

# HIV Transmission and the Cost-Effectiveness of Methadone Maintenance

## ABSTRACT

**Objectives.** This study determined the cost-effectiveness of expanding methadone maintenance treatment for heroin addiction, particularly its effect on the HIV epidemic.

**Methods.** We developed a dynamic epidemic model to study the effects of increased methadone maintenance capacity on health care costs and survival, measured as quality-adjusted life-years (QALYs). We considered communities with HIV prevalence among injection drug users of 5% and 40%.

**Results.** Additional methadone maintenance capacity costs \$8200 per QALY gained in the high-prevalence community and \$10 900 per QALY gained in the low-prevalence community. More than half of the benefits are gained by individuals who do not inject drugs. Even if the benefits realized by treated and untreated injection drug users are ignored, methadone maintenance expansion costs between \$14 100 and \$15 200 per QALY gained. Additional capacity remains cost-effective even if it is twice as expensive and half as effective as current methadone maintenance slots.

**Conclusions.** Expansion of methadone maintenance is cost-effective on the basis of commonly accepted criteria for medical interventions. Barriers to methadone maintenance deny injection drug users access to a cost-effective intervention that generates significant health benefits for the general population. (*Am J Public Health.* 2000;90:XXX-XXX)

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Injection drug use is an important cause of the spread of HIV and the principal route of HIV transmission among heterosexuals in the United States.<sup>1</sup> More than 35% of the new HIV cases are among injection drug users, their sexual partners, and their offspring.<sup>2</sup>

Prevention programs for injection drug users may reduce HIV transmission by reducing risky behavior.<sup>3-7</sup> Substance abuse treatment, especially methadone maintenance, reduces risky behavior and consequent infection with HIV.<sup>8-18</sup> However, expansion of methadone maintenance programs or even the continuation of existing programs is controversial. One prominent politician has suggested that publicly funded methadone maintenance programs should be discontinued.<sup>19</sup>

In this article, we seek to determine the cost-effectiveness of expanding methadone maintenance programs, with emphasis on their role in preventing the spread of HIV. Several studies have investigated the costs and benefits of methadone maintenance,<sup>20-26</sup> focusing on health care costs (but not specifically on HIV-related health care costs) and the costs associated with unemployment (lost wages, increased burdens on the welfare system) and criminal behavior. These studies found reduced property theft to be the principal benefit of treatment. Barnett<sup>27</sup> analyzed the cost-effectiveness of methadone maintenance as a general health intervention but did not explicitly account for reductions in HIV and related mortality that would occur as a result of expansion of treatment programs.

A comprehensive evaluation of any program that prevents the spread of HIV must consider the dynamic nature of epidemics. A program that reduces HIV transmission benefits not only those who receive the intervention but also those whom they may infect. The number of indirect infections must be modeled dynamically to reflect the changing prevalence of HIV. Dynamic models have been created to estimate the cost and effectiveness of HIV prevention efforts such as

needle exchange programs,<sup>28,29</sup> counseling and testing,<sup>30,31</sup> programs to change sexual behaviors,<sup>32</sup> potential HIV vaccines,<sup>33</sup> and antiretroviral therapies.<sup>34,35</sup>

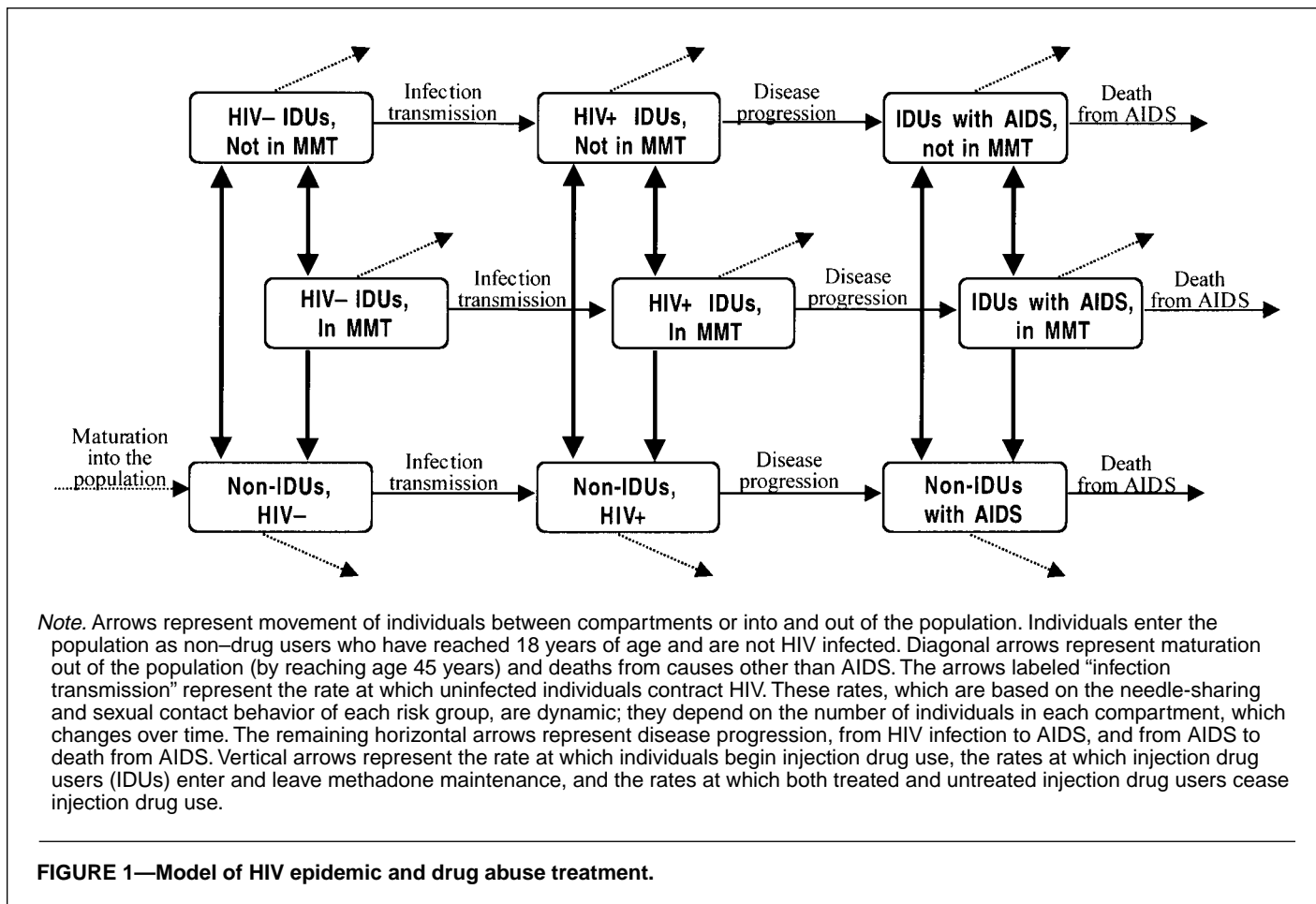
Kahn et al.<sup>36</sup> estimated the effect of a 1-year program of methadone maintenance on HIV transmission among injection drug users, their sex partners, and offspring. They used a 5-year horizon and found that providing methadone maintenance to injection drug users would cost \$48 000 to \$60 000 per (undiscounted) HIV infection averted (expressed in 1998 dollars). The analysis considered only the cost of methadone maintenance; it did not consider changes in health care costs that would occur. Benefits were measured in terms of HIV infections averted; neither increased survival nor quality of life was considered.

