# Effects of naloxone distribution alone or in combination with addiction treatment with or without pre-exposure prophylaxis for HIV prevention in people who inject drugs: a cost-effectiveness modelling study

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## Summary

**Background** In the USA, an epidemic of opioid overdose deaths is occurring, many of which are from heroin. Combining naloxone distribution with linkage to addiction treatment or pre-exposure prophylaxis (PrEP) for HIV prevention through syringe service programmes has the potential to save lives and be cost-effective. We estimated the outcomes and cost-effectiveness of five alternative strategies: no additional intervention, naloxone distribution, naloxone distribution plus linkage to addiction treatment, naloxone distribution plus PrEP, and naloxone distribution plus linkage to addiction treatment and PrEP.

**Methods** We developed a decision analytical Markov model to simulate opioid overdose, HIV incidence, overdose-related deaths, and HIV-related deaths in people who inject drugs in Connecticut, USA. Model input parameters were derived from published sources. We compared each strategy with no intervention, as well as simultaneously considering all strategies. Sensitivity analysis was done for all variables. Linkage to addiction treatment was referral to an opioid treatment programme for methadone. Endpoints were survival, life expectancy, quality-adjusted life-years (QALYs), number and percentage of overdose deaths averted, number of HIV-related deaths averted, total costs (in 2015 US$) associated with each strategy, and incremental cost per QALY gained.

**Findings** In the base-case analysis, compared with no additional intervention, the naloxone distribution strategy yielded an incremental cost-effectiveness ratio (ICER) of $323 per QALY, and naloxone distribution plus linkage to addiction treatment was cost saving compared with no additional intervention (greater effectiveness and less expensive). The most efficient strategies (ie, those conferring the greatest health benefit for a particular budget) were naloxone distribution combined with linkage to addiction treatment (cost saving), and naloxone distribution combined with PrEP and linkage to addiction treatment (ICER $95 337 per QALY) at a willingness-to-pay threshold of $100 000. In probabilistic sensitivity analysis, the combination of naloxone distribution, PrEP, and linkage to addiction treatment was the optimal strategy in 37% of iterations and the combination of naloxone distribution and linkage to addiction treatment was the optimal strategy in 34% of iterations.

**Interpretation** Naloxone distribution through syringe service programmes is cost-effective compared with syringe distribution alone, but when combined with linkage to addiction treatment is cost saving compared with no additional services. A strategy that combines naloxone distribution, PrEP, and linkage to addiction treatment results in greater health benefits in people who inject drugs and is also cost-effective.

**Funding** State of Connecticut Department of Public Health and the National Institute of Mental Health.



*Lancet Public Health* 2017; 2: e133–40

Published Online February 9, 2017 http://dx.doi.org/10.1016/S2468-2667(17)30006-3

**This online publication has been corrected. The corrected version first appeared at thelancet.com/public-health on April 3, 2017**

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## Introduction

In the USA, an epidemic of drug overdose deaths is occurring; most of these deaths (61%) involve some type of opioid.[1] The surge in overdose deaths from heroin in recent years (tripling from 2010 to 2014) contributes to nearly half of all opioid deaths (following natural and semisynthetic opioids such as morphine, oxycodone, and hydrocodone).[1] 33 US states have syringe service programmes in roughly 200 cities,[2] which in some areas serve as a venue for community distribution of naloxone. Naloxone is an opioid antagonist that reverses the potentially fatal respiratory or central nervous system depression caused by opioid overdose.[3] Community-based opioid overdose prevention programmes that include the distribution of naloxone to non-medical bystanders have been shown to improve the ability of bystanders to recognise and effectively respond to an overdose[4] and to reduce opioid overdose deaths.[4–8] A recent economic analysis showed that such programmes are cost-effective (US$438 per quality-adjusted life-year [QALY] gained) when targeted at people who use heroin, even after taking into consideration the likely continued use of heroin after surviving an overdose.[9]

## Research in context

### Evidence before this study

Evidence suggests that community-based naloxone distribution improves the ability of bystanders to recognise and effectively respond to an opioid overdose and is cost-effective. However, a more comprehensive strategy to maximise the health of people who inject drugs is likely to require additional services that aim to address the underlying substance use disorder or reduce transmission of HIV and hepatitis C virus (HCV). Such services include linkage to addiction treatment and pre-exposure prophylaxis (PrEP) for HIV prevention. We searched PubMed on Dec 21, 2015, and again on June 15, 2016, with the search terms Naloxone AND (PrEP or pre-exposure prophylaxis) Naloxone AND ("drug treatment" OR "addiction treatment" OR methadone), without any restrictions for date of publication or geographical location. We also searched bibliographies of relevant articles. Although combination strategies are not new, we did not identify any published research that reported their effectiveness, feasibility, or value.

### Added value of this study

Mathematical models are important to inform policy and decision making to ascertain whether the possible advantages of combination strategies will be attenuated when considering the downstream costs associated with treating substance use disorders, HIV, hepatitis C, and their sequelae, or amplified because of the cases of HIV and hepatitis C that are averted. In this study, we investigated the effects of naloxone distribution alone or in combination with addiction treatment with or without PrEP. We did not explicitly model HCV or its treatment.

