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▶ **Opiate substitution treatment and HIV transmission in people who inject drugs: systematic review and meta-analysis.**

MacArthur G.J., Minozzi S., Martin N. et al.
BMJ: 2012, 345. e5945.



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The first study to synthesise the relevant evidence adds weight to the conclusion that methadone programmes protect dependent opiate injectors against HIV infection, and that the evidence in their favour is more convincing than for alternative types of treatments.

SUMMARY Drug injectors are vulnerable to infection with HIV and other blood-borne viruses due to shared use of injecting equipment as well as sexual behaviour. This review aimed to assess the degree to which this risk is affected by [opioid](#) maintenance and detoxification programmes involving the prescription of opiate-type drugs such as methadone to dependent injectors to reduce their reliance on illegal drugs such as heroin.

Previous reviews (notably a recent [Cochrane systematic review](#)) have generally concluded that by reducing the number of injections and the sharing of injecting equipment, opioid maintenance programmes reduce cases of HIV infection. However, these reviews have been based on a small number of primary studies with limited numbers of participants, and to date no review has attempted to amalgamate results into a unified estimate of the effect of opioid prescribing programmes on HIV transmission. The featured review and [meta-analysis](#) aimed to fill this gap in the literature. Importantly, it focused on actual HIV infections, not changes in risk behaviour thought to affect the risk of infection.

The analysts looked not just for trials which randomly allocated patients to opioid prescribing versus other (or no) programmes, but also for studies which followed up patients entering opioid prescribing programmes in the normal way and assessed whether they were less likely than other more or less comparable patients to become infected with HIV. Even if this was not the main purpose of the study, the full text was read in case it mentioned a link with prescribing programmes. Researchers who had followed up injectors and recorded HIV infections but did not in their reports mention the association with prescribing programmes were contacted to see if nevertheless they had collected this data.

In the event, none of the 15 studies found by this comprehensive search were randomised trials, and all assessed the impact of methadone treatment rather than the prescribing of buprenorphine or other medications. In the absence of randomisation, all the studies were highly vulnerable to their results reflecting not the impact of prescribing programmes, but pre-existing differences in the motivations of injectors who did versus did not enter methadone programmes, or in their abilities to avoid infection, including perhaps their use of other services such as needle exchanges. Just six of the studies attempted to improve comparability by adjusting their results for known and relevant differences between their opioid prescribing patients and comparison injectors.

Over 26,738 person-years of follow-up, the 15 studies documented 1,016 new HIV infections among injectors in the USA, Canada, the UK, The Netherlands, Austria, Italy, Thailand, Puerto Rico and China. It was expected that such different contexts and studies would produce varying estimates of the link between prescribing programmes and HIV infection, so their results were amalgamated on the basis that the resulting figure did not represent a true assessment of the link which varied only by chance, but that the strength of the link really did vary in different contexts. Reasons for this variation were explored including geographical region, monetary incentives to participate in the study, where and how participants were recruited to the study (eg, at a clinic, also by outreach, or in non-treatment settings), length of treatment, and proportions of women and ethnic minorities in the caseloads.

Main findings

Most studies assessed methadone maintenance as one of a range of factors possibly affecting risk of HIV infection, and most found the treatment was associated with a lower risk. Of the 15 studies, data could be pooled from nine which documented 819 HIV infections over 23,608 person-years of follow-up.

These studies mainly sampled men (61–92%) and participants were typically aged 26 to 30. Proportions

Key points

This review amalgamated results from relevant studies to assess the degree to which risk of HIV infection is affected by [opioid](#) maintenance and detoxification programmes such as methadone maintenance.

It found methadone maintenance was associated with a statistically significant 54% reduction in the risk of HIV infection, which varied substantially between the studies. Methadone detoxification was not associated with a lower risk of infection.

These results are the plausible consequence of methadone maintenance reducing the number of occasions during which a virus can be transmitted by reducing the number of times patients inject and re-use other injectors' equipment.

However, none of the studies had sought to eliminate other influences on infection risk by randomly allocating patients to methadone programmes versus no or alternative treatments.

These studies mainly sampled men (81-93%) and participants were typically aged 20 to 39. Proportions of patients who became infected varied substantially across the studies, so rather than pooling results in terms of numbers of infections, the analysts calculated how much bigger or smaller the proportion of prescribing patients was who became infected each year, compared to the proportion of comparison injectors. For example, if over five years 10 out of 100 comparison injectors became infected but just 5 patients of methadone programmes, the reduction in the rate of infection would have been 50%. It would remain 50% if the respective numbers of infections were 2 and 1 or 50 and 25, evening out differences in the overall risk of infection in the different contexts of the studies, and leaving only a figure reflecting how much lower this risk was among methadone patients than other injectors.