We developed a dynamic model of the HIV epidemic to assess the cost-effectiveness of expanding methadone maintenance, including its effect on HIV transmission, quality of life, and all causes of death. We considered the cost of methadone maintenance and other health care costs, including the cost of treatment for HIV/AIDS. We also determined the cost-effectiveness of incremental methadone maintenance slots that are less effective in reducing risky behavior and/or more expensive than current slots.

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**FIGURE 1—Model of HIV epidemic and drug abuse treatment.**

## Methods

We created a dynamic compartmental model of the HIV epidemic in a population of adults, aged 18 to 44. Full details of the model are provided elsewhere.<sup>37</sup> We divided the population into 9 disjoint groups ("compartments") defined by HIV infection status and risk group (Figure 1) and modeled the size of each compartment over time with a set of simultaneous nonlinear differential equations. We defined 3 risk groups: injection drug users not in methadone maintenance; injection drug users currently in methadone maintenance; and the general population, comprising all individuals who do not inject heroin (but may use drugs). The 3 infection states were HIV uninfected, HIV infected prior to progression to AIDS, and AIDS. Infection transmission occurred as a result of needle sharing and sexual contacts.

Data and sources are shown in Table 1. For some parameters, we estimated values on the basis of information from various sources; in such cases, we chose a value near the middle of the reported range. In cases in which few data were available, we adapted information on closely related quantities or selected

values from the best available information. We constructed 2 models: (1) 40% HIV prevalence among injection drug users, characteristic of a community such as New York City, and (2) 5% HIV prevalence among injection drug users, characteristic of a community such as Los Angeles, Calif.

We assumed that injection drug users not in treatment inject 200 times per year in the low-prevalence community and 225 times per year in the high-prevalence community<sup>38-44</sup> and that they share needles 20% of the time,<sup>5,40-43,45-47</sup> leading to 40 and 45 risky injections per year, respectively, in the 2 communities.

Methadone maintenance reduces but does not eliminate risky injection. A survey of 424 injection drug users in New Haven, Conn, found that injection drug users in treatment had 60% fewer injections than injection drug users not in treatment.<sup>44</sup> A study of 388 injection drug users who remained in methadone treatment for at least 1 year found that the prevalence of drug injection decreased by 71% compared with the prevalence among injection drug users not in treatment.<sup>48</sup> A study of injection drug users in a special methadone maintenance pro-

gram for HIV-infected individuals found that injection frequency dropped from 28 days per month to 7 days per month, suggesting a 75% decrease in injection frequency.<sup>48</sup> A review of data from 24 methadone maintenance programs found that among individuals who remained in methadone treatment for at least 6 months, 1% to 47% had positive urinalyses for heroin,<sup>49</sup> with the average (assuming all programs to be the same size) being 16%. This suggests an 84% drop in injection frequency.

A study of 239 injection drug users in Australia found that individuals in methadone maintenance were half as likely to report having injected with a used needle or syringe in the previous 6 months as those not in treatment.<sup>45</sup> Another study of 189 injection drug users found that injection drug users in methadone maintenance shared needles an average of 1.7 times in 3 months, whereas untreated injection drug users shared needles 6.0 times in 3 months, suggesting a 72% reduction in needle sharing.<sup>5</sup> The US General Accounting Office<sup>48</sup> reported on a study<sup>50</sup> that found that 9% of the injection drug users in methadone maintenance shared needles, whereas 48% of the injection drug users not

