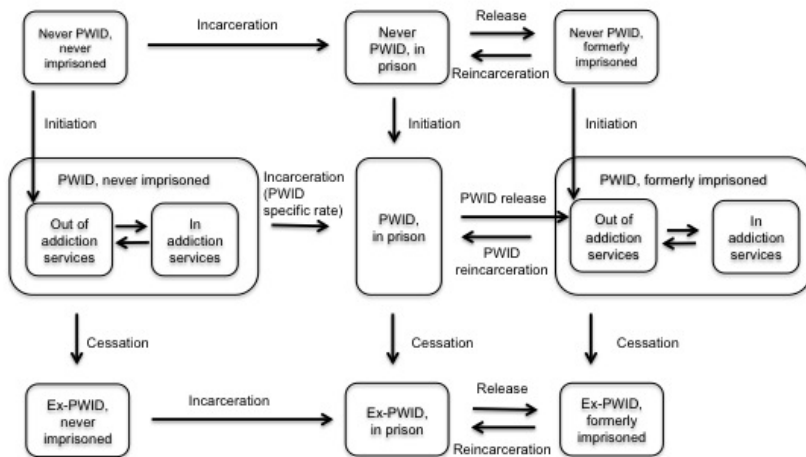
(a)



(b)

Appendix figure 1. HCV disease progression model schematics. Schematics show treatment (a) and diagnosis (b) model components. Solid black lines indicate transitions for both PWID and ex-PWID. Dashed black lines indicate PWID transitions only. For PWID, uninfecteds can be retested due to continuing risk behaviour; ex-PWID are not retested in the model.

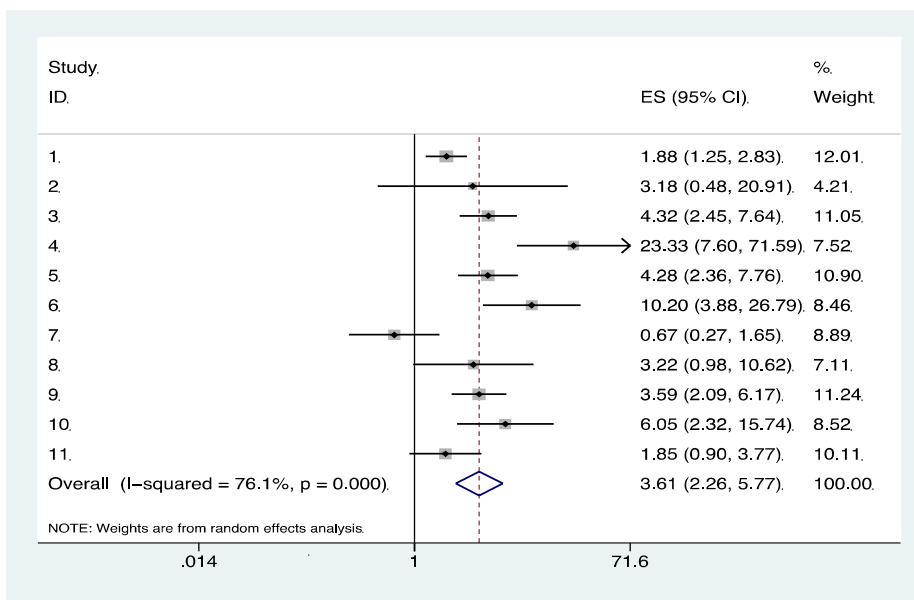
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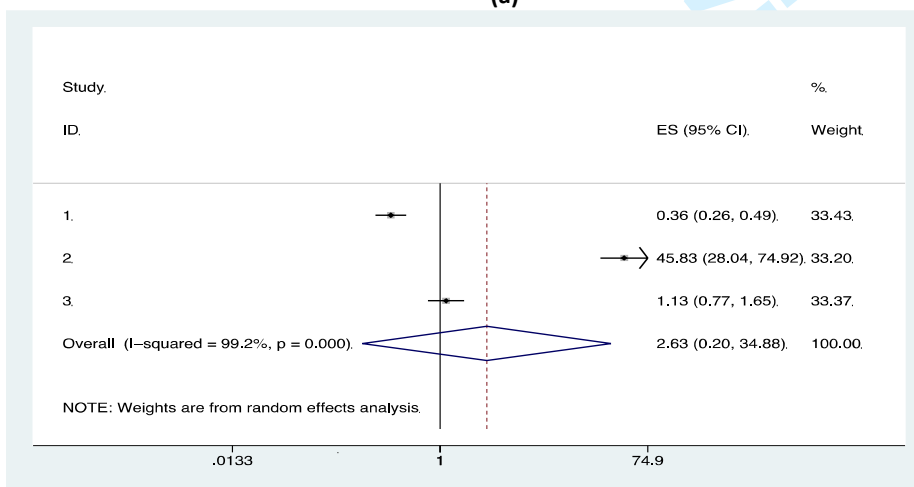
Model is stratified by age ([15-19, [20-24], [25-29], [30-54], [55-64], [65-74], [75+]), includes death from all compartments, overdose death from PWID compartments, and inflow to the youngest 'Never PWID, never imprisoned' compartment.