On this basis, pooling results across the nine studies showed methadone maintenance programmes were associated with a statistically significant 54% reduction in the risk of HIV infection, which as expected varied substantially between the studies. Narrowing in on the six studies which attempted to adjust for differences between injectors in versus not in treatment resulted in a lower but still statistically significant estimate of a 40% reduction in risk of infection. Narrowing in on the five studies least vulnerable to bias resulted in a similar estimate.

Except for weak evidence (just two studies assessed durations over a year) that more time in methadone maintenance might be more protective against HIV than shorter times, none of the factors investigated for their possible influence on the relative effectiveness of methadone maintenance were found to have been influential.

The review also looked for detoxification studies which used reducing doses of methadone or other opioid medications to withdraw patients from opiate-type drug use and assessed possible impacts on HIV infection. The four relevant studies all concerned methadone-based detoxifications, and three compared these treatments against no treatment at all. Among these three, there was no evidence that detoxification was associated with a decreased risk of HIV infection – in fact, the reverse: risk was significantly and substantially higher among detoxification patients. The comparator in the remaining study was methadone maintenance, and this was non-significantly associated with a slightly lower risk of infection than detoxification using the same medication.

The authors' conclusions

The findings highlight the important protective effect of methadone treatment (and probably too other similar treatments such as buprenorphine maintenance) in the prevention of HIV among opiate injectors. Such treatment is associated with an average 54% reduction in the risk of new HIV infections, and treatments lasting over a year may be yet more protective. In contrast, there was no evidence that methadone detoxification is associated with a reduction in the risk of HIV transmission.

Conclusions in respect of methadone maintenance are consistent with those of a [Cochrane systematic review](#). The current assessment extends and strengthens this conclusion by basing it on 11 more studies and an additional 924 cases of new HIV infection occurring during an additional 25,660 person years of follow-up, and by amalgamating the results.

Methadone maintenance probably exerts its protective effect via its [established ability](#) to reduce the frequency of injecting, the sharing of injecting equipment, and overall drug-related HIV risk. Involvement in such treatment, as part of a package of interventions, might also increase engagement with health services and access to care and services focused on HIV prevention. Also, injectors already infected with HIV comply better and respond better to anti-AIDS treatments if they are in [opioid](#) prescribing programmes, which might reduce the likelihood of their transmitting infection.

Methadone maintenance can act synergistically with needle exchange programmes and anti-AIDS treatments to more effectively protect against new cases of infection than any one of these interventions on their own.

Despite strong associations and plausible mechanisms through which opioid prescribing might protect against HIV, a major limitation of this analysis is that all the studies on which it was based simply followed up people entering treatment in the normal way rather than randomly allocating them to opioid prescribing versus an alternative. Many of the included studies did not attempt to adjust for differences between patients who did and did not enter methadone programmes; those which did adjust still produced findings consistent with a strong (if somewhat weakened) protective effect of methadone maintenance. Also, the possibility cannot be discounted that part of the impact of opioid prescribing programmes is attributable to additional interventions such as attendance at needle exchange programmes, psychosocial interventions, practical support, or supervised injection facilities.

FINDINGS COMMENTARY The main [predecessor review](#) explained in detail why “Combined totals have not been calculated for any of the analyses included in this review as the studies varied in a number of aspects and most studies were associated with a high risk of bias ... making the validity of combined totals doubtful.” With perhaps just as variable a set of studies, the featured analysis took a different line, amalgamating the results but at the same time trying to account for the variation between the studies, which was substantial. This variation means that the estimated risk-reduction figure cannot be relied on as a guide to what can be expected of any particular methadone programme, but varies significantly with the context.

Despite variation in the size and statistical significance of the link, every single study uncovered after what appears to have been an exhaustive search found methadone maintenance associated with a reduced risk of becoming infected with HIV. The consistency of the results is reassuring, but no substitute for rigorous studies which can eliminate the sources of bias inevitable when patients and services choose or choose not to engage in treatment. This means the results may instead have been due to other factors. Perhaps, for example, injectors particularly stable and motivated to avoid infection are the ones who choose to enter and get accepted by methadone programmes – patients who might have avoided infection anyway through other means such as needle exchange or restricting their sharing of injecting equipment; the next paragraph offers an illustration of the problems. Despite these caveats, for the reasons explained below, it seems near certain that on average methadone maintenance, and probably too similar programmes using other opiate-type medications, do protect dependent opiate injectors against HIV, and that the evidence in their favour is more convincing than for other types of treatments for these patients.