### Implications of all the available evidence

Our analyses suggest that naloxone distribution through syringe service programmes is cost-effective compared with no additional intervention. The addition of linkage to addiction treatment is cost saving compared with either no additional intervention or naloxone distribution alone. Combining PrEP with naloxone distribution and linkage to addiction treatment resulted in the greatest health gains and is cost-effective, with an ICER of less than US$100 000 per quality-adjusted life-year gained.

Although community-based naloxone distribution is clearly beneficial and cost-effective, a more comprehensive strategy to maximise the health of people who inject drugs is likely to require additional components that aim to address the underlying substance use disorder[10,11] or reduce transmission of HIV and hepatitis C virus (HCV). We assess the effects of combining naloxone distribution with linkage to addiction treatment, with or without pre-exposure prophylaxis (PrEP) for HIV prevention. Addiction treatment for people who inject drugs has been shown to substantially improve the health of not only people who inject drugs, but also the general population because of the reduction in HIV infections. This strategy is also cost-effective, with one economic study reporting a cost per additional QALY of $11923 (US$ 2015).[12] PrEP has been shown to substantially reduce the probability of HIV infection in people who inject drugs, but the value of expanding PrEP is variable, with the cost per QALY gained in the range of $50 000–350 000, and sensitive to HIV prevalence and the cost of PrEP.[13,14]

Mathematical models are important to inform policy and decision making because it is difficult to tell whether the advantages of combination strategies will be attenuated when considering the downstream costs associated with treating substance use disorders, HIV, hepatitis C, and their sequelae, or amplified because of the cases of HIV and hepatitis C that are averted. We investigated the health benefit and cost-effectiveness of the current naloxone distribution programme in Connecticut, USA, as well as three novel combination strategies that combine naloxone distribution with linkage to addiction treatment with or without PrEP.

## Methods

### Description of strategies

We compared five strategies: (1) no additional intervention, (2) naloxone distribution, (3) naloxone distribution plus linkage to addiction treatment, (4) naloxone distribution plus PrEP, and (5) naloxone distribution plus linkage to addiction treatment and PrEP. The no additional intervention strategy served as a comparator and assumed a scenario in which none of the other four strategies were added to syringe exchange. The naloxone distribution strategy reflects the current strategy in Connecticut in which overdose kits consisting of two prefilled syringes of naloxone, atomisers for intranasal administration, gloves, alcohol pad, rescue breathing mask, and written instructions are distributed via mobile syringe service programmes, AIDS service organisations, and other community-based organisations. Naloxone distribution plus linkage to addiction treatment is an untested strategy (but based on established programmes[15–18]), in which referral to methadone treatment is added to existing naloxone programmes and operates concurrently. The naloxone distribution plus PrEP strategy, in which PrEP is added to the existing naloxone programme, is also untested. The final strategy combines all of the strategies described.

### Opioid overdose Markov model

The research questions, model structure, and parameters were developed and selected in consultation with programme implementation and policy experts at the Connecticut Department of Public Health and discussed with other experts in the field of addiction and HIV infection who are knowledgeable about service delivery for individuals in Connecticut who use drugs. We developed a decision analytical Markov model (appendix) to simulate opioid overdose in HIV-negative people who inject drugs in Connecticut to estimate the short-term (5 years) and long-term (time horizon of 5, 10, and 20 years) survival, life expectancy, QALY, number and percentage of overdose deaths averted, number of HIV-related deaths averted, total costs associated with each strategy, and incremental cost-effectiveness ratio (ICER). For all strategies, we assumed that in each year 30% of the cohort received the services offered in that strategy, with the exception of strategies that included linkage to addiction treatment, in which 6% entered methadone treatment. For example, in the strategy that consisted of naloxone distribution, linkage to addiction treatment, and PrEP, 30% of participants received naloxone, 6% entered methadone treatment, and 30% started PrEP. We took a more conservative approach in selecting the 6% estimate and tested a less restrictive range (up to 96% annual enrolment) in sensitivity analysis. Because enrolment or re-enrolment into addiction treatment can occur without exposure to active engagement, we included a baseline annual probability of 4% enrolment.

The initial cohort consisted of 5400 HIV-negative people who inject drugs who were not on PrEP. Because we did not find published estimates specifically for Connecticut, we estimated this value by applying the proportion of current heroin users in the USA in 2014 (0·2%)[19] to the population of Connecticut aged 15 years and older (2 967 252), and then subtracted out the number of HIV-infected people who inject drugs based on prevalence estimates (9%).[20] Discontinuation of injecting behaviour was influenced by entering addiction treatment, addiction treatment efficacy (25% annual discontinuation if enrolled in addiction treatment), a non-fatal overdose episode (6% per episode), and relapse to injection drug use (7% per year). Because we found no empirical studies reporting the likelihood of discontinuing injection drug use after an overdose, we followed the assumptions reported by Coffin and colleagues[9] and used a 6% probability per episode. Because rates in the model were constant over time, we chose a lower rate of relapse to injection drug use to avoid overestimation over a 20-year time horizon and, in sensitivity analysis, tested higher values up to 85%, which many experts have observed in practice. In view of the gap in the current understanding of PrEP adherence in people who inject drugs,[21] we assumed an annual rate that was similar for antiretroviral therapy for this same population (adherence probability of 41%). PrEP adherence affects the efficacy of PrEP and thereby affects transmission probability of HIV. This assumption may or may not reflect reality and thus wide margins were tested in sensitivity analysis. HIV infection was informed by injecting status and PrEP use, and once HIV-positive the likelihood of detection was 50%, a function of the rate of HIV testing and test sensitivity. Among individuals with detected HIV infection, we assumed that HIV antiretroviral therapy was initiated and 41%[22] achieved acceptable adherence, of whom 55%[23] achieved viral suppression. Rates for discontinuing injecting behaviour and entering addiction treatment were unaffected by HIV status. Excess mortality was lower in individuals who achieved HIV viral suppression (0·003) compared with those who did not (0·02).