TABLE 1—Data and Sources

	Base-Case Value(s) <sup>a</sup>	Source
<b>Demographic data</b>		
Total population size	1 000 000	Assumed
Fraction of population who are injection drug users	0.007, 0.025	Calculated <sup>37</sup>
HIV prevalence among injection drug users, %	5, 40	Assumed
HIV prevalence in population, % <sup>b,c</sup>	0.17, 3.01	Calculated <sup>2,37,126</sup>
Annual rate of transition from non-injection drug user to injection drug user (per person per year) <sup>b</sup>	0.00057, 0.0025	Calculated <sup>37</sup>
Non-HIV death rates, injection drug users not in methadone maintenance treatment, %/year	3	40, 127–129
Non-HIV death rates, injection drug users in methadone maintenance treatment, %/year	1.13	40, 127–129
Non-HIV death rates, non-injection drug users, %/year	0.14	58
Rate of maturation into and out of the population, %/year	3.99	58
<b>Treatment program data</b>		
Fraction of injection drug users in methadone maintenance treatment, % <sup>d</sup>	15	64–67, 130, 131
Fraction of injection drug users who leave methadone maintenance treatment and resume injection drug use, per year, % <sup>e</sup>	31.5	13, 51, 52
Fraction of injection drug users who leave methadone maintenance treatment and quit injection drug use and enter the general population, per year, % <sup>e</sup>	3.5	13, 51–55
<b>Sexual behavior</b>		
Annual no. of new sex partners among injection drug users	3.5	16, 43, 67, 132–136
Proportion of injection drug user sexual partners who are injection drug users, % <sup>f</sup>	10, 50	132, 133, 137–140
Annual no. of new sex partners among non-injection drug users	1.2	141–147
Condom use among injection drug users, % <sup>g</sup>	20	16, 40, 43, 47, 67, 134
Condom use among non-injection drug users, % <sup>g</sup>	30	143, 145, 148, 149
Reduction in no. of new sexual partners for individuals with AIDS, %	75	Assumed
<b>Drug injection behavior</b>		
Annual no. of injections per injection drug user not in methadone maintenance treatment <sup>g</sup>	200, 225	38–44
Annual no. of injections per injection drug user in methadone maintenance treatment <sup>h</sup>	40, 45	41, 44, 48, 49
Fraction of injections that are shared, injection drug users not in methadone maintenance treatment, %	20	5, 40–43, 45–47
Fraction of injections that are shared, injection drug users in methadone maintenance treatment, % <sup>i</sup>	6	5, 45, 48, 50
Annual no. of risky injections per injection drug user not in methadone maintenance treatment <sup>h</sup>	40, 45	Calculated
Annual no. of risky injections per injection drug user in methadone maintenance treatment <sup>i</sup>	2.4, 2.7	Calculated
Net reduction in risky injections associated with methadone maintenance treatment, % <sup>k</sup>	94	Calculated
Reduction in risky injections for injection drug users with AIDS, %	75	Assumed
<b>HIV transmission</b>		
Chance of HIV transmission per sexual partner with an individual who is HIV infected and does not have AIDS, % <sup>l</sup>	5	150–155
Chance of HIV transmission per sexual partner with an individual who has AIDS, % <sup>l</sup>	11	150–155
Condom effectiveness in preventing HIV transmission, %	90	156, 157
Chance of HIV transmission per risky injection, % <sup>m</sup>	0.5	41
<b>Disease progression</b>		
Mean time from initial infection to AIDS for non-injection drug users and injection drug users not in methadone maintenance treatment, y	11.5	Derived <sup>n</sup>
Mean time from initial infection to AIDS for injection drug users in methadone maintenance treatment, y	12.2	Derived <sup>n</sup>
Mean time from AIDS to death for all persons with AIDS, y	2.6	Derived <sup>n</sup>
<b>Quality-adjustment multipliers</b>		
Uninfected member of the general population	1.00	
Asymptomatic non-injection drug users who are HIV infected <sup>o</sup>	0.90	62
Members of the general population with AIDS <sup>p</sup>	0.53	62
Injection drug users not in methadone maintenance treatment	0.80	Assumed; see text
Injection drug users in methadone maintenance treatment	0.90	Assumed; see text
<b>Annual costs<sup>q</sup></b>		
Methadone maintenance slot, \$	5250	57
Non-HIV-related health care cost for members of the general population, \$ <sup>r</sup>	1210	58
Non-HIV-related health care cost per injection drug user not in methadone maintenance treatment, \$	3850	21
Non-HIV-related health care cost per injection drug user in methadone maintenance treatment, \$	3011	21
Average HIV care cost, asymptomatic non-injection drug users and injection drug users not in methadone maintenance treatment, \$ <sup>s</sup>	4803	59–61
Average HIV care cost, asymptomatic injection drug users in methadone maintenance treatment, \$ <sup>s</sup>	10545	59–61
Average HIV care cost, all persons with AIDS, \$ <sup>t</sup>	32551	59–61
Discount rate, %	3	56

**TABLE 1—Footnotes**

<sup>a</sup>When 2 numbers are shown, they correspond to the 2 communities considered: HIV prevalence among injection drug users of 5% and 40%.

<sup>b</sup>These quantities were calculated so that they were based on published sources, were within reasonable ranges, and had values such that, over the 10-year time horizon, overall HIV prevalence would be stable, with 25% to 35% of all HIV cases from injection drug users and an approximately constant proportion of the population being an injection drug user.

<sup>c</sup>Indicates prevalence within the 18- to 44-year age range. Prevalence was set within ranges contained in the *HIV/AIDS Surveillance Report*,<sup>2</sup> assuming that the majority of HIV cases are among persons aged 18 to 44 years.

<sup>d</sup>Nationally, there are methadone maintenance treatment slots for approximately 10% to 20% of injection drug users, although some states have more slots, and some states have none.<sup>130,131</sup> We assumed a value of 15%.

<sup>e</sup>We assumed that there is a 65% annual continuance in methadone maintenance treatment and that 90% of the individuals who quit methadone maintenance treatment each year will return to regular injection drug use. Thus, 31.5% ( $0.9 \times 35\%$ ) leave methadone maintenance treatment and return to injection drug use, and 3.5% ( $0.1 \times 35\%$ ) leave methadone maintenance treatment and enter the general population.

<sup>f</sup>The indicated references show that injection drug users have a significant proportion of sexual contacts with other injection drug users. We assumed a lower proportion in the low-prevalence community to reflect the smaller number of injection drug users as a proportion of the total population and the fact that it may be more difficult for injection drug users to find other injection drug users for sexual partners.

<sup>g</sup>We assumed a value within a wide reported range.

<sup>h</sup>We assumed that injection drug users in methadone maintenance treatment inject 20% as often as those not in methadone maintenance treatment, based on the cited sources.

<sup>i</sup>We assumed that injection drug users in methadone maintenance treatment share needles 30% as often as injection drug users not in methadone maintenance treatment; thus,  $0.2 (30\% = 6\%$ .

<sup>j</sup>Calculated from the above numbers as (number of injections)  $\times$  (fraction of injections that are shared).

<sup>k</sup>Based on our calculated numbers of risky injections, the ratio of the number of risky injections among injection drug users in methadone maintenance treatment to the number of injections among injection drug users not in methadone maintenance treatment is  $3.9/65 = 0.06$  in the low-prevalence community and  $4.65/77.5 = 0.06$  in the high-prevalence community. In both cases, this represents a 94% reduction in the rate of risky injection.

<sup>l</sup>Per partner sexual transmission rates range from 1%<sup>151</sup> to more than 20%.<sup>154</sup> We assumed the same rates used in other analyses (e.g., Brandeau et al.<sup>30</sup>), which reflect the wide range of reported estimates.