An illustration of the possible sources of bias is provided by [the US study](#) which registered the largest risk-reduction among the reviewed studies, and was one of the six which adjusted its results for differences between the patients. Set in Philadelphia, it recruited patients from the largest local methadone programme, but nearly half those randomly sampled and initially asked to join the study did not, leaving a question mark over how representative the final sample (others were selected to replace them) was of the entire caseload. Their HIV infection record over the next 18 months

(injectors were selected to replace them) was of the entire caseload. Their HIV infection record over the next 10 months was compared against opiate injectors who despite being contacted in the area surrounding the clinic and in contact with its patients who referred them to the study, had not been in treatment for at least the past 10 months. All but a few rejected treatment throughout the study despite being encouraged by the researchers and treatment being readily available. How representative they were of the city's out-of-treatment injectors is unclear, but the biggest concern is that they must have differed materially from the patients – the reasons why they had not been in treatment while the patients had. Even on some of the variables assessed by the study, the two sets of injectors did differ significantly, but missing from this analysis was any assessment of how well motivated or how well placed they were to avoid infection, regardless of their treatment status. In calculating that the risk of becoming infected versus not was over five times greater among patients consistently in methadone treatment versus those not in treatment, the analysis took in to account differences in the race, sex, age, and needle-sharing behaviour of the two sets of injectors. This may have disadvantaged methadone treatment, since one of its beneficial effects – to reduce needle-sharing – was statistically eliminated from the analysis. Nevertheless, this set of variables seems far from capturing what makes one injector more likely to become infected than another, and therefore far from evening out the playing field to reveal the true effects of being in a methadone programme.

Despite these limitations, what substantially strengthens the inference that methadone programmes really are an active ingredient in HIV prevention is that the links in the chain which would lead to such an effect have been observed and are plausible ways infection would be avoided. **Opioid** prescribing programmes **have been shown** to reduce the number of occasions during which a virus can be transmitted by reducing the number of times patients inject and – probably associated with this – the number of times they re-use other injectors' equipment, both the intended and logical results of substituting an oral drug for an injected one.

Not just about effectiveness – coverage matters

The review's findings may underestimate of overall benefits across a local population of opioid injectors. Included studies started at the point where injectors had entered opioid prescribing programmes, and assessed their risk of becoming infected. But there is another major feature of these programmes which might be crucial to risk reduction – their ability to engage large numbers of opioid users in treatment. The risk-reduction benefits identified by the analysis may not only be greater than those associated with other treatments, but they are likely to be extended to far greater numbers in areas with readily accessible opioid prescribing programmes. Across an entire population of opioid injectors, the result (identified for example **in Barcelona**) is likely to be reduced HIV-related mortality.

In 2005 the World Health Organization added methadone (and buprenorphine) to its List of Essential Medicines, **partly because** "The accumulated data demonstrate that methadone maintenance treatment is a major public health tool in ... HIV/AIDS prevention" – the effectiveness issue dealt with in the featured review – but also because it is capable of widespread implementation and the engagement of a large proportion of the at-risk population in treatment. This conclusion was boosted by **an analysis for the European Union** which found methadone maintenance cost-effectively prolongs and improves the lives of a population of opioid injectors by averting HIV infections, and that the cost of doing so is typically below the cost of treating the infections, creating health service savings. Such findings led to **joint guidance** from Europe's drug and infection control agencies to feature opioid maintenance treatments among the seven key intervention components which should be applied and combined to achieve maximum protection from infection.

The mathematical model used in the analysis for the European Union showed that as the proportion of local drug users engaged in treatment increases, costs per averted infection dramatically decrease, and benefits across all drug users in or out of treatment escalate. This is because the treatment is capable of removing a large proportion of drug users from networks of injecting equipment sharing, leading to a form of 'herd immunity'. This analysis and others found that benefits in respect of hepatitis C infection are much less convincing, and likely to be substantial at a population level only in very high quality programmes which reduce equipment sharing to very low levels and prevent relapse to injecting drug use.

To a lesser extent, these qualities have a similar influence on HIV prevention, spotlighting the importance of features of the programmes and the regulatory environment within which they operate which can undermine their infection-prevention potential. Among those **described for a US think-tank** are limited implementation, regulations restricting the import and supply of methadone, restrictions on the types of patients who can enter the programmes (eg, to those who have been failed by other treatments), under-dosing, and counterproductive rules and disciplinary procedures which deter patients and lead to many being discharged from treatment.

The featured review considered only treatments which feature opioid prescribing. **Another review** has surveyed treatment in general to assess its actual or potential preventive impact on HIV infection. By far the strongest evidence was for methadone maintenance programmes, though there was some too for buprenorphine maintenance and, where neither is available, for prescribing the opiate-blocking drug naltrexone.

For all Effectiveness Bank analyses related to the reduction of infection risk behaviour by methadone maintenance run **this search**.

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