See Online for appendix

We defined overdose as the rapid onset of loss of consciousness (accompanied by minimal responsiveness) from which arousal was difficult or impossible.[24,25] Overdose and overdose-related death was modelled through a series of probabilistic events that could occur in each cycle. We assumed the likelihood of an overdose per year was 7·7%, with an 85% chance the overdose was witnessed, a 39% chance that naloxone was administered if the bystander had a naloxone kit, and a 97% likelihood of survival if the kit was used. If no kit was used and paramedics were not dispatched, survival was 86%. On the basis of findings from several studies[4,26,27] showing that the likelihood of calling paramedics was reduced if naloxone was administered, we assumed a 69% reduction in the likelihood of paramedics being dispatched in such cases. Mortality was based on overdose survival, HIV status, and background age and sex specific mortality rates reported in US life tables.[28] Model validation is discussed in the appendix. The model was developed in Excel 2013 and all analyses were done in Excel.

### Model parameters, costs, and utilities

Model input parameters were derived from published sources (appendix). The cost of the naloxone kit reflects the current price that the Connecticut Department of Public Health pays per dose of naloxone ($33×2 doses=$66) plus costs associated with distribution ($10 per recipient). Paramedic dispatch cost ($3182) included basic life support response, transport to the emergency department, and an assessment. Admission to hospital after an assessment, which occurred in 11% of dispatch cases, cost $15 845. The annual cost of PrEP per person ($11 800) included the cost of medication, four doctor visits, and laboratory tests. The annual cost of HIV antiretroviral treatment per patient ($32 652) was taken from a recent study[29] in which the costs of medication and care for HIV-positive people who inject drugs were estimated by use of data from a consortium of hospital and community-based HIV care sites in the USA. The annual cost of methadone treatment per person was $4821, which is based on findings from a study[30] that estimated costs for 25 methadone treatment programmes in 12 states in the USA and included in its estimate the cost of personnel and direct and indirect costs

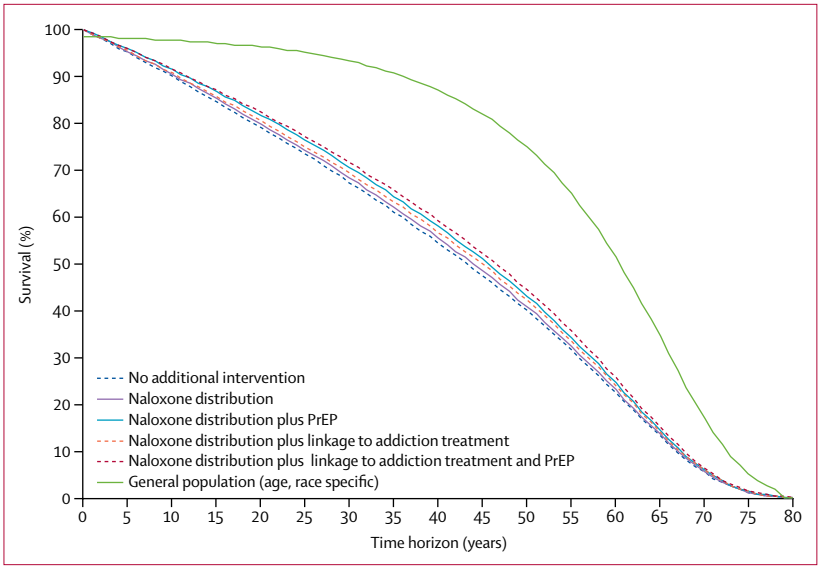


***Figure 1*: Lifetime survival probability by strategy**
PrEP=pre-exposure prophylaxis.

for patient assessment, medical services, individual and group counselling, methadone, patient education, and case management. All costs were converted into 2015 US$ and discounted at an annual rate of 3%.[31]

### Base case and sensitivity analysis

For each intervention strategy, we projected survival probability, life expectancy, QALY, and cost, and then compared projections to the no additional intervention strategy to estimate health effects. To identify the most efficient strategies, ICERs for each strategy were compared for a time horizon of 20 years. Inefficient strategies were disqualified from consideration on the basis of strong and weak dominance. A cost-effectiveness threshold of $100 000 per QALY was used, which approximates the cost-effectiveness of the US health system in the aggregate, and therefore reflects the opportunity cost of spending money on a particular programme rather than on a standard alternative programme.[32] The starting age of the cohort was 22 years. In one-way sensitivity analysis, we paid particular attention to addiction treatment enrolment, addiction treatment efficacy, rate of relapse to injection drug use, and PrEP adherence, because there is ample uncertainty about their precision and they were shown to have substantial effects on the value of some strategies. Overall model uncertainty was tested in probabilistic sensitivity analysis, in which we drew 10 000 random values from specified probability distributions for each parameter (beta distribution for rates, probabilities, and utilities, and gamma distribution for costs).[33,34]

### Role of the funding source

The funder of the study consulted on the study design and selection of parameters, provided Connecticut-specific cost data, and provided feedback on this report. All authors had access to the raw data. The corresponding author had full access to all of the data in the study and had final responsibility for the decision to submit for publication.