Appendix figure 2. General model flow schematic (each PWID and ex-PWID compartment includes HCV infection sub-compartments).

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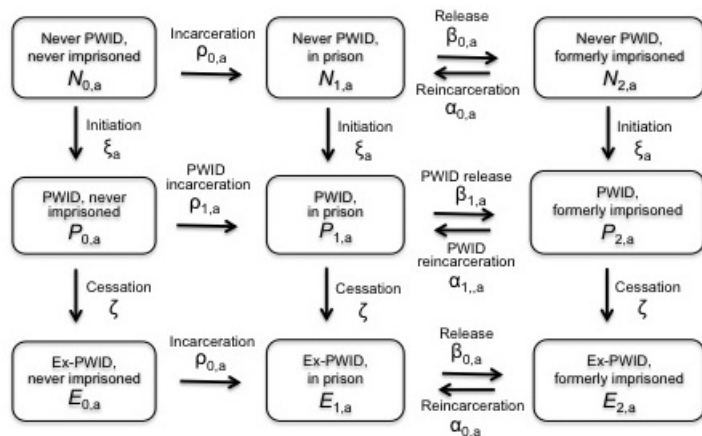


(a)



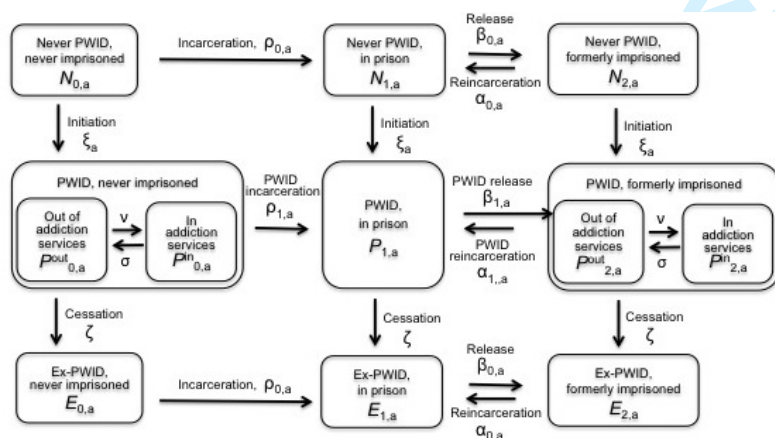
(b)

Appendix figure 3. Random effects meta-analysis results for the dried blood spot intervention effect on testing rate (proportional increase in testing rate). Results shown for (a) addiction services and (b) prison.



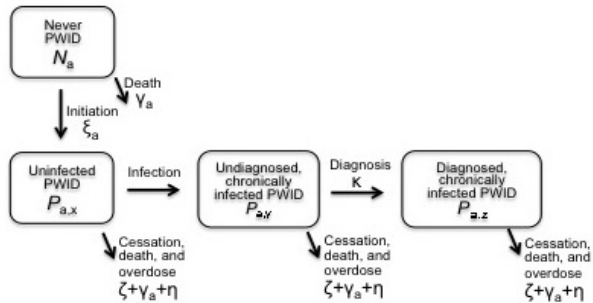
Model is stratified by age ([15-19, [20-24], [25-29], [30-54], [55-64], [65-74], [75+]), includes death from all compartments, overdose death from PWID compartments, and inflow to the youngest 'Never PWID, never imprisoned' compartment.

Appendix figure 4. Simplified model #1 schematic.



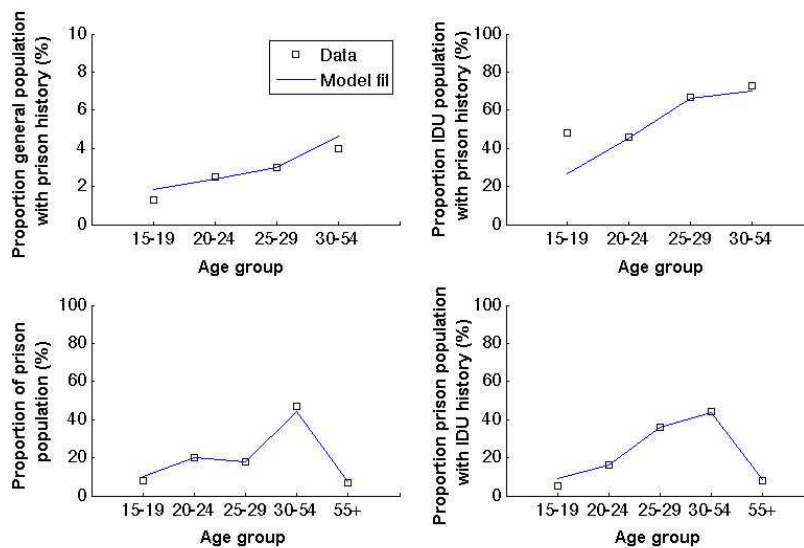
Model is stratified by age ([15-19, [20-24], [25-29], [30-54], [55-64], [65-74], [75+]), includes death from all compartments, overdose death from PWID compartments, and inflow to the youngest 'Never PWID, never imprisoned' compartment.