<sup>m</sup>Studies of transmission from accidental needlestick have found slightly lower rates.<sup>158–161</sup> We know of only one study that has used models to estimate the transmission probability from deliberate shared injections.<sup>41</sup>

<sup>n</sup>Recent studies show a strong survival, CD4 cell count, and viral load advantage associated with drug regimens that include protease inhibitors, although no exact figure is known.<sup>162–166</sup> We assumed that protease inhibitors lengthen life in persons with asymptomatic HIV by a factor of 1.5. Thus, we assumed that mean time from HIV infection to development of AIDS is 9.8 years with no protease inhibitors<sup>167</sup> and 14.7 years with protease inhibitors, and mean time from development of AIDS to death is 2.1 years with no protease inhibitors<sup>167,168</sup> and 3.15 years with protease inhibitors. We assumed that 55% of those receiving HIV care receive protease inhibitors.<sup>61</sup> We assumed that 39% of the asymptomatic non-injection drug users and injection drug users not in methadone maintenance treatment receive HIV care (the proportion receiving care varies with stage of infection)<sup>37</sup>; 95% of the asymptomatic injection drug users in methadone maintenance treatment receive HIV care; and 95% of all persons with AIDS receive HIV care.

<sup>o</sup>Bayoumi and Redelmeier<sup>62</sup> found quality-adjusted life-year (QALY) multipliers of 0.8 for individuals with asymptomatic HIV who know their status. The QALY multipliers they estimated fall between the values obtained in 2 other studies of individuals who are HIV infected.<sup>63,169</sup> We assumed

that half of all individuals with HIV are aware of their status, yielding an average of 0.9 for our model.

<sup>p</sup>Bayoumi and Redelmeier<sup>62</sup> found QALY multipliers of 0.64 for minor AIDS and 0.42 for major AIDS. The QALY multipliers they estimated fall between the values obtained in 2 other studies of individuals who are HIV infected.<sup>63,169</sup> We used the value 0.53, which is the average of 0.64 and 0.42.

<sup>q</sup>All costs are expressed in 1998 dollars. Costs were inflated based on the *Consumer Price Index*.<sup>170</sup>

<sup>r</sup>Calculated as a weighted average of annual health care costs for individuals aged 18 to 24, 25 to 34, and 35 to 44 given by the annual Consumer Expenditure Survey<sup>58</sup> and inflated to 1998 dollars.

<sup>s</sup>Costs were estimated on the basis of stages 1, 2, and 3 of HIV disease (defined by CD4 cell count<sup>59</sup>). We estimated the annual average cost of HIV care for individuals in these 3 stages who receive care to be \$9597, \$12077, and \$15565, respectively, based on information about the costs of different types of care<sup>59,60</sup> and the fraction of individuals receiving each type of care.<sup>61</sup> We assumed that the fraction of non-injection drug users and injection drug users not in methadone maintenance treatment who receive care in each disease stage is 25%, 50%, and 75%, respectively; this yields average annual HIV care cost for a non-injection drug user or an injection drug user not in methadone maintenance treatment in each stage of \$2455, \$6295, and \$12283, respectively. We assumed that 95% of the injection drug users in methadone maintenance treatment in each disease stage receive care; this yields average annual HIV care cost for an injection drug user in methadone maintenance treatment in each stage of \$9121, \$11499, and \$14908, respectively. We assumed that the distribution of asymptomatic individuals who are HIV infected among these stages is 54.4%, 35.6%, and 10.0%, respectively, corresponding to the approximate length of time spent in each disease stage.<sup>59</sup> Details of the cost calculations for HIV care in stages 1, 2, and 3 are shown elsewhere.<sup>37</sup>

<sup>t</sup>Assumes that the cost of AIDS care is \$33377 per person per year<sup>59–61</sup> and that 95% of individuals with AIDS receive AIDS care. Details of the cost calculations for AIDS care are shown elsewhere.<sup>37</sup>

in treatment shared needles, indicating an 81% reduction in needle sharing.

We assumed that injection drug users in methadone maintenance inject 20% as often as injection drug users not in treatment (an 80% reduction in frequency) and share 30% as often as injection drug users not in treatment (a 70% reduction in sharing), leading to a 94% reduction in risky injections among injection drug users in methadone maintenance

( $20\% \times 30\% = 6\%$  as many risky injections). We varied this rate in sensitivity analysis.

We assumed that 3.5% of methadone clients successfully “graduate” each year (i.e., leave methadone maintenance and stop injection drug use), whereas another 31.5% of methadone clients quit each year and return to untreated injection drug use. These estimates are based on studies showing that 60% to 65% of methadone clients remain in treatment after 1 year,<sup>13,51</sup> approximately 1%

of untreated injection users per year spontaneously recover,<sup>52</sup> and 2% to 5% of methadone clients per year detoxify and become abstinent.<sup>53–55</sup>

Following standard cost-effectiveness analyses for health-related interventions, we considered all health care costs, including costs of HIV care and other health care, as well as the cost of methadone maintenance. We measured health benefits in terms of quality-adjusted life-years (QALYs) gained,

TABLE 2—Summary of Results

Case Considered <sup>a</sup>	Cost per QALY Gained, \$	
	Low-Prevalence Community	High-Prevalence Community
Base case	10 900	8 200
Modified quality-of-life assumptions		
Only effect of treatment on quality of life is in preventing HIV infection	15 600	10 000
Assume no value to years of life lived by both treated and untreated injection drug users	15 200	14 100
No quality adjustment to any years of life lived <sup>b</sup>	17 200	12 100
Modified cost and effectiveness assumptions		
New treatment slots half as effective as existing slots	16 700	20 300
New treatment slots twice as costly as existing treatment slots	26 700	21 000
New treatment slots half as effective and twice as costly as existing slots	36 100	38 300

Note. QALY = quality-adjusted life-year.

<sup>a</sup>Base-case data are given in Table 1. All cases described in this table use the base-case data, except as indicated. All cases assume that new treatment slots represent a 10% expansion in treatment capacity.