## Results

Survival was greatest for the strategy combining naloxone distribution, PrEP, and linkage to addiction treatment, followed by the naloxone distribution plus PrEP strategy, the naloxone distribution plus linkage to addiction treatment strategy, naloxone distribution alone, and no additional intervention (figure 1). Survival at 20 years was 82·8%, 82·4%, 81·1%, 80·6%, and 79·8%, respectively.

The combination of naloxone distribution, PrEP, and linkage to addiction treatment prevented the most HIV-related deaths (21 HIV-related deaths averted in 20 years), followed by naloxone distribution plus PrEP (15 HIV-related deaths averted), and naloxone distribution plus linkage to addiction treatment (four HIV-related deaths averted; table 1). However, more HIV-related deaths occurred with the naloxone distribution strategy compared with no additional intervention (two additional deaths in 20 years). The greater number of HIV-related deaths is explained by the improved likelihood of overdose survival with the naloxone distribution strategy and continued exposure to HIV infection. Similarly, the strategy that combined naloxone distribution, PrEP, and linkage to addiction treatment prevented the most overdose deaths (149 overdose deaths averted in 20 years, a 21% reduction in deaths compared with no additional intervention), followed by naloxone distribution plus PrEP (127 overdose deaths averted, an 18% reduction compared with no additional intervention), naloxone distribution plus linkage to addiction treatment (69 overdose deaths averted, a 10% reduction compared with no additional intervention), and naloxone distribution alone (44 overdose deaths averted, 6% reduction compared with no additional intervention).

In the base case analysis, compared with no additional intervention, the naloxone distribution strategy yielded an ICER of $323 per QALY. Naloxone distribution plus linkage to addiction treatment was cost saving compared with no additional intervention (greater gain in QALYs and less costly).

When all strategies were simultaneously considered (table 2), naloxone distribution plus linkage to addiction treatment was cost saving compared with no additional intervention, naloxone distribution alone, and naloxone distribution plus PrEP. Thus, the latter three interventions were judged to be dominated strategies (more costly and less effective compared with an alternative) and removed from consideration. The combination of naloxone distribution, PrEP, and linkage to addiction treatment produced better health outcomes, but was also more costly compared with the naloxone distribution plus linkage to addiction treatment strategy and yielded an ICER of $95 337. Therefore, at the societal willingness-to-

| | Number of HIV-related deaths averted | Number of overdose deaths averted | Proportion of overdose deaths averted (%) | Individual life expectancy (years) | Survival probability (%) |
|---|---|---|---|---|---|
| **5 years** | | | | | |
| No additional intervention | Reference | Reference | Reference | 4·9 | 95·2% |
| Naloxone distribution | 0·0 | 14 | 6·6% | 4·9 | 95·5% |
| Naloxone distribution plus PrEP | 1·0 | 42 | 20·2% | 4·9 | 96·0% |
| Naloxone distribution plus linkage to addiction treatment | 0·0 | 16 | 7·7% | 4·9 | 95·5% |
| Naloxone distribution plus PrEP and linkage to addiction treatment | 1·0 | 44 | 21·1% | 4·9 | 96·1% |
| **10 years** | | | | | |
| No additional intervention | Reference | Reference | Reference | 9·5 | 90·1% |
| Naloxone distribution | 0 | 25 | 6·5% | 9·5 | 90·5% |
| Naloxone distribution plus PrEP | 5 | 77 | 19·7% | 9·6 | 91·6% |
| Naloxone distribution plus linkage to addiction treatment | 1 | 34 | 8·7% | 9·6 | 90·7% |
| Naloxone distribution plus PrEP and linkage to addiction treatment | 6 | 84 | 21·6% | 9·6 | 91·7% |
| **20 years** | | | | | |
| No additional intervention | Reference | Reference | Reference | 18·0 | 79·3% |
| Naloxone distribution | –2 | 44 | 6·3% | 18·1 | 80·0% |
| Naloxone distribution plus PrEP | 15 | 127 | 18·2% | 18·3 | 81·9% |
| Naloxone distribution plus linkage to addiction treatment | 4 | 69 | 9·8% | 18·1 | 80·6% |
| Naloxone distribution plus PrEP and linkage to addiction treatment | 21 | 149 | 21·2% | 18·3 | 82·4% |

PrEP=pre-exposure prophylaxis.

***Table 1:*** **Population health outcomes at time horizons of 5, 10, and 20 years**

pay threshold of $100 000 per QALY, the preferred strategy was the combination of naloxone distribution, PrEP, and linkage to addiction treatment, whereas if lower willingness-to-pay (ie, more stringent) thresholds were used, the naloxone distribution plus linkage to addiction treatment strategy was preferable.

