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Optimal Control of Harm Reduction in Preventing HIV and Hepatitis C Among Drug Users

C. Gavrila, HA Pollack, J. Caulkins, PM Kort, G. Feichtinger, G. Tragler

I. Introduction

Blood-borne diseases pose the principal threat to the health of injection drug users (IDU). Human immunodeficiency virus (HIV) infections among IDU account for an estimated 25 percent of new HIV infections in the United States, a figure that does not include many cases attributed to sexual transmission involving injection drug users.¹

Hepatitis C (HCV), though less lethal than HIV, is far more widespread among IDU, with prevalence far above 50 percent in many populations.²⁻⁴ HCV among current and former drug users is now the most common diagnosis requiring liver transplantation in the United States.^{2, 5} A blood-borne agent spread through sharing of infected needles, cookers, cotton, and other injection equipment,^{3, 4, 6, 7} HCV is efficiently transmitted through infected needles. In one study, between 3 and 9 percent of hospital workers exposed to HCV through needle-sticking accidents subsequently contracted the virus.⁵ For this reason, treatment and prevention interventions have proved less successful in slowing HCV infection than they have in slowing the spread of HIV.^{2, 3, 5, 8-11}

Harm reduction interventions, principally syringe exchange programs (SEP) and methadone maintenance treatment (MMT), are the principal levers available to policymakers in slowing infectious disease spread. Provision of sterile injection equipment through SEP is the paradigmatic example of harm reduction. Many SEP include components designed to reduce drug use. Even if these interventions have no impact on the frequency and duration of clients' drug use, SEP seeks to reduce infectious

disease spread through provision of sterile syringes. Methadone treatment seeks explicitly to halt or reduce injection drug use and is a more intensive and costly intervention than syringe exchange.¹² MMT interventions also include harm reduction elements, such as instruction in proper use of bleach or overdose risk.

Many studies indicate that SEP can slow the spread of HIV among IDU.¹³⁻¹⁶ Several studies indicate that MMT is also effective in slowing HIV spread.¹⁷⁻²³ Both kinds of interventions appear markedly less successful in slowing HCV, even in populations that successfully maintain low HIV prevalence.^{2, 3, 5, 8-11}

Pollack (2001) presents an explicit epidemiological analysis that highlights the differing effectiveness and cost-effectiveness of SEP in addressing the two blood-borne epidemics. This analysis, based upon the New Haven Needle Exchange Program, suggests that an imperfect intervention is highly effective in HIV prevention but has little impact on long-run prevalence of HCV.²⁴ This analysis focused on steady-state comparisons and did not consider transient effects. Pollack (forthcoming) provides a more complex epidemiological analysis of MMT.²³ Examining the cost-effectiveness of both kinds of intervention, this paper explores the average and marginal costs of MMT per averted infection. Although both analyses are intertemporal, program features are assumed constant over time.

The current paper extends these analyses *considerably* by *employing a dynamic optimization approach*. *In this framework the optimal level of methadone treatment is determined over time, depending on the size of the IDU population and the number of infected IDUs. As a result the number of “treatment slots” M need not be constant but might vary over the course of an epidemic. The optimal policy maximizes the net benefits*

associated with treatment intervention. *We show how it depends on parameters like infectivity rate (much higher for HCV than for HIV), the costs of intervention, the social costs of injection drug use and the costs associated positive serostatus for blood-borne disease. We find three principal results (hopefully we can extend this somewhat by pointing at differences in optimal policy between HCV and HIV):*

- M(t) should indeed vary over time in response to local conditions. *Methadone treatment is less efficient if either the number of infected IDUs is low (indicating a low risk of infection for IDUs that are not infected (yet)) or when almost all IDUs are infected (not many uninfected IDUs left to which prevention is targeted).*
- Under realistic parameters, some level of intervention is cost-effective to prevent blood-borne disease, *except when almost nobody or everybody is infected.*
- Disease eradication is not optimal within our model.

II. Analytic Model

We start by presenting the dynamics in Pollack (2000). Table 1 (*here we should argue why these parameter values are realistic*) shows the definition of pertinent variables.

If $N(t)$ is the number of IDUs, it is given by the relationship

$$\dot{N}(t) = \theta - [N(t) - M(t)]\delta - M\omega \quad (1)$$

Here θ is the exogenous inflow of drug users. M is the number of clients in the harm reduction intervention. $[N(t)-M(t)]\delta$ is the outflow of users not in treatment. $M\omega$ is the outflow of in-treatment IDUs.