<sup>b</sup>These cost-effectiveness ratios correspond to cost per life-year gained.

and we measured all costs and benefits over a 10-year time horizon. To reflect the economic principle that present value is higher than deferred value, we discounted both costs and effectiveness at 3%.<sup>56</sup>

We assumed that methadone maintenance costs \$5250 per person annually, based on analysis of data from some 600 methadone maintenance programs.<sup>57</sup> We estimated that members of the general population incur \$1210 in annual non-HIV-related health care costs,<sup>58</sup> injection drug users not in methadone maintenance incur \$3850 in annual non-HIV-related health care costs,<sup>21</sup> and injection drug users in methadone maintenance incur \$3011 in annual non-HIV-related health care costs.<sup>21</sup> Injection drug users in treatment have lower costs than injection drug users not in treatment, because they have fewer drug injection-related health problems.

Available evidence suggests that many individuals who are HIV infected are unaware of their status; the evidence also indicates, however, that injection drug users entering treatment are screened for HIV and most individuals who are HIV infected and who are aware of their status obtain anti-retroviral drugs. We assumed that 95% of the individuals who are HIV infected and in methadone maintenance receive anti-retroviral therapy but that only 48% of other individuals who are HIV infected receive anti-retroviral therapy. For asymptomatic members of the general population who are HIV infected and for injection drug users not in methadone maintenance, we estimated the annual cost of HIV care to be \$4803.<sup>59-61</sup> For

asymptomatic injection drug users who are HIV infected and in methadone maintenance, we estimated the annual HIV care cost to be \$10 545, attributable to their greater level of awareness of their infection status. We estimated that AIDS care costs \$32 551 annually for all individuals with AIDS.<sup>59-61</sup> Full details of our cost calculations are provided elsewhere.<sup>37</sup>

We used QALYs as the measure of treatment effectiveness. Quality adjustments reflect the quality of life in different health states. The adjustments range from 1, representing perfect health, to 0, representing death. We based the quality adjustments for HIV infection and AIDS on a self-assessment survey of patients.<sup>62</sup> Little research has been done on the appropriate quality adjustments for mental illness, and we are aware of none for substance abuse disorders. We used quality adjustments of 0.80 for untreated injection drug use and 0.90 for time spent in methadone treatment. These values may be compared with quality adjustments for other conditions that limit activities, such as those for moderate angina (0.92), migraine (0.87), ulcer (0.84), and severe angina (0.82).<sup>63</sup> We assumed that the combined effect of HIV infection and injection drug use status on quality of life was multiplicative; for example, an injection drug user who is HIV infected was assigned a quality-of-life multiplier of 0.72, which is the product of the multiplier for HIV without AIDS (0.9) and the multiplier for untreated injection drug use (0.8).

We defined the base cases with the parameter values in Table 1. We validated the

model by comparing its 10-year projection with recent trends in the growth of the HIV epidemic. The base cases were designed to generate relatively stable HIV prevalence among injection drug users and non-injection drug users, at levels consistent with current data, with a relatively stable proportion of the population being injection drug users. In addition, the base cases were designed to generate approximately 25% to 30% of HIV cases that result directly from injection drug use, reflecting current US estimates.<sup>2</sup> The base cases were created to enable us to compare the effects of expanding methadone maintenance programs in different injection drug user populations but were not intended to provide detailed epidemic projections. We chose a 10-year time horizon, because it is long enough to capture the nonlinear effects of the HIV epidemic but not so long as to overestimate the lasting effect of expanding methadone maintenance programs, given possible future changes in treatment or behavior.

We assumed that 15% of injection drug users are initially in methadone maintenance.<sup>64-67</sup> To assess the effect of additional methadone maintenance capacity, we used the dynamic model to project the number of individuals in each compartment over the time horizon, given a 10% increase in the number of methadone maintenance slots and assuming that additional slots are as costly and as effective in reducing risky behavior as existing slots. We determined the incremental effect on total cost and QALYs experienced in the entire population. We performed extensive 1-way sensitivity analyses.

## Results

We first modeled expansion with new methadone maintenance slots that have the same cost and effectiveness as existing slots. Results are summarized in Table 2. Of the total population of 1 000 000 in the high-prevalence community, the model started with 25 000 injection drug users, 3750 of whom were in methadone maintenance. The 10% expansion (375 new slots) had a net present cost of \$17.0 million over the 10-year time horizon. The expansion averted 264 (discounted) HIV infections (306 undiscounted infections, reducing HIV prevalence after 10 years by 0.022% compared with the base case and reducing annual HIV incidence by approximately 30.6 per million people) and caused the population to gain 1300 (discounted) QALYs. Much of the treatment cost was offset by reductions in HIV care cost, resulting in a net incremental

TABLE 3—Summary of Sensitivity Analyses

	Range Considered		Cost per QALY Gained			
			Low-Prevalence Community		High-Prevalence Community	
	Minimum Value	Maximum Value	CE at Minimum Value	CE at Maximum Value	CE at Minimum Value	CE at Maximum Value
<b>Death rates</b>						
Non-HIV-related, injection drug users not in methadone maintenance treatment	1.13%	5%	\$13 900	\$9 700	\$5 800	\$9 500
Non-HIV-related, injection drug users in methadone maintenance treatment	0.14%	3%	\$10 000	\$14 300	\$8 800	\$6 400
<b>Treatment completion</b>						
Fraction of injection drug users leaving methadone maintenance treatment who quit injection drug use and enter the general population, per year	0.35%	10%	\$16 900	\$1 100	\$13 600	\$1 000
Fraction of injection drug users not in methadone maintenance treatment who quit and enter the non-injection drug user population, per year	0	5%	\$10 900	\$18 300	\$7 200	\$12 800
<b>Sexual behavior</b>						
Annual no. of new sex partners among injection drug users	1	10	\$12 400	\$6 500	\$8 700	\$11 300
Proportion of injection drug user sexual partners who are injection drug users	5%	90%	\$11 000	\$9 700	\$4 600	\$13 300
Condom use among injection drug users	10%	60%	\$10 600	\$11 900	\$8 200	\$8 300
Increased condom use among injection drug users in methadone maintenance treatment <sup>a</sup>	1	2	\$10 900	\$10 400	\$8 200	\$6 100
Reduction in no. of sexual partners among injection drug users in methadone maintenance treatment <sup>a</sup>	0	75%	\$9 400	\$10 900	\$8 200	\$8 400
<b>Drug injection behavior</b>						
Annual no. of injections per injection drug user not in methadone maintenance treatment <sup>b</sup>	100	500	\$14 500	Cost saving	\$14 100	\$10 100
Reduction in injection frequency due to methadone maintenance treatment <sup>c</sup>	50%	95%	\$10 700	\$11 300	\$7 600	\$9 500
Fraction of injections that are shared, injection drug users not in methadone maintenance treatment <sup>d</sup>	5%	50%	\$15 500	Cost saving	\$17 200	\$11 300
Reduction in sharing associated with methadone maintenance treatment	0	95%	\$11 500	\$10 700	\$10 300	\$7 500
<b>HIV transmission</b>						
Chance of HIV transmission per risky injection <sup>e</sup>	0.1%	1%	\$15 700	Cost saving	\$15 100	\$9 100
Quality-adjustment multipliers <sup>f</sup>						
Injection drug users in methadone maintenance treatment if multiplier for injection drug users not in methadone maintenance treatment is 0.8	0.8	1	\$15 500	\$8 400	\$10 600	\$6 700
Injection drug users in methadone maintenance treatment if multiplier for injection drug users not in methadone maintenance treatment is 0.25	0.25	1	\$15 300	\$3 700	\$12 800	\$3 500
<b>Annual costs</b>						
Methadone maintenance slot	\$2 000	\$8 000	\$1 100	\$19 200	\$300	\$14 900
Multiplier for incremental health care costs of injection drug users <sup>g</sup>	0	2	\$13 600	\$8 200	\$9 900	\$6 400
Non-HIV-related health care costs of injection drug users not in methadone maintenance treatment	\$3 011	\$6 011	\$13 500	\$4 200	\$10 100	\$3 200
Multiplier for HIV care costs of injection drug users not in methadone maintenance treatment	0	2.5	\$12 600	\$8 300	\$15 000	Cost saving
Multiplier for HIV care costs of non-injection drug users and injection drug users not in methadone maintenance treatment <sup>h</sup>	0	2.5	\$13 200	\$7 400	\$15 600	Cost saving