Appendix figure 5. Simplified model #2 schematic.

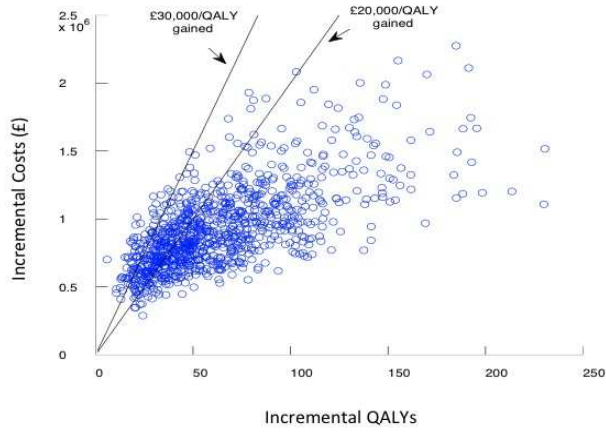


Model is stratified by age ([15-19, [20-24], [25-29], [30-54], [55-64], [65-74], [75+]) and includes inflow to the youngest [15-19] 'Never PWID' compartment.

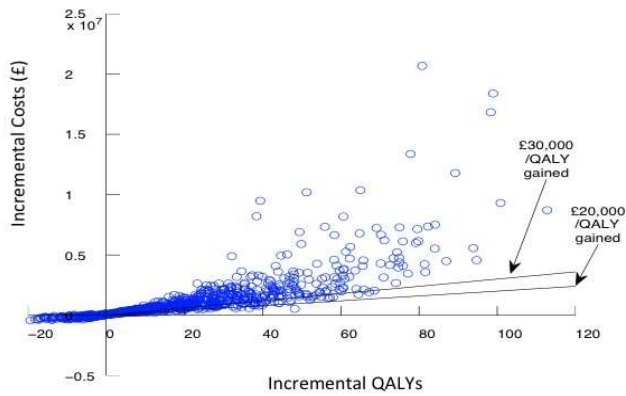
Appendix figure 6. Simplified model #3 schematic.



Appendix figure 7. Example of one characteristic model fit to the prison data (injecting duration 11 years, PWID incarceration duration 4 months, PWID overdose rate 1% per year). The top left shows the age-distributed proportion of general population with a custodial sentence. The bottom left shows the age-distribution within the prison population. The top right shows the proportion of PWID who have previously been incarcerated. The bottom right shows the proportion of prisoners who report ever PWID. Additionally, the model was fit to proportion of the general population imprisoned (simulated 0.21% as compared to 0.2%[22, 23]) and the proportion of population PWID (simulated 0.58% as compared to 0.65%[19])



(a)



(b)

Appendix figure 8. Incremental costs and incremental QALYs for each of the 1000 simulation runs. Results shown for (a) addition services and (b) prison interventions.