In sensitivity analysis, when the annual probability of relapse (return to injection drug use) increased to 18·9% (among individuals enrolled in addiction treatment), naloxone distribution plus linkage to addiction treatment was no longer cost saving compared with naloxone distribution alone because of the added cost associated with increased HIV infections (table 3), although the strategy was still cost-effective even at the highest plausible value of 85% (ICER $16 792; figure 2). When the likelihood of discontinuing injection drug use because of treatment declined to less than 23·7%, naloxone distribution plus linkage to addiction treatment was no longer cost saving, but was still cost-effective at the lowest plausible value of 8·6% (ICER $10 293). When the likelihood of entering addiction treatment for strategies that included referral to addiction treatment was less than 5·5%, the naloxone distribution plus linkage to addiction treatment strategy remained dominant and QALYs increased (90 716 *vs* 68 114 QALYs) while costs decreased ($209 880 493 *vs* $279 037 947). Strategies that included referral to addiction treatment became unfavourable when the probability of addiction treatment enrolment dropped below the baseline value of 4%. When the scale of strategy implementation reached 90% participation, naloxone distribution plus linkage to addiction treatment was no longer cost saving compared with no additional intervention (threshold 58%) and yielded an ICER of $1317.

For several variables, variation raised ICERs for the strategy combining naloxone distribution, PrEP, and

| | Life expectancy (years) | QALY | Cost (US$ 2015) | ICER (US$)* |
|---|---|---|---|---|
| **Most efficient strategies** | | | | |
| Naloxone distribution plus linkage to addiction treatment | 97 843 | 68 114 | 279 037 947 | .. |
| Naloxone distribution plus PrEP and linkage to addiction treatment | 98 810 | 68 746 | 339 304 861 | 95 337 |
| **Dominated strategies removed from consideration** | | | | |
| Naloxone distribution plus PrEP | 98 693 | 67 294 | 335 144 357 | .. |
| No additional intervention | 97 145 | 66 343 | 281 741 918 | .. |
| Naloxone distribution | 97 614 | 66 660 | 281 844 303 | .. |

The most efficient strategies are sorted by cost (ascending). Note that the default strategy (no additional intervention) is itself strongly dominated. The naloxone distribution plus PrEP strategy yielded greater unadjusted life expectancy than the naloxone distribution plus linkage to addiction treatment strategy, but the disutility associated with injection drug use adversely affected quality of life. ICER=incremental cost-effectiveness ratio. PrEP=pre-exposure prophylaxis. QALY=quality-adjusted life-year. *Incremental difference in cost divided by the incremental difference in QALY.

***Table 2:*** **QALY, cost, and ICER at 20 years**

| | ICER (US$) |
|---|---|
| **Relapse to injection drug use; annual probability threshold >18·9%** | |
| Naloxone distribution | .. |
| Naloxone distribution plus linkage to addiction treatment | 33 |
| Naloxone distribution plus PrEP and linkage to addiction treatment | 70 492 |
| **Discontinuing injection drug use after treatment; annual probability threshold <23·7%** | |
| Naloxone distribution | .. |
| Naloxone distribution plus linkage to addiction treatment | 45 |
| Naloxone distribution plus PrEP and linkage to addiction treatment | 71 933 |
| **Entering treatment, baseline without intervention; annual probability threshold <5·5%** | |
| Naloxone distribution | .. |
| Naloxone distribution plus PrEP | 86 593 |
| **Strategy scale or participation; annual probability threshold <58%** | |
| No intervention | .. |
| Naloxone distribution plus linkage to addiction treatment | 16 |
| Naloxone distribution plus PrEP and linkage to addiction treatment | 158 093 |

ICER=incremental cost-effectiveness ratio. PrEP=pre-exposure prophylaxis.

***Table 3:*** **Sensitivity analysis showing scenarios when naloxone distribution plus linkage to addiction treatment was no longer cost saving**

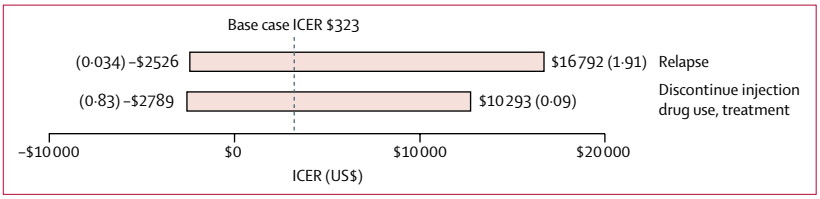


***Figure 2:*** **Scenarios when naloxone distribution plus linkage to addiction treatment is no longer cost saving compared with naloxone distribution alone**
Corresponding rates are in parentheses.

linkage to addiction treatment above the $100 000 threshold (compared with the naloxone distribution plus linkage to addiction treatment strategy; figure 3 and appendix). The combination of naloxone distribution, PrEP, and linkage to addiction treatment was higher than the $100 000 threshold when the annual likelihood of HIV infection while on PrEP was higher than 1·6%, PrEP adherence was less than 38·7%, and the cost of PrEP was greater than $12 300. Scenarios related to injection drug use that pushed the ICER above the threshold included when addiction treatment enrolment was greater than 6·4%, discontinuing injection drug use in the linkage to addiction treatment strategy was greater than 46·7%, discontinuing injection drug use after an overdose episode was greater than 9·5%, relapse to injection drug use was less than 40%, HIV incidence without PrEP was less than 2·1%, disutility associated with active injection drug use in individuals who were HIV negative was less than 0·61, and disutility associated with discontinued injection drug use in individuals who were HIV negative was less than 0·90. Scenarios related to overdose that raised the ICER above the threshold included when the likelihood of overdose was less than 7%, the likelihood of paramedic dispatch when no kit was used was more than 32·3%, and the likelihood of surviving overdose without intervention was more than 58%. An annual discount rate of less than 2·5% also raised the ICER above $100 000.