Note. QALY = quality-adjusted life-year; CE = cost-effectiveness ratio.

<sup>a</sup>In the base case, we assumed methadone maintenance treatment caused no increase in condom use and no reduction in the number of sexual partners. We varied these numbers to account for the fact that injection drug users in methadone maintenance treatment may have increased access to safe-sex education and condom availability programs.

<sup>b</sup>In the high-prevalence community, the lowest cost-effectiveness ratio was \$7 400, corresponding to 300 injections per year.

<sup>c</sup>In the base case, we assumed methadone maintenance treatment caused an 80% reduction in injection frequency.

<sup>d</sup>In the high-prevalence community, the lowest cost-effectiveness ratio was \$7 400, corresponding to a sharing rate of 27.5% among injection drug users not in methadone maintenance treatment.

<sup>e</sup>In the high-prevalence community, the minimum cost-effectiveness ratio was \$7 400, corresponding to a needle-share transmission rate of 0.67%.

<sup>f</sup>Two-way sensitivity analysis was performed on quality-adjustment multipliers.

<sup>g</sup>The incremental health care costs of injection drug users not in methadone maintenance treatment and injection drug users in methadone maintenance treatment were varied simultaneously.

<sup>h</sup>Both costs were varied simultaneously.

cost of \$10.9 million and a cost-effectiveness ratio of \$8200 per QALY gained.

In the low-prevalence community, we assumed that there were initially 7000 injection drug users, 1050 of whom were in methadone maintenance. The 10% expansion (105 new slots) had a net present cost of \$4.8 million over the 10-year time horizon. The expansion averted 34 (discounted) HIV infections (40 undiscounted infections, reducing HIV prevalence after 10 years by 0.003% compared with the base case and reducing annual HIV incidence by approximately 4.0 per million people), caused the population to gain 301 (discounted) QALYs, and had a net incremental cost of \$3.3 million, resulting in a cost-effectiveness ratio of \$10900 per QALY gained.

In both communities, significant benefits were realized by both injection drug users and the general population. In the high-prevalence community, 58% of the QALYs gained and 28% of the HIV infections averted were among members of the general population; in the low-prevalence community, 71% of the QALYs gained and 36% of the HIV infections averted were among members of the general population. The benefits accrued by the general population are so significant that our results are not very sensitive to the quality adjustments assigned to the lives of injection drug users.

We tested the sensitivity of our model to these quality adjustments by considering 3 scenarios:

1. Some policymakers may be unwilling to accept the relatively high quality adjustments we assigned to the lives of injection drug users. However, even if *no value whatsoever* is assigned to the lives of injection drug users (i.e., all injection drug users and all individuals in methadone maintenance are assigned a quality of life of 0), expansion of methadone maintenance costs \$14 100 per QALY gained in the high-prevalence community and \$15200 per QALY gained in the low-prevalence community.

2. Conversely, some policymakers may believe that our quality adjustments overstate the benefits of methadone maintenance treatment. If no reduction in quality of life is associated with injection drug use (i.e., quality adjustments are due to only HIV infection), additional methadone maintenance capacity costs \$10000 per QALY gained in the high-prevalence community and \$15600 per QALY gained in the low-prevalence community.

3. Finally, if only raw life-years are measured, the cost-effectiveness ratios are \$12 100 per life-year gained in the high-prevalence community and \$17200 per life-year gained in the low-prevalence community. The

cost-effectiveness ratios increase when quality adjustment is ignored, because they no longer reflect improvements in quality of life associated with avoiding HIV infection or entering methadone maintenance.

We performed 1-way sensitivity analyses to test the extent to which our results were affected by our assumptions. We varied all model parameters relating to behavior, quality adjustments, death rates, treatment program data, and costs, with wide ranges of values that have been reported in the literature. We found cost-effectiveness ratios of less than \$20000 per QALY gained in all cases. We considered a 5% discount rate, the recommended alternative,<sup>56</sup> and the cost-effectiveness ratios shifted only slightly. We also considered different expansion sizes (up to doubling of current program sizes), assuming that new slots have the same cost and effectiveness as current slots. The calculated cost-effectiveness ratios were similar to those in Table 2.