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	Mean value	Distribution	Reference
Transition probabilities per year (all probabilities converted to instantaneous rates)			
Mild to moderate	0.025	Beta($\alpha=38.0859, \beta=1485.3516$)	[3]
Moderate to cirrhosis	0.037	Beta($\alpha=26.905, \beta=700.2582$)	[3]
Cirrhosis to decompensated cirrhosis	0.039	Beta($\alpha=14.6168, \beta=360.1732$)	[3]
Cirrhosis/decomp. cirrhosis to HCC	0.014	Beta($\alpha=1.9326, \beta=136.1074$)	[3]
Decompensated cirrhosis/HCC to LT	0.03	Beta($\alpha=6.5256, \beta=210.9945$)	[3]
Decompensated cirrhosis to death	0.13	Beta($\alpha=147.03, \beta=983.97$)	[3]
HCC to death	0.43	Beta($\alpha=117.1033, \beta=155.23$)	[3]
LT to death	0.21	Beta($\alpha=16.2762, \beta=61.2294$)	[3]
Post transplant to death	0.057	Beta($\alpha=22.9017, \beta=378.8825$)	[3]
Health state utilities/disutilities per year			
Ex-PWID age 15-19			
Uninfected	0.94		[25]
Mild	0.77	Beta($\alpha=521.2375, \beta=155.6943$)	[3, 26]
Moderate	0.66	Beta($\alpha=168.2461, \beta=86.6723$)	[3, 26]
Cirrhosis	0.55	Beta($\alpha=47.1021, \beta=38.5381$)	[3, 26]
Decompensated cirrhosis	0.45	Beta($\alpha=123.75, \beta=151.25$)	[3, 26]
Hepatocellular carcinoma	0.45	Beta($\alpha=123.75, \beta=151.25$)	[3, 26]
Liver transplant	0.45	Beta($\alpha=123.75, \beta=151.25$)	[3, 26]
Post transplant	0.67	Beta($\alpha=59.2548, \beta=29.1852$)	[26, 27]
Mild - on treatment	0.66	Beta($\alpha=115.706, \beta=59.6063$)	[3, 26]
Moderate - on treatment	0.55	Beta($\alpha=47.1021, \beta=38.5381$)	[3, 8, 26]
Cirrhosis - on treatment	0.46	Beta($\alpha=3953, \beta=4641$)	[8]
Mild SVR	0.82	Beta($\alpha=65.8678, \beta=14.4588$)	[3, 26]
Moderate SVR	0.72	Beta($\alpha=58.0608, \beta=22.5792$)	[3, 8, 26]
Cirrhosis SVR	0.61	Beta($\alpha=58.0476, \beta=37.1124$)	[27]
PWID age 15-19			
Uninfected	0.74	Uniform(0.67,0.8)	[28]
HCV disease states		As in ex-PWID, but reduced by PropPWID [†]	Assumed
Disutility with age			
20-24	0		[25]
25-29	0.005		[25]
30-54	0.049		[25]
55-64	0.14		[25]
65-74	0.16		[25]
75+	0.21		[25]
Costs (£ per year, except where noted)			
Mild diagnosed	169	PPI [†] ×Gamma($k=25.6995, \theta=5.3698$)	[3, 26]
Moderate diagnosed	880	PPI [†] ×Gamma($k=88.8502, \theta=8.0698$)	[3, 26]
Cirrhosis diagnosed	1,397	PPI [†] ×Gamma($k=24.2342, \theta=46.9584$)	[3, 26]
Decompensated cirrhosis	11,199	PPI [†] ×Gamma($k=36.0249, \theta=253.1582$)	[3, 26]
Hepatocellular carcinoma	9,980	PPI [†] ×Gamma($k=18.1081, \theta=448.8045$)	[3]
Liver transplant (per transplant)	33,561	PPI [†] ×Gamma($k=89.7536, \theta=304.5004$)	[3]
Cost of care in year of liver transplant	11,614	PPI [†] ×Gamma($k=13.7788, \theta=686.4168$)	[3]
Post transplant	1,701	PPI [†] ×Gamma($k=15.2189, \theta=91.0053$)	[3]
Mild SVR	318	PPI [†] ×Gamma($k=28.8141, \theta=8.9887$)	[3]
Moderate SVR	880	PPI [†] ×Gamma($k=88.8502, \theta=8.0698$)	[3]
Cirrhosis SVR	1,397	PPI [†] ×Gamma($k=24.2342, \theta=46.9584$)	[3]
Undiagnosed states			
PegIFN+RBV drug only	0		
24 weeks, halved/doubled for 12/48 wks	5,320	Uniform (4788, 5852)	[29]
Treatment delivery			

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9	Ex-PWID, 12 weeks	1,912	Varied, see appendix	See appendix [3]
10	Ex-PWID, 24 weeks	2,057	Varied, see appendix	See appendix [3]
11	Ex-PWID, 48 weeks	2,326	Varied, see appendix	See appendix [3]
12	PWID, 12 weeks	2,193	Varied, see appendix	See appendix
13	PWID, 24 weeks	2,435	Varied, see appendix	See appendix
14	PWID, 48 weeks	2,900	Varied, see appendix	See appendix
15	Testing costs in all settings except prison	115.21	Uniform +/- 50%	See appendix
16	Testing costs in prison	144.21	Uniform +/- 60%	See appendix
17	PCR RNA test (if antibody positive)	73.67		[30]
18	Testing and treatment parameters			
19	Proportion PWID diagnosed (initial)	50%		[14]
20	Proportion PWID treated (initial)	0%		Assumption
21	Proportion ex-PWID diagnosed (initial)	30%	Uniform (24%, 36%)	Assumption [15]
22	Proportion of diagnosed ex-PWID treated (initial)	10%	Uniform (5%, 15%)	Estimated <10% diagnosed chronic infections [14]
23	Proportion HCV genotype 1	50%		[10, 14]
24	Sustained viral response(SVR) with pegIFN+RBV			
25	Genotype 1 mild/moderate	0.45	Uniform (0.4, 0.5)	[10, 13, 31, 32]
26	Genotype 2/3 mild/mod	0.8	Uniform (0.75, 0.85)	[10, 13, 33]
27	Genotype 1 cirrhosis	0.25	55% reduction from mild/mod	[11]
28	Genotype 2/3 cirrhosis	0.6	75% reduction from mild/mod	[11]
29	Antiviral treatment duration with pegIFN+RBV (weeks)			
30	Genotype 1 SVR	48		[10]
31	Genotype 1 non-SVR	12		[10]
32	Genotype 2/3	24		[10]
33	Distribution of PWID HCV tests			
34	GP	38.4%		§
35	Prison	11.5%		§
36	Addiction services	29.4%		§
37	Other	20.7%		§
38	Proportion who are referred and attend referral	35%	Uniform (25%, 45%)	[34, 35]
39	Proportion in referral who initiate treatment within 2 years (excl. prison)			
40	Ex-PWID	50%	Uniform(40%, 60%)	[34-37]
41	PWID	5.5%	Uniform(1%, 10%)	Assumption
42	Treatment initiation rate after 2 years in referral (excl. prison) per year			
43	Ex-PWID	10%	Uniform(5%, 15%)	Assumption
44	PWID	3%	Uniform(1%, 5%)	Assumption
45	Treatment rates in prison		Half out-of- prison rates	Assumption ⁱⁱ
46	Yield (proportion tests Ab+)			
47	GP	2.7%		§
48	Prison	14.7%		§
49	Addiction services	17.7%		§
50	Other	1.7%		§