The results of the probabilistic sensitivity analysis are shown in the cost-effectiveness acceptability curves (appendix) and show the likelihood of a strategy being judged as the optimal strategy (ie, yielding the highest net benefit) for a range of willingness-to-pay thresholds. The combination of naloxone distribution, PrEP, and linkage to addiction treatment was the optimal strategy in 37% of iterations using a willingness-to-pay of $100 000, followed by naloxone distribution plus linkage to addiction treatment, which was the optimal strategy 34% of the time. The naloxone distribution plus PrEP strategy, naloxone distribution alone, and no additional intervention were optimal strategies 11%, 10%, and 8% of the time, respectively, at that threshold. At lower thresholds (<$85 300), naloxone distribution plus linkage to addiction treatment maintained the highest probability of being the optimal strategy.

## Discussion

Our analyses suggest that naloxone distribution through syringe service programmes provides good value for money compared with no additional intervention. The addition of linkage to addiction treatment saves money compared with either no additional intervention or naloxone distribution alone. Combining PrEP with naloxone distribution and linkage to addiction treatment resulted in the greatest health gains and was cost-effective, with an ICER of less than $100 000 per QALY gained.

Deterministic and probabilistic sensitivity analyses showed that results pertaining to the cost-saving determination of combined naloxone distribution and linkage to addiction treatment compared with naloxone distribution alone were robust. Only when relapse to injection drug use increased to more than 18·9% and when the likelihood of discontinuing injection drug use declined to less than 23·7% was the combined strategy no longer cost saving, although in both cases the combined strategy was good value for money even at maximum plausible values. Conversely, for the all-inclusive strategy (naloxone distribution, linkage to addiction treatment, and PrEP), ICERs were more sensitive to variation and several scenarios pushed ICERs above $100 000.

The ICER for the naloxone distribution strategy compared with the no additional intervention strategy was $323 per QALY, which is similar to the ICER of $421 reported in a recent modelling study that compared community naloxone distribution with no intervention.[9] Although we found no modelling studies that assessed our combination of interventions, we did identify two that assessed the individual components. Zaric and colleagues[12] compared methadone treatment alone versus no intervention and reported ICERs of $11 923 (US$ 2015) in settings with a low prevalence of HIV and $15 850 in settings with a high prevalence of HIV. These

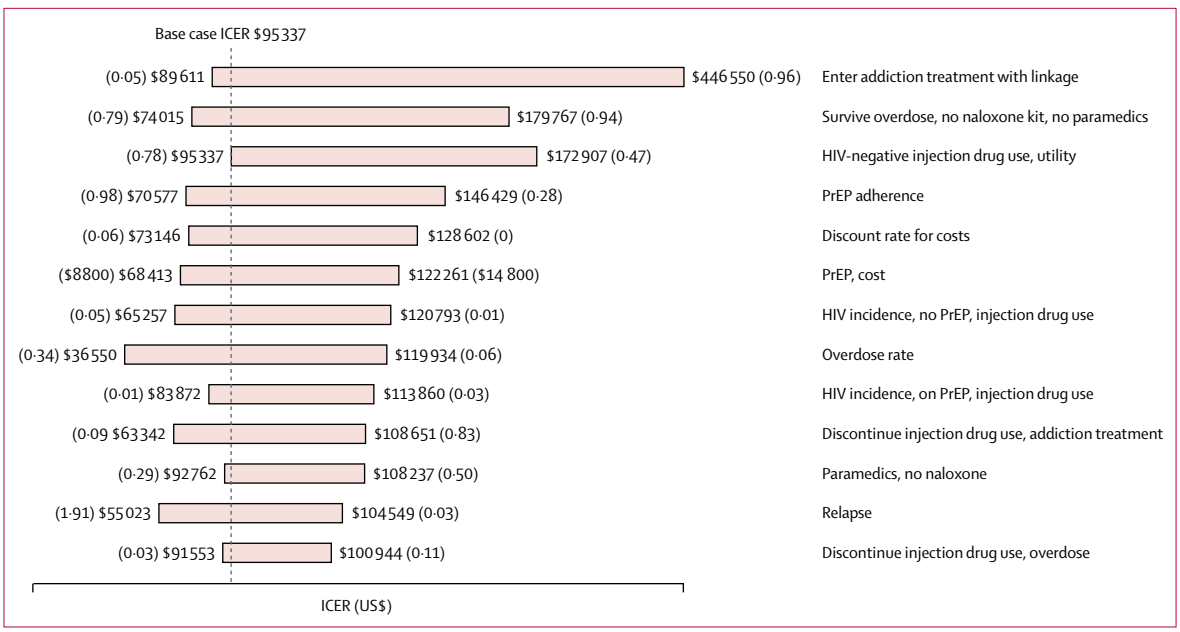


***Figure 3*: Scenarios when ICERs for the combination of naloxone distribution, PrEP, and linkage to addiction treatment were more than US$100 000**
Corresponding rates are in parentheses. ICER=incremental cost-effectiveness ratio. PrEP=pre-exposure prophylaxis.