Following Pollack (2000), the number of infected IDUs over time is governed by

$$\dot{I}(t) = -\delta\left[1 - \frac{M}{N}\right]I(t) + \kappa\lambda\left[1 - \frac{M}{N}\right]\left[1 - \frac{I}{\Omega N}\right]I - \frac{M\omega I}{N} \quad (2)$$

On the right-hand-side, the first term represents the exit rate of out-of-treatment IDUs. The middle term represents disease incidence among individuals who needle-share and do not participate in harm reduction interventions. The last term, $\mu\gamma(I(M/N))$ (*note that $\mu\gamma$ equals ω , cf. Table 1*), represents the exit rate of in-treatment infected IDUs from the population.

In contrast to earlier work, we allow treatment slots to vary over time. $M(t)$ is then chosen to maximize the present discounted value of the stream of benefits and costs associated with harm reduction intervention. This results in

$$\min_{M(t)} \int_0^{\infty} e^{-rt} [g(M(t)) + vI(t) + \rho N(t)] dt \quad (3)$$

Here $g(M)$ is the amount of money required to include $M(t)$ people in treatment. Given “diminishing returns” in outreach to motivated IDUs and in service costs, we assume that $g(\cdot)$ is a convex function with $g(0)=0$, $g'(M)>0$, $g''(M)>0$.

It makes sense that only IDUs will get methadone treatment so that $0 \leq M(t) \leq N(t)$.

v is the annual social cost per infected user, and ρ represents the non-infection-related social costs that accompany drug use. We set $g(M)=a_1M+a_2M^2$ to indicate the convex character of outreach and treatment costs as one enrolls less motivated or more

troubled clients into treatment interventions. [Perhaps ρ should be set to zero since our posited intervention does not alter $N(t)$ when $a=0$. *YES*]

The analysis of the “full model” that includes both states N and I is complex. In the present paper, we simplify matters by assuming that $N(t)$ is constant, which corresponds to the case $a=\omega-\delta=0$ and $N(t)=N^*=\theta/\delta$. This corresponds to the case that harm reduction makes drug use less dangerous, but has no impact on the number of IDUs.

III. Analysis

Under the assumption $\mu\gamma-\delta=0$, let us analyze the case that $N(t)$ is constant at some value N^* . For this to happen, N reaches steady-state $N^*=\theta/\delta$. Grouping terms yields

$$\dot{I} = I[-\delta - a\frac{M}{N} + [1 - \frac{M}{N}][b - \frac{fI}{N}]] \quad (4)$$

To make the model more tractable, we work with the below state and control variables

$$\pi = \frac{I}{N}, \quad U = \frac{M}{N} \quad (5)$$

Here π is the proportion of IDUs who are infected, and U is the proportion of IDUs who receive the intervention. In this case, the full model reduces to (*in the formula below “ J ” should be “ π ”*)

$$\min_{M(t)} \int_0^{\infty} e^{-rt} [g(UN) + vNJ + \rho N] dt = \max_{M(t)} (N^*)^2 \int_0^{\infty} e^{-rt} \left[\frac{g(UN)}{(N^*)^2} + \frac{v}{N^*} \pi + \rho N^* \right] dt$$

$$= \max_{M(t)} (N^*)^2 \int_0^{\infty} e^{-rt} F[\pi, U] dt$$

s.t.

$$N = N^*, \quad (6)$$

$$\dot{\pi} = \pi(-\delta + (1-U)(b - f\pi)),$$

$$0 \leq \pi \leq 1, \quad 0 \leq U \leq 1$$

This is an optimal control model with one state variable, π , and one control variable, U . Over time, the decision-maker has to fix its control variable in such a way that the objective is optimized. This should be done while taking into account the movement of the state variable, and the restrictions on the values of control and state. Pontryagin's maximum principle (see, e.g., Feichtinger and Hartl (1986)) provides conditions that a solution has to satisfy in order to be optimal. Applying the maximum principle yields the following system of ordinary differential equations:

$$\dot{\pi} = -\delta\pi + f\pi(1-U)(\Omega - \pi),$$

$$\dot{U} = -\frac{1}{2a_2(a+b-f\pi)} * (2a_2brU - 2a_2f\pi rU - (a^2 - b^2)\pi v + 2bf\pi^2 v - f^2\pi^3 v$$

$$+ a((a_1 + 2Ua_2)(f\pi + r) + \pi(f\pi - b)v)) + 2a_2f\pi U\delta + a_1(br + f\pi(\delta - r))$$

$$0 \leq \pi \leq 1, \quad 0 \leq U \leq 1$$

Setting $a=0$ yields

$$\dot{\pi} = -\delta\pi + f\pi(1-U)(\Omega - \pi),$$

$$\dot{U} = -\frac{1}{2a_2(b-f\pi)} * (2a_2brU - 2a_2f\pi rU + b^2\pi v + 2bf\pi^2 v - f^2\pi^3 v$$

$$+ 2a_2f\pi U\delta + a_1(br + f\pi(\delta - r))$$

$$0 \leq \pi \leq 1, \quad 0 \leq U \leq 1$$

[Are these correct?] Examining steady-state values at positive prevalence, we

have

$$\pi^* = \Omega \left[1 - \frac{\delta}{\kappa \lambda (1 - U^*)} \right],$$

The above analysis leads immediately to:

Proposition 1. It is not optimal to eradicate the infection.