Appendix table 1. Model parameters. [†]PropPWID=(uninfected PWID utility value for age 15-19)/(uninfected ex-PWID utility for age 15-19). [‡]PPI=Hospital and Community Health Services Pay and Prices Index inflation factor. [§]Health Protection Agency (HPA) unpublished data from the 2010 Sentinel Surveillance. ^{||}Iain Brew, HMP Leeds, unpublished data. HCC= hepatocellular carcinoma; T=liver transplant; SVR=sustained viral response; pegIFN=pegylated interferon; RBV= ribavirin

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HCV testing costs- baseline	Mean value (in 2011 £)	Distribution /notes	Units	Ref.
Assessment	1.78	1 minute (average nurse and consultant doctor cost [*])	Per test	[30]
Pre-test discussion and test	53.50	30 minutes (average nurse and consultant doctor cost [*])	Per test	[30]
Post-test results	44.58	25 minutes (average nurse and consultant doctor cost [*])	Per test	[30]
ELISA test	15.35		Per test	[30]
Additional assessment time (prison only)	29	Assuming 20 min. with nurse	Per test	Estimated from timings in [30]
Total test costs in all settings except prison	115.21	Uniform +/- 50%	Per test	
Total test costs in prison setting	144.21	Uniform +/- 60% [†]	Per test	
PCR RNA test (if antibody positive)	73.67		Per year	[30]

Appendix table 34. Baseline HCV testing costs. ^{*} Assuming a consultant cost per hour of £127, and a staff-nurse cost per patient contact hour of £87 (median estimate for band 5 GP nurse, used as higher than estimate of £84 per hour for same band hospital day ward nurse) as found in the Unit Costs of Health and Social Care 2011[43]. [†] Greater uncertainty surrounding costs of testing in prison is due to uncertainty surrounding method of test offer (on prison entry, BBV/sexual health screening, or during routine health check).

HCV antiviral treatment costs	Mean value (in 2011 £)	Distribution	Ref.
PegIFN+RBV drug only			
12 weeks	2,660*	Halved from sampled cost at 24 wks	[29]
24 weeks	5,320*	Uniform (4788, 5852)	[29]
48 weeks	10,640*	Doubled from sampled cost at 24 wks	[29]
Treatment delivery			
12 weeks			
Staff	307	Varied by staff cost variation [†]	[3]
Tests	1,605	Varied by test cost variation [‡]	[3]
24 weeks			
Staff	374	Varied by staff cost variation [†]	[3]
Tests	1,683	Varied by test cost variation [‡]	[3]
48 weeks			
Staff	504	Varied by staff cost variation [†]	[3]
Tests	1,822	Varied by test cost variation [‡]	[3]
Additional treatment delivery for PWID			
PWID extra nurse time			
12 weeks	129	Varied by staff cost variation [†] and PWID staff time variation [§]	[1]"
24 weeks	159		[1]"
48 weeks	220		[1]"
PWID extra basic assessments			
12 weeks			
Staff	58	Varied by test cost variation [‡] , staff cost variation [†] , and PWID staff time variation [§]	[1]"
Tests	43		[1]"
24 weeks			
Staff	97		[1]"
Tests	71		[1]"
48 weeks			
Staff	174		[1]"
Tests	129		[1]"
PWID psychiatric visits	51	Varied by staff cost variation [†] and PWID staff time variation [§]	[1]"

Appendix table 42. HCV antiviral treatment costs. *Average peginterferon cost between alfa-2a (Pegasys) and alfa-2b(ViraferonPeg), and average ribavirin cost between Copegus and Rebetol. [†]Test value calculated by multiplying mean test cost with a test cost variation parameter, uniformly sampled between 0.8 and 1.2. [‡]Staff value calculated by multiplying mean staff cost by a staff cost variation parameter, uniformly sampled between 0.8 and 1.2. [§]PWID staff cost calculated by multiplying mean staff cost by a staff cost variation parameter and an extra PWID staff time variation parameter (both uniformly sampled between 0.8 and 1.2). "Graham Foster, Consultant Hepatologist, *personal communication*. pegIFN=pegylated interferon; RBV=ribavirin.