ICERs differ from our finding that linkage to addiction treatment is cost saving. Both our study and the study by Zaric and colleagues show the substantial health benefits gained from addiction treatment as a result of HIV infections averted. However, there are fundamental differences between models; increasing the cost of addiction treatment and lowering the cost of HIV care to levels approximating those used in the study by Zaric and colleagues produced results trending in their direction (ie, greater cost and effectiveness of the naloxone distribution plus linkage to addiction treatment strategy compared with no intervention). The discrepancy in the costs used might be attributable to actual changes in the cost of treatment, because costs used by Zaric and colleagues reflect the cost of treatments in 1996–98, while ours reflect current-day costs.

Bernard and colleagues[35] reported an ICER of $253 000 per QALY for PrEP use in people who inject drugs, which is more than double the ICER generated in our analysis ($95 337). Although there are important methodological differences between our model and theirs, when we align our inputs, particularly increasing enrolment into addiction treatment, these differences diminish. Other previous studies that assessed the value of PrEP in at-risk individuals also reported ICERs well above $100 000 per QALY, for example as high as $350 353 in men who have sex with men.[14] Cost-effectiveness of PrEP was attained when it was targeted at very high-risk individuals, for example $48 430 per QALY when annual HIV incidence was 2·3% (which is similar to our estimate of 2·6%).[13] Notably, combination interventions including PrEP were cost-effective even though we assumed that adherence would be low (30%) in injection drug users. The differences between the PrEP models are extensive, thus it is difficult to comment on whether results differ because of differences in model approach, structure, or inputs. Yet, across all studies, results were sensitive to HIV prevalence, HIV incidence, and the cost of PrEP. In all studies, cost-effectiveness of PrEP improved when HIV incidence or prevalence was high.

Our study has several limitations. The combined interventions considered in the analysis have yet to be tested and thus the true effect of combining strategies is unknown. We used estimates for treatment enrolment, adherence, and efficacy based on studies that tested the strategy components independently. We also only analysed one model of linkage to addiction treatment (methadone via an opioid treatment programme) and recognise that in practice people might also independently or in combination be enrolled in other types of programmes (ie, inpatient treatment, office-based buprenorphine). Moreover, we did not simulate hepatitis C infection or downstream societal effects such as crime and incarceration, which could have affected our results. The addition of such pathways is likely to lead to more favourable results for strategies that include linkage to addiction treatment, because they would reduce the number of people who inject drugs compared with the other strategies, thereby leading to a reduced risk of hepatitis C infection and possibly reduced crime and incarceration. Finally, we did not consider whether possession of naloxone encourages riskier heroin use, although if we assume risker heroin use would lead to an increase in the overdose rate, we may have captured this effect in our sensitivity analysis when

we varied the annual overdose rate to the upper bound of 0·34. At this higher level, the results did not change.

In future research, we recommend trials that test the efficacy and feasibility of combined strategies and that identify possible alternative modes of delivery. We also recommend extending current modelling work to include hepatitis C infection, HIV and HCV co-infection, and the effect and cost of newer direct-acting antivirals to treat hepatitis C.

#### Contributors

JU and RSB contributed to the design of the study, developed the model, did the analysis, interpreted the results, and drafted the report. DAF, MB, and RR-S provided significant feedback on the parameter estimates, design of the study, interpretation of results, and draft of the report.

#### Declaration of interests

We declare no competing interests.

#### Acknowledgments

This study was funded by the Connecticut Department of Public Health and was supported in part by Award Number P30MH062294 from the National Institute of Mental Health.

#### References

1 Rudd RA, Aleshire N, Zibbell JE, Gladden RM. Increases in drug and opioid overdose deaths—United States, 2000-2014. *MMWR Morb Mortal Wkly Rep* 2016; **64:** 1378–82.

2 The Henry J Kaiser Family Foundation. Sterile syringe exchange programs, 2014. http://kff.org/hivaids/state-indicator/syringe-exchange-programs/ (accessed May 26, 2016).

3 US National Library of Science. NARCAN- naloxone hydrochloride spray. Daily Med, 2015. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=724df050-5332-4d0a-9a5f-17bf08a547e1 (accessed Jan 6, 2016).

4 Clark AK, Wilder CM, Winstanley EL. A systematic review of community opioid overdose prevention and naloxone distribution programs. *J Addict Med* 2014; **8:** 153–63.

5 Walley AY, Xuan Z, Hackman HH, et al. Opioid overdose rates and implementation of overdose education and nasal naloxone distribution in Massachusetts: interrupted time series analysis. *BMJ* 2013; **346:** f174.

6 Maxwell S, Bigg D, Stanczykiewicz K, Carlberg-Racich S. Prescribing naloxone to actively injecting heroin users: a program to reduce heroin overdose deaths. *J Addict Dis* 2006; **25:** 89–96.

7 Bird SM, Parmar MK, Strang J. Take-home naloxone to prevent fatalities from opiate-overdose: protocol for Scotland's public health policy evaluation, and a new measure to assess impact. *Drugs* 2015; **22:** 66–76.

8 Bird SM, McAuley A, Perry S, Hunter C. Effectiveness of Scotland's National Naloxone Programme for reducing opioid-related deaths: a before (2006-10) versus after (2011-13) comparison. *Addiction* 2016; **111:** 883–91.

9 Coffin PO, Sullivan SD. Cost-effectiveness of distributing naloxone to heroin users for lay overdose reversal. *Ann Intern Med* 2013; **158:** 1–9.

