ALCOHOL DRUG FINDINGS *Research analysis*

Hepatitis C virus treatment as prevention among injecting drug users: who should we cure first?

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In the UK context, this study's findings imply that to prevent new cases it is best to focus expensive new treatments for hepatitis C infection on injectors who infrequently share their injecting equipment – patients most likely to be found and recruited via needle exchanges and addiction treatment services.

SUMMARY Blood-borne infections such as hepatitis C can be spread by the sharing of contaminated injecting equipment. Individuals infected with hepatitis C can be cured through antiviral treatments, a prospect made more realistic by the new range of more easily tolerated and more rapidly acting medications. Not only does cure forestall the development of severe liver disease, it also means that (barring re-infection) the injector will no longer be able to spread the virus to others.

However, only a small proportion of infected injectors are treated for their infection, and in most settings, universal treatment is not possible due to financial constraints or shortcomings in systems for accessing and providing treatment. Since the new treatment options are very expensive, it is important to consider how to optimise their benefits, not just for the patient, but for the entire population of injectors.

One strategy might be to target treatment at injectors depending on how likely they are to transmit the virus. New infections are most likely to be averted by curing 'high-risk' injectors who often share their injecting equipment, but they are also most likely to become re-infected, limiting the benefits of their treatment for themselves and for injectors as a whole. Through a simulation model based on what is known about the relevant factors, the featured study assessed the expected impact of such targeting on numbers of new infections when hepatitis C infection was more or less prevalent among injectors. The focus was on the expected impact of the newer treatments, but (not reported here) the study also assessed the older treatments.

Key points
From summary and commentary

A simulation model based on what is known about the relevant factors assessed the expected impact on new infections of targeting treatment for hepatitis C infection at injectors at different degrees of risk of spreading the disease.

Under core assumptions, where fewer than a third of injectors are already infected or fewer than half syringes contaminated, new infections are best averted by treating injectors who frequently risk infection by sharing injecting equipment; when the virus is more widespread, low-risk injectors are the best target.

These conclusions are dependent on assumptions which may not be realistic or valid in the UK context.

First the model estimates the 'steady state' proportion of injectors who would currently be infected depending on rates of sharing of injecting equipment among that injecting population. The critical next stage estimates how much the number of new infections would fall if one of the infected injectors is treated for their infection, and how this impact would differ if they were at high versus low risk of spreading infection. Based on surveys of injectors, the analysis assumed that high-risk injectors share injecting equipment (both giving and receiving) about seven times more frequently than low-risk injectors. The resulting computations include infections prevented further down the transmission chain; those not infected by the focal patient will not infect others, who (unless they become infected by other people) will in turn not be able to spread infection.

Main findings

In essence the implications of the findings were that when the virus is relatively uncommon among injectors, it is best to cure infected high-risk injectors. When it is relatively common, low-risk injectors are the preferred target.

Based on core assumptions, when 32% of the injectors in a population are infected with hepatitis C, the preventive impact of treating one high-risk injector equals that of treating a low-risk injector; in each case, just under one new infection is averted. When the virus is *less* common, the number of averted infections progressively rises to two, but rises more steeply if a high-risk injector is treated, making this the better prevention choice. On the other side of the graph, as the virus becomes *more* common, the number of infections prevented falls, by definition reaching zero when everyone is already infected. However, it falls more slowly if a low-risk injector is treated, reversing the preferred prevention choice to treating relatively low-risk injectors.

This reversal happens because when the virus is rare, the benefits of preventing high-risk injectors spreading it to many people outweighs the risk that they themselves will become re-infected. When the virus is already very common, few injectors are left to be infected, partially neutralising the virus-spreading potential of higher risk injectors. Then it becomes best to treat lower risk injectors who are less likely to become re-infected.

Alternative assumptions

The scenarios above were based on the proportion of injectors currently infected. Another way to express the prevalence of the virus is as the proportion of *syringes* in circulation among injectors which carry the virus, a metric more directly related to the chances of becoming infected. Based on core assumptions, when 32% of injectors are infected – the 'break-even' point when preventive impacts are the same for high- and low-risk injectors – at the same time 50% of syringes will be contaminated. Unlike the proportion of injectors, the break-even point expressed as a proportion of syringes remains unchanged by variations in transmission and progression risks, the success rate or

duration of treatment, and the distribution of risk behaviour levels within the population of injectors

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One of the core assumptions behind these calculations is that injectors share injecting equipment with other injectors regardless of their respective risk levels. An alternative assumption is that they tend to share with people at the same risk level as themselves. The more they do so, the greater the range of prevalence levels of the virus at which it is best to treat low-risk injectors to prevent further spread, and the greater the advantage of treating low-risk versus higher risk injectors. For example, if 70% of the sharing events occur with people at the same risk level as oneself, treating low-risk injectors becomes preferable when just over 20% rather than over 32% of injectors are infected, and at around the infection prevalence rate in the UK (about 40%), the extra benefit of treating a low-risk versus a high-risk injector becomes substantially greater than under core assumptions.