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	Model	Input parameters	Data used to fit model	Parameters estimated through model fitting
Fit #1	Simplified model 1 (Appendix figure 2)	<ul style="list-style-type: none"> • Sampled cessation rate • Sampled overdose rate • Sampled PWID prison release rate • Death rates by age • Prison release rate for never-PWID or ex-PWID by age • Injecting initiation age distribution • (Rough estimate) entry rate of never-PWID aged 15-19. 	<ul style="list-style-type: none"> • Proportion general population with a custodial sentence by age • Proportion of PWID population previously imprisoned by age • Age distribution of current prisoners • Proportion of prisoners ever-PWID by age • Proportion of the population currently imprisoned • Prevalence of PWID in general population 	<ul style="list-style-type: none"> • Incarceration rates by age • Re-incarceration rates by age • PWID incarceration rates by age • PWID re-incarceration rates by age • Injecting initiation rate
Fit #2	Simplified model 2 (Appendix figure 4)	<ul style="list-style-type: none"> • Input and output parameters from Fit #1 • Sampled addiction services duration • (Rough estimate) entry rate of never-PWID aged 15-19. 	<ul style="list-style-type: none"> • Proportion PWID in contact with addiction services 	<ul style="list-style-type: none"> • Recruitment rate into addiction services
Fit #3	Simplified model 3 (Appendix figure 5)	<ul style="list-style-type: none"> • Sampled cessation rate • Sampled overdose rate • Death rates by age • Injecting initiation age distribution • Fit injecting initiation rate (Fit #1) • (Rough estimate) entry rate of never-PWID aged 15-19. 	<ul style="list-style-type: none"> • Proportion PWID diagnosed 	<ul style="list-style-type: none"> • Overall (not setting-specific) PWID testing rate
Fit #4	Full model (figures 1 and 2 of the main text) without ex-PWID	<ul style="list-style-type: none"> • All model parameters from Fits #1-3 and sampled sets. • (Rough estimate) entry rate of never-PWID aged 15-19. 	<ul style="list-style-type: none"> • HCV PWID chronic prevalence 	<ul style="list-style-type: none"> • Infection rate, π
Fit #5	Full model	<ul style="list-style-type: none"> • All model parameters from Fits #1-4 and sampled sets. 	<ul style="list-style-type: none"> • Total population size (fit to 1000 PWID) 	<ul style="list-style-type: none"> • Entry rate of never-PWID in the 15-19 age group

Appendix table 53. Model fitting procedure summary

Telaprevir/boceprevir scenario parameters	Value	Units	Notes	Ref.
Proportional increase in SVR for genotype 1 patients	68%	-		[44, 45]
Average duration of treatment for genotype 1	37	weeks	Assume 50% have a rapid viral response (RVR) and only require 26 weeks treatment (24 weeks telaprevir, 28 weeks boceprevir). The remaining 50% require 48 weeks. In trials, 58-65% achieve RVR.	[44, 45]
Telaprevir or boceprevir drug cost only (pegIFN+RBV cost additional)	£19,600	per treatment	Mean cost between telaprevir (12 weeks, £22,398) and boceprevir (24 weeks, £16,800). Cost in addition to 37 weeks pegIFN+RBV (sampled as in table 1 of main text)	[46, 47]

Appendix table 64. Telaprevir/boceprevir sensitivity analysis parameters. pegIFN=pegylated Interferon; RBV=ribavirin; RVR=rapid viral response; SVR=sustained viral response.

Health state utilities/disutilities per year	Mean	Distribution	Ref.
Ex-PWID			
Mild diagnosed [age 15-19]	0.77	Beta($\alpha=521.2375$, $\beta=155.6943$)	[3, 26]
Moderate diagnosed [age 15-19]	0.66	Beta($\alpha=168.2461$, $\beta=86.6723$)	[3, 26]
Compensated cirrhosis diagnosed [age 15-19]	0.55	Beta($\alpha=47.1021$, $\beta=38.5381$)	[3, 26]
Undiagnosed stages		Diagnosed state utility value + 0.09	[28]
Mild SVR [age 15-19]	0.82	Beta($\alpha=65.8678$, $\beta=14.4588$)	[3, 26]
Moderate SVR [age 15-19]	0.72	Beta($\alpha=58.0608$, $\beta=22.5792$)	[3, 8, 26]
Compensated cirrhosis SVR [age 15-19]	0.61	Beta($\alpha=58.0476$, $\beta=37.1124$)	[27]
PWID			
HCV disease states		As in ex-PWID, but reduced by PropPWID [†]	Assumed

Appendix table 75. Disutility on diagnosis sensitivity analysis parameters
[†]PropPWID=(uninfected PWID utility value for age 15-19)/(uninfected ex-PWID utility for age 15-19).
 SVR=sustained viral response.