10 Wilson DP, Donald B, Shattock AJ, Wilson D, Fraser-Hurt N. The cost-effectiveness of harm reduction. *Int J Drug Policy* 2015; **26** (suppl 1)**:** S5–11.

11 Volkow ND, Frieden TR, Hyde PS, Cha SS. Medication-assisted therapies—tackling the opioid-overdose epidemic. *N Engl J Med* 2014; **370:** 2063–66.

12 Zaric GS, Barnett PG, Brandeau ML. HIV transmission and the cost-effectiveness of methadone maintenance. *Am J Public Health* 2000; **90:** 1100–11.

13 Juusola JL, Brandeau ML, Owens DK, Bendavid E. The cost-effectiveness of preexposure prophylaxis for HIV prevention in the United States in men who have sex with men. *Ann Intern Med* 2012; **156:** 541–50.

14 Paltiel AD, Freedberg KA, Scott CA, et al. HIV preexposure prophylaxis in the United States: impact on lifetime infection risk, clinical outcomes, and cost-effectiveness. *Clin Infect Dis* 2009; **48:** 806–15.

15 Strathdee SA, Ricketts EP, Huettner S, et al. Facilitating entry into drug treatment among injection drug users referred from a needle exchange program: results from a community-based behavioral intervention trial. *Drug Alcohol Depend* 2006; **83:** 225–32.

16 Kidorf M, King VL, Peirce J, Kolodner K, Brooner RK. A treatment reengagement intervention for syringe exchangers. *J Subst Abuse Treat* 2011; **41:** 415–21.

17 Rapp RC, Otto AL, Lane DT, Redko C, McGatha S, Carlson RG. Improving linkage with substance abuse treatment using brief case management and motivational interviewing. *Drug Alcohol Depend* 2008; **94:** 172–82.

18 Havens JR, Cornelius LJ, Ricketts EP, et al. The effect of a case management intervention on drug treatment entry among treatment-seeking injection drug users with and without comorbid antisocial personality disorder. *J Urban Health* 2007; **84:** 267–71.

19 Center for Behavioral Health Statistics and Quality. Behavioral health trends in the United States: results from the 2014 National Survey on Drug Use and Health (HHS publication no. SMA 15-4927, NSDUH series H-50). Rockville, MD: Substance Abuse and Mental Health Services Administration, 2015.

20 Spiller MW, Broz D, Wejnert C, Nerlander L, Paz-Bailey G. HIV infection and HIV-associated behaviors among persons who inject drugs—20 cities, United States, 2012. *MMWR Morb Mortal Wkly Rep* 2015; **64:** 270–75.

21 Amico KR, Stirratt MJ. Adherence to preexposure prophylaxis: current, emerging, and anticipated bases of evidence. *Clin Infect Dis* 2014; **59** (suppl 1)**:** S55–60.

22 Arnsten JH, Demas PA, Grant RW, et al. Impact of active drug use on antiretroviral therapy adherence and viral suppression in HIV-infected drug users. *J Gen Intern Med* 2002; **17:** 377–81.

23 Arnsten JH, Demas PA, Farzadegan H, et al. Antiretroviral therapy adherence and viral suppression in HIV-infected drug users: comparison of self-report and electronic monitoring. *Clin Infect Dis* 2001; **33:** 1417–23.

24 Sporer KA. Acute heroin overdose. *Ann Intern Med* 1999; **130:** 584–90.

25 Boyer EW. Management of opioid analgesic overdose. *N Engl J Med* 2012; **367:** 146–55.

26 Bennett AS, Bell A, Tomedi L, Hulsey EG, Kral AH. Characteristics of an overdose prevention, response, and naloxone distribution program in Pittsburgh and Allegheny County, Pennsylvania. *J Urban Health* 2011; **88:** 1020–30.

27 Lankenau SE, Wagner KD, Silva K, et al. Injection drug users trained by overdose prevention programs: responses to witnessed overdoses. *J Community Health* 2013; **38:** 133–41.

28 Arias E. United States life tables, 2010. *Nat Vital Stat Rep* 2014; **63:** 1–63.

29 Schackman BR, Fleishman JA, Su AE, et al. The lifetime medical cost savings from preventing HIV in the United States. *Med Care* 2015; **53:** 293–301.

30 Zarkin GA, Dunlap LJ, Wedehase B, Cowell AJ. The effect of alternative staff time data collection methods on drug treatment service cost estimates. *Eval Program Plann* 2008; **31:** 427–35.

31 Weinstein MC, Siegel JE, Gold MR, Kamlet MS, Russell LB. Recommendations of the Panel on Cost-effectiveness in Health and Medicine. *JAMA* 1996; 276: 1253–58.

32 Braithwaite RS, Meltzer DO, King JT, Jr, Leslie D, Roberts MS. What does the value of modern medicine say about the $50,000 per quality-adjusted life-year decision rule? *Med Care* 2008; **46:** 349–56.

33 Fenwick E, Claxton K, Sculpher M. Representing uncertainty: the role of cost-effectiveness acceptability curves. *Health Econ* 2001; **10:** 779–87.

34 Briggs A, Sculpher M, Claxton K. Decision modeling for health economic evaluation. Oxford: Oxford University Press, 2006.

35 Bernard CL, Brandeau ML, Humphreys K, et al. Cost-effectiveness of HIV preexposure prophylaxis for people who inject drugs in the United States. *Ann Intern Med* 2016; published online April 26. DOI:10.7326/M15-2634.