Table 3 shows results of the sensitivity analysis for those parameters to which the results were most sensitive. Factors relating to drug injection behavior, treatment completion, costs of methadone maintenance and health care, and quality adjustment had the greatest effect on the results. For example, if untreated injection drug users inject or share more frequently than we assumed, then expansion of methadone maintenance is more cost-effective than we estimated. The base case assumed that methadone clients inject 80% less often than injection drug users not in treatment; if the reduction is only 50%, then the cost per QALY gained is \$10700 in the low-prevalence community and \$7600 in the high-prevalence community. The base case assumed a 3.5% annual "graduation rate" (the rate at which injection drug users leave methadone maintenance and become abstinent) from methadone maintenance; if the graduation rate is only 0.35%, then the cost-effectiveness ratios become \$16900 and \$13600, respectively.

Some studies have found lower methadone maintenance costs than we estimated<sup>68</sup>; if methadone maintenance can be provided for \$2000 per person annually, the cost-effectiveness ratios become \$1100 and \$300, respectively. If untreated injection drug users incur the same non-HIV-related health care costs as injection drug users in methadone maintenance (\$3011 annually), then the cost-effectiveness ratios are higher—\$13 500 and \$10 100, respectively—than in the base case. Lower quality-of-life multipliers for untreated injection drug use and methadone maintenance increase the cost-effectiveness ratios; for example, if untreated injection drug users and

injection drug users in methadone maintenance are assigned a quality-adjustment multiplier of 0.25, the ratios become \$15300 and \$12800, respectively.

Protease inhibitors and other antiretroviral drugs are an important component of the cost of HIV care.<sup>60</sup> The extent to which socially disadvantaged populations know about and use such drugs is uncertain,<sup>69-71</sup> and recent anecdotal evidence suggests that some individuals in treatment experience unpleasant reactions from the combination of methadone and protease inhibitors, making them less willing to pursue both forms of treatment simultaneously.<sup>72</sup> Sensitivity analysis revealed that expansion of methadone maintenance is cost-effective under a variety of assumptions about how widely protease inhibitors are used and what benefits they convey.

Expanded methadone maintenance capacity may reach injection drug users who are less successfully treated than those currently in treatment; expansion also may be more costly than current treatment. We considered the case of incremental slots that are half as effective as current slots in reducing risky behavior; effectiveness was measured by both the reduction in the rate of risky needle sharing by injection drug users in treatment and the rate at which those leaving treatment cease drug injection. We varied these dimensions simultaneously: a 50% decrease in effectiveness represents a 50% decrease in the graduation rate and a reduction in risky needle sharing that is 50% less than the reduction assumed in the base case.

We considered the case of incremental slots that are twice as costly as current slots. Results are shown in Table 2. If additional treatment slots are as costly as methadone maintenance but half as effective in reducing risky behavior, the cost-effectiveness ratios are \$20300 and \$16700 per QALY gained in the high- and low-prevalence communities, respectively. If additional slots are as effective as methadone maintenance but twice as costly, the cost-effectiveness ratios are \$21000 and \$26700, respectively. If new slots are half as effective and twice as costly as methadone maintenance, the ratios are \$38300 and \$36100, respectively.

## Discussion

We used commonly accepted criteria for judging health care interventions and found that expansion of methadone maintenance programs is a cost-effective use of health care resources. Although no strict threshold exists for judging the cost-effectiveness of a medical intervention, it has been suggested that ratios (expressed in

1998 dollars) less than \$33 000 per QALY gained are cost-effective, and ratios greater than \$170 000 per QALY gained are “questionable in comparison with other health care expenditures.”<sup>73</sup> More recent opinions suggest that a cost-effectiveness ratio as high as \$50 000 to \$60 000 per QALY gained represents a cost-effective use of resources.<sup>74,75</sup>

Our base cases yielded cost-effectiveness ratios of \$8200 and \$10 900 per QALY gained in the high- and low-prevalence communities, respectively. Sensitivity analysis revealed that expansion of methadone maintenance capacity with new slots of average cost and effectiveness has a ratio of less than \$20 000 per QALY gained; at twice the cost and half the effectiveness, expansion has a ratio of less than \$40 000 per QALY gained.

Expansion of methadone maintenance programs increases HIV care costs, because methadone clients are more likely to be screened for HIV and to receive HIV care than untreated injection drug users. However, such expansion also reduces HIV care costs by preventing new infections. Methadone expansion increases quality of life and years of survival via reduced injection drug use, reduced HIV transmission, and reduced morbidity and mortality. These factors have an important effect on the cost-effectiveness ratio. Use of a dynamic model allowed us to capture these effects.

A previous study estimated that providing methadone maintenance to injection drug users for 1 year would cost \$48 000 to \$60 000 per (undiscounted) HIV infection averted over 5 years (expressed in 1998 dollars).<sup>36</sup> Our analysis, which considers a permanent expansion of methadone maintenance and which uses a more comprehensive cost model, found that expansion of methadone maintenance capacity would cost approximately \$41 000 per (discounted) HIV infection averted in the high-prevalence community (264 discounted HIV infections averted over the 10-year time horizon with a net present incremental cost of \$10.9 million) and \$97 000 per (discounted) HIV infection averted in the low-prevalence community (34 HIV infections averted with a net incremental cost of \$3.3 million).

The cost-effectiveness ratios that we found compare favorably with those of many other health care interventions not related to HIV,<sup>73,76,77</sup> as well as with ratios determined for other HIV-related interventions. Treatment with trimethoprim-sulfamethoxazole for *Pneumocystis carinii* pneumonia and toxoplasmosis in patients who are HIV infected with CD4 cell counts of 200/ $\mu$ L or less has a cost-effectiveness ratio of \$16 000 per QALY gained,<sup>78</sup> prophylaxis for *Mycobacterium avium* complex in patients who

are HIV infected with CD4 cell counts less than 50/ $\mu$ L has a cost-effectiveness ratio between \$35 000 per QALY gained and \$74 000 per QALY gained,<sup>78</sup> and prophylaxis for cytomegalovirus retinitis has a ratio of at least \$160 000.<sup>79,80</sup> Chemoprophylaxis following high-risk occupational exposure to HIV has a cost-effectiveness ratio of \$37 000,<sup>81</sup> and that following sexual exposure to HIV has a cost-effectiveness ratio of \$6300.<sup>82</sup> Other HIV prevention programs have been found to have more favorable cost-effectiveness ratios than we estimated for expansion of methadone maintenance programs; for example, an intervention to increase condom use among high-risk urban women has a ratio of \$2000,<sup>83</sup> and a skills training program for men who have sex with men was estimated to be cost saving.<sup>84</sup>

Methadone maintenance is provided solely to injection drug users, whereas HIV-related interventions are also provided to other individuals. If policymakers assign a lower value to the lives of injection drug users than to other individuals, they may not be convinced that an intervention that targets drug users is worth funding. We found that much of the benefit of methadone maintenance is realized by the general population: approximately half of the HIV infections averted, and more than half of the QALYs gained, are among non-injection drug users. We also found that expansion of methadone capacity is cost-effective even if the decision maker adopts the extreme viewpoint that the lives of injection drug users have absolutely no value.