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10 [1] Martin NK, Miners A, Vickerman P, Foster G, Hutchinson S, Goldberg D, et al. The
11 cost-effectiveness of HCV antiviral treatment for injecting drug user populations.
12 *Hepatology* 2012;55:49-57.
- 13 [2] Micallef JM, Kaldor JM, Dore GJ. Spontaneous viral clearance following hepatitis C
14 infection: a systematic review of longitudinal studies. *J Viral Hepat* 2006;13:34-41.
- 15 [3] Shepherd J, Jones J, Hartwell D, Davidson P, Price A, Waugh N. Interferon alfa
16 (pegylated and non-pegylated) and ribavirin for the treatment of mild chronic hepatitis C: a
17 systematic review and economic evaluation. *Health Technology Assessment* 2007;11:1-224.
- 18 [4] Martin NK, Vickerman P, Foster GR, Hutchinson SJ, Goldberg DJ, Hickman M. Can
19 antiviral therapy for hepatitis C reduce the prevalence of HCV among injecting drug user
20 populations? A modelling analysis of its prevention utility. *Journal of Hepatology*
21 2011;54:1137-1144.
- 22 [5] Martin NK, Vickerman P, Hickman M. Mathematical modelling of Hepatitis C
23 Treatment for Injecting Drug Users. *Journal of Theoretical Biology* 2011;274:58-66.
- 24 [6] Vickerman P, Hickman M, May M, Kretzschmar M, Wiessing L. Can hepatitis C virus
25 prevalence be used as a measure of injection-related human immunodeficiency virus risk in
26 populations of injecting drug users? An ecological analysis. *Addiction* 2009;105:311-318.
- 27 [7] Sutton AJ, Gay NJ, Edmunds WJ, Andrews NJ, Hope VD, Gilbert RL, et al. Modelling
28 the hepatitis B vaccination programme in prisons. *Epidemiol Infect* 2006;134:231 - 242.
- 29 [8] Sutton AJ, Edmunds WJ, Sweeting MJ, Gill ON. The cost-effectiveness of screening
30 and treatment for hepatitis C in prisons in England and Wales: a cost-utility analysis. *Journal*
31 *of Viral Hepatitis* 2008;15:797-808.
- 32 [9] Hickman M, McDonald T, Ali J, Nichols T, Hope V, Skidmore S, et al. Increasing the
33 uptake of hepatitis C virus testing among injecting drug users in specialist drug treatment
34 and prison settings by using dried blood spots for diagnostic testing: a cluster randomized
35 controlled trial. *Journal of Viral Hepatitis* 2008;15:250-254.
- 36 [10] NICE. Peginterferon alfa and ribavirin for the treatment of mild chronic hepatitis C:
37 National Institute for Health and Clinical Excellence; 2006.
- 38 [11] Bruno S, Shiffman M, Roberts SK, Gane EJ, Messinger D, Hadziyannis SJ, et al. Efficacy
39 and Safety of Peginterferon Alfa-2D (40KD) Plus Ribavirin in Hepatitis C Patients with
40 Advanced Fibrosis and Cirrhosis. *Hepatology* 2010;51:388-397.
- 41 [12] Hellard M, Sacks-Davis R, Gold J. Hepatitis C Treatment for Injection Drug Users: A
42 Review of the Available Evidence. *Clinical Infectious Diseases* 2009;49:561-573.
- 43 [13] Aspinall A, Corson S, Doyle J, Grebely J, Hutchinson S, Dore GJ, et al. Treatment of
44 hepatitis C virus among people who are actively injecting drugs: a systematic review and
45 meta-analysis. *Clinical Infectious Diseases* 2013;(in press).
- 46 [14] Health Protection Agency Colindale. Hepatitis C in the UK 2011; July 2011.
- 47 [15] Health Protection Agency. Data tables of the Unlinked Anonymous Monitoring
48 Survey of HIV and Hepatitis in Injecting Drug Users Surveillance Update: July 2011; 2011.
- 49 [16] Turner K, Hutchinson S, Craine N, Hope V, Palmateer N, Vickerman P, et al. The
50 impact of needle and syringe provision and opiate substitution therapy on the incidence of
51 Hepatitis C virus in injecting drug users: pooling of UK evidence. *Addiction* 2011;106:1978-
52 1988.
- 53
54
55
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4
5
6
7 [17] Hickman M, Hope V, Brady T, Madden P, Jones S, Honor S, et al. Hepatitis C virus
8 (HCV) prevalence, and injecting risk behaviour in multiple sites in England in 2004. *Journal of*
9 *Viral Hepatitis* 2007;14:645-652.
- 10 [18] Cornish R, Macleod J, Strang J, Vickerman P, Hickman M. Risk of death during and
11 after opiate substitution treatment in primary care: prospective observational study in UK
12 General Practice Research Database. *BMJ* 2010;341.
- 13 [19] Harris RJ, Ramsay M, Hope VD, Brant L, Hickman M, Foster GR, et al. Hepatitis C
14 prevalence in England remains low and varies by ethnicity: an updated evidence synthesis.
15 *European Journal of Public Health* 2011;Epub ahead of print.
- 16 [20] Prime J, White S, Liriano S, K P. Criminal careers of those born between 1953 and
17 1978, England and Wales: Home Office, Statistical Bulletin; 2001.
- 18 [21] Ministry of Justice. Offender Management Statistics Quarterly Bulletin, April to June
19 2011, England and Wales; 2011.
- 20 [22] Ministry of Justice. Population in Custody Tables August 2010; 2010.