Another core assumption is that even after being treated for their infection, few injectors stop injecting, and sharing injecting equipment continues, risking re-infection. If instead treatment of infection is combined with successful treatment of addiction, or other interventions which prevent any further sharing of injecting equipment, the risk of re-infection becomes zero. With their higher tendency to become re-infected taken out of the equation, in this scenario it is always best in prevention terms to treat the infections of high-risk injectors, no matter how prevalent the virus. To the extent that interventions fail to prevent further sharing, the preference for treating low-risk injectors at high prevalence levels becomes reinstated.

The authors' conclusions

Targeting treatment of hepatitis C infection according to how often the patient shares injecting equipment could enhance the preventive impacts of the treatment. In the past, treatment has been withheld from active injectors partly on the basis that may become re-infected. Though this may happen, treating injectors at high risk of acquiring and spreading infection may nevertheless be the optimal strategy when fewer than half the syringes in circulation are contaminated, equivalent under core assumptions to fewer than about a third of injectors being already infected. High-risk injectors may also be the preferred target if at the same time as treating infection, effective measures taken to prevent further risky sharing. When more than half of all syringes are contaminated, it becomes preferable to treat lower risk injectors.

Such a strategy depends on being able to identify the risk level of prospective patients, and on their access to treatment and their willingness to be treated. High-risk injectors might, for example, be found in specific venues such as 'shooting galleries', homeless shelters or prisons. Lower risk injectors might be concentrated among those already participating in harm-reduction interventions.

Because of the stability of the implications despite varying scenarios, the best way to decide on who to target first is not to assess the proportion of injectors infected, but the proportion of syringes contaminated with the virus, especially if this can be measured among all syringes, not just those handed in at syringe exchanges.

These considerations relate only to preventive impact, not the benefits of treating an individual's infection, regardless of whether this prevents other people becoming infected. Generally however, added preventive benefit would still make targeting of the kind recommended above the preferred strategy, though this could alter in certain circumstances, such as in the treatment of people already suffering substantial liver damage.

One factor which would alter the advisability of targeting is whether injectors often switch risk levels, sometimes sharing frequently, other times relatively infrequently. In another study, the authors of the featured study calculated that if injectors switched between low- and high-risk behaviour more than once every 20 months, targeting would no longer enhance preventive effects.

FINDINGS COMMENTARY A commentary on the featured analysis asked whether the strategy of picking who to treat – and by implication who *not* to – is ethical. Though arguing that universal access to health care is a human right, the authors acknowledged that the "prohibitively high cost" of new treatments for chronic hepatitis C infection mean not everyone can be treated. It is, however, possible to reconcile on the one hand not *refusing* treatment to anyone with chronic infection, with on the other actively trying to find certain categories of infected injectors to engage in treatment in order to maximally save others also becoming infected.

The featured analysis suggests that when (as in the UK) about 40% of injectors are already currently infected, in preventive terms it is best to target injectors who share their injecting equipment infrequently compared to other injectors – patients most likely to be found and recruited via needle exchanges and addiction treatment services. However, at 40% prevalence the extra benefit is slight and depends on higher risk injectors forfeiting their otherwise preferential position because they are highly likely to be become re-infected after being treated. There is evidence this risk has been over-estimated, undermining the implication of the featured analysis that in countries like the UK, low-risk injectors are the preferred target.

Further undermining any targeting strategy is the instability in how often an individual shares injecting equipment. This instability could, argued the commentary, be such that any remaining extra preventive benefits from targeting treatment are not worth the resources it would take to do the targeting. Instability is likely to be at its greatest when injectors frequently cycle in and out of treatment – not unusual in Britain.

In Australia a study which assumed that 60% of injectors were infected with hepatitis C calculated that for maximum reduction of the prevalence of the virus among injectors, treatment for hepatitis C infection should be focused on the equivalent of what the featured study termed high-risk injectors – those out of treatment and injecting and sharing at about eight times the rate of injectors engaged in methadone treatment. This result seems at odds with the featured study's preference for low-risk injectors at the same prevalence level, though much depends on the assumptions fed in to the models.

For more on the prevention of the spread of hepatitis C see the Effectiveness Bank hot topic.

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