Even though methadone maintenance treatment is not completely effective in reducing risky behavior, it reduces risky behavior enough to have a significant effect on the HIV epidemic. The value of imperfect interventions has also been observed in models of HIV screening and counseling programs.<sup>30,31,85</sup>

Our analysis found that expansion of capacity to treat injection drug users is cost-effective, even if it is more costly and less effective than current methadone maintenance programs. This may be the case if new recruits into methadone maintenance programs are harder to reach, harder to monitor, or less willing to change their behavior than those already in treatment.

Injection drug users fail to receive treatment for a variety of reasons. Methadone maintenance clinics are regulated by restrictive federal, state, and local rules. These rules require the drug to be dispensed daily from a specially licensed clinic and sometimes limit the duration of treatment or the dose.<sup>9,86,87</sup> Public funds are not sufficient to treat all who require treatment,<sup>88</sup> and many injection drug users who pay privately for methadone main-

tenance discontinue for financial reasons.<sup>89</sup> Even if regulatory and financial barriers to methadone maintenance were reduced or eliminated, many injection drug users still would not enter treatment.<sup>90</sup> Our analysis has shown that expansion of methadone maintenance programs is a cost-effective use of health care resources and suggests that these barriers deny access to a cost-effective therapy. In addition, alternatives to methadone maintenance, including medical models of dispensing methadone,<sup>91</sup> the use of levo- $\alpha$ -acetylmethadol (LAAM),<sup>92</sup> and drugs such as buprenorphine,<sup>93</sup> may be cost-effective.

Our analysis had several limitations. We adopted a 10-year time horizon, because of our concern that longer-term projections would be inaccurate. We did not include the effect of methadone maintenance treatment on the criminal justice and welfare systems; their inclusion would make expansion of methadone maintenance appear even more cost-effective. HIV prevalence, the behavior of injection drug users, and the availability, content, and effectiveness of methadone maintenance treatment vary by geographic region; these variations would likely cause some geographic differences in the cost-effectiveness ratio.

Our analysis did not include the effect of cocaine injection. Little information exists on cocaine injection in the United States, although some evidence indicates that cocaine injection has declined.<sup>94</sup> Cocaine injection is clearly a risk factor for HIV<sup>95</sup>: injection cocaine users are more likely than injection opiate users to share drug injection equipment and to engage in other high-risk behaviors.<sup>44,96,97</sup> The risks associated with injection cocaine use extend to individuals in methadone maintenance.<sup>98,99</sup> Evidence regarding the effect of methadone maintenance on cocaine use is mixed: some individuals increase cocaine use after entering methadone treatment,<sup>44</sup> but the overall effect may be a reduction in injection cocaine use.<sup>44,96</sup> Methadone maintenance clients who also inject cocaine may not reduce risky behavior by as much as clients who do not inject cocaine, so the exclusion of cocaine injection practices from our model may have overstated the benefit of methadone maintenance.

Our analysis was based on a compartmental model, similar to that used in other analyses of the spread of HIV<sup>100</sup> and other diseases<sup>101–104</sup> and the cost and effectiveness of HIV prevention programs.<sup>30–34,105,106</sup> All individuals within a given compartment are assumed to behave the same, on average. An alternative approach is to examine disease transmission through social networks by considering how individuals form and break social connections within a network.<sup>107,108</sup>

Studies in various US cities have identified large social networks of injection drug users.<sup>109-118</sup> A key conclusion of these studies is that prevention efforts are more effective when they are targeted to individuals who are centrally located in high-risk networks than when they reach individuals on the periphery of such networks. If incremental methadone capacity were targeted to injection drug users who are centrally located in networks, then such expansion would likely be more cost-effective than we have estimated; and if incremental capacity reached injection drug users located on the periphery of networks, then such expansion would likely be less cost-effective than we have estimated.

We made modest adjustments for the effect of substance abuse disorders on quality of life (0.8 for untreated injection drug use and 0.9 for time spent in methadone maintenance). Data on the appropriate adjustment for substance abuse disorders are limited. Individuals who are addicted to heroin likely have comorbid psychiatric disorders, including depression, schizophrenia, anxiety disorders, and other mental illnesses,<sup>119-121</sup> and comorbid medical diseases, including hepatitis, soft tissue infections, and many other diseases.<sup>122,123</sup> Quality adjustments have been estimated to be 0.45 for depression,<sup>124</sup> 0.61 for mild schizophrenia,<sup>125</sup> and 0.29 for severe chronic schizophrenia.<sup>125</sup> These values are significantly lower than the quality adjustments that we made for injection drug use. Future work on the cost-effectiveness of substance abuse treatment will benefit from an improved estimate of the quality adjustment for injection drug use.

Recent political campaigns have sought to eliminate access to methadone maintenance programs, asserting that they "simply substitute one dependency for another and that abstinence from drugs is a more moral and decent approach to curing addiction."<sup>19</sup> Our analysis suggests that methadone maintenance, even if it does not lead to a complete or permanent cessation of drug use, is a cost-effective intervention that can play an important role in preventing the spread of HIV and in improving the length and quality of life for injection drug users and the general population. □

## Contributors

G. S. Zaric performed much of the literature review and data synthesis and all of the computer analyses and contributed to building the model. P. G. Barnett conceived of the need for the study, performed early literature research, and wrote much of the first draft of the paper. M. L. Brandeau developed the basic dynamic model, wrote the Methods section of the paper, and was involved in revising the paper. All 3 authors worked together on the design of the model,

the selection of the parameters, the choice of analyses, and the interpretation of the results.

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Query 1: Are the first 2 sentences of paragraph beginning "Available evidence suggests that many individuals who are HIV infected" edited as meant?