- 21 [23] Office for National Statistics. Population Estimates for UK, England and Wales,
22 Scotland and Northern Ireland, Mid-2010; 2010.
- 23 [24] Carroll RJ, Ruppert D. Transformation and Weighting in Regression: Chapman and
24 Hall; 1988.
- 25 [25] Kind P, Hardman G, Macran S. UK Population Norms for EQ-5D: University of York;
26 2008.
- 27 [26] Wright M, Grieve R, Roberts J, Main J, HC T. Health benefits of antiviral therapy for
28 mild chronic hepatitis C: randomised controlled trial and economic evaluation. *Health*
29 *Technol Assess* 2006;10.
- 30 [27] Hartwell D, Jones J, Baxter L, Shepherd J. Peginterferon alfa and ribavirin for chronic
31 hepatitis C in patients eligible for shortened treatment, re-treatment, or in HCV/HIV co-
32 infection: a systematic review and economic evaluation. *Health Technol Assess* 2011;15:1-
33 210.
- 34 [28] McDonald S, Hutchinson SJ, Palmateer N, Allen E, Cameron S, Goldberg D, et al.
35 Decrease in health-related quality of life associated with awareness of hepatitis C virus
36 infection among people who inject drugs in Scotland. *Journal of Hepatology* 2013;58:460-
37 466.
- 38 [29] British Medical Association. British National Formulary, number 62: BMJ Publishing
39 Group; 2011.
- 40 [30] Stein K, Dalziel K, Walker A, Jenkins B, Round A, Royle P. Screening for Hepatitis C in
41 injecting drug users: A cost utility analysis. *Journal of Public Health* 2004;26:61-71.
- 42 [31] Hadziyannis SJ, Sette H, Morgan TR, Balan V, Diago M, Marcellin P, et al.
43 Peginterferon- α 2a and Ribavirin Combination Therapy in Chronic Hepatitis C. *Annals of*
44 *Internal Medicine* 2004;140:346-355.
- 45 [32] McHutchison JG, Lawitz EJ, Shiffman ML, Muir AJ, Galler GW, McCone J, et al.
46 Peginterferon Alfa-2b or Alfa-2a with Ribavirin for Treatment of Hepatitis C Infection. *New*
47 *England Journal of Medicine* 2009;361:580-593.
- 48 [33] Shiffman ML, Suter F, Bacon BR, Nelson D, Harley H, Sola R, et al. Peginterferon Alfa-
49 2a and Ribavirin for 16 or 24 Weeks in HCV Genotype 2 or 3. *N Engl J Med* 2007;357:124-
50 134.
- 51 [34] Irving WL, Smith S, Cater R, Pugh S, Neal KR, Coupland CAC, et al. Clinical pathways
52 for patients with newly diagnosed hepatitis C - What actually happens. *Journal of Viral*
53 *Hepatitis* 2006;13:264-271.
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5
6
7 [35] Castelnuovo E, Thompson-Coon J, Pitt M, Cramp M, Siebert U, Price A, et al. The
8 cost-effectiveness of testing for hepatitis C in former injecting drug users. Health
9 Technology Assessment 2006;2006:32.
- 10 [36] Jowett SL, Agarwal K, Smith BC, Craig W, Hewett M, Bassendine DR, et al. Managing
11 chronic hepatitis C acquired through intravenous drug use. Q J Med 2001;94:153-158.
- 12 [37] Foster G, Goldin RD, Main J, Murray-Lyon I, Hargreaves S, Thomas HC. Management
13 of chronic hepatitis C: clinical audit of biopsy based management algorithm. BMJ
14 1997;315:453-458.
- 15 [38] Sweeting MJ, De Angelis D, Ades AE, Hickman M. Estimating the prevalence of ex-
16 injecting drug use in the population. Stats Meth Med Res 2009;18:381-395.
- 17 [39] Vickerman P, Miners A, Williams J. Assessing the cost-effectiveness of interventions
18 linked to needle and syringe programmes for injecting drug users. In: NICE, editor. London;
19 2008.
- 20 [40] Taylor A, Munro A, Allen E, Dunleavy K, Cameron S, Miller L, et al. Low incidence of
21 hepatitis C virus among prisoners in Scotland. Addiction 2013;108:1296-1304.
- 22 [41] Government Actuary's Department. Interim life tables 1980-82 to 2004-06: Office for
23 National Statistics.
- 24 [42] Hay G, Gannon M, MacDougall J, Eastwood C, Williams K, Millar T. Capture-recapture
25 and anchored prevalence estimation of injecting drug users in England: national and
26 regional estimates. Statistical Methods in Medical Research 2009;18:323-339.
- 27 [43] Personal Social Services Research Unit. Unit Costs of Health and Social Care 2011:
28 University of Kent; 2011.
- 29 [44] Jacobson IM, McHutchison JG, Dusheiko G, Di Bisceglie AM, Reddy KR, Bzowej NH, et
30 al. Telaprevir for Previously Untreated Chronic Hepatitis C Virus Infection. N Engl J Med
31 2011;364:2405-2416.
- 32 [45] Poordad F, McCone J, Bacon BR, Bruno S, Manns MP, Sulkowski MS, et al. Boceprevir
33 for Untreated Chronic HCV Genotype 1 Infection. N Engl J Med 2011;364:1195-1206.
- 34 [46] NELM.NHS.UK Press Release. Janssen Cilag launches telaprevir (Incivo) 375mg tablets
35 for the treatment of genotype 1 chronic hepatitis c. 2011 [cited; Available from:
36 <http://www.nelm.nhs.uk>
- 37 [47] NELM.NHS.UK Press Release. MD launches boceprevir (Victrelis) for the treatment of
38 chronic hepatitis C in the UK. 2011 [cited; Available from: <http://www.nelm.nhs.uk>
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