Proof. (others must supply)

Although calculations are complex, the intuition behind Proposition 1 is simple.

The payoff to treatment is extremely low when prevalence is low. Note that the number of new infections per unit time is

$$I = N(\pi + \delta\pi) = Nf\pi(1-U)(\Omega - \pi) = \pi[Nf(1-U)\Omega] - \pi^2[Nf(1-U)\Omega]$$

If the marginal cost of treatment is some positive c , the marginal cost per averted infection at zero prevalence is

$$K = \frac{c}{\left[\frac{\partial I}{\partial U} \right]_{\pi=0}} = \frac{c}{\frac{\partial}{\partial U} Nf\pi(1-U)(\Omega - \pi) \Big|_{\pi=0}} = \infty$$

So it is never optimal to completely eradicate the infection through this kind of harm reduction intervention. This result has nothing to do with the defects of an available intervention. We assume that the posited intervention is perfectly effective in protecting participants against infectious disease transmission (*we could reintroduce the β into the model (see Pollack (Vienna conference paper)) and analyze the effects of having $\beta < 1$, although I do not expect spectacular changes*). Since the marginal benefits of services are a quadratic function that goes to zero at zero prevalence, it is never cost-effective to drive prevalence all the way to zero.

Cost-effectiveness

For infectious disease control, cost-effectiveness is an important concern. Given the optimal policy, one can then compute the cost of intervention per averted infection. In particular, suppose that $\{I_0(t)\}$ is the time-path of new infections per unit time absent intervention. In similar fashion, let $\{M(t), I_1(t)\}$ be the time-paths of service provision and new infections per unit time under the optimal policy. Then the cost per averted infection associated with intervention is given by

$$CE = \frac{\int_0^{\infty} e^{-rt} g[M(t)] dt}{\int_0^{\infty} e^{-rt} [I_0(t) - I_1(t)] dt}$$

An example.

To illustrate qualitative results, can we simulate the following: All values corresponding to HCV with $\kappa=0.03$ (*This is HCV, should we also do HIV?*), $a=0$, $\delta=1/4000$, $v=(\$10, \$20, \$50)$, $a_1=5$, and $a_2=1.25e-6$? Can we then compare these with $M(t)$ set to a constant value to see how the payoffs and time-histories differ (*This constant value should be that value of M that gives the highest objective value, given that M is not allowed to change over time*). Here we should insert the graph that shows how $M(t)$ behaves as function of time. The same for $I(t)$.

As shown in the example, the optimal allocation of harm reduction services varies over time.

Sensitivity Analysis

[Can we repeat the analysis with $N=2000$, $g(M)=5M+0.0000025$ (*this should be 0.00000125?*) M^2 , and with the daily “cost” of infection \$10, \$25, and \$50? Figure 1 shows the phase diagram in the base case.]

[Phase diagrams]

Qualitative features:

Applying standard control methods, the phase diagram depicted in Figure 1 is obtained. In the figure we see that treatment is large especially for intermediate values of the number of infected IDUs, and decreases to zero when this number is low or almost equal to N^ . The intuition is that methadone treatment is ineffective when either the number of infected IDUs is low (i.e., relatively low risk of infection, since almost nobody is there to spread the disease), or when it approaches the size of the total IDU population. In the latter case most of the IDUs are already infected, so the number of potential new infections is low. Also, we see that in the longer term a steady state value for the number of infected IDUs and the number of treatment slots prevails. (Here we must also present an (implicit) expression for the steady state value of π and U , and carry out some comparative statics on that.)*

Discussion

In case we have nice results we should say something about differences HCV-HIV and mention the possible extension to analyze a population that suffers from both (See Jon's Memo #38 (Sept 17, 2001)).

This paper explores optimal allocation of harm reduction services. In doing so, it also explores the cost-effectiveness of resulting interventions. It explores an idealized harm reduction intervention—one that eliminates disease risk for all program participants but that does not alter the underlying frequency or duration of injection drug use. It uses a random-mixing epidemiological model, and applies optimal control theory to derive the optimal path of services to maximize the net benefits associated with infectious disease control among injection drug users. Optimal control theory provides a useful tool to explicitly investigate the tradeoffs between protection and program cost. We also calculate traditional cost-effectiveness measures along the optimal time-path of the intervention.

We present numerical examples showing that the optimal trajectory of services significantly varies over time, in response to epidemic conditions. [compare the static and dynamic solutions; cost-effectiveness results]

In addition to simulation results, we demonstrate a central formal result: it is never optimal to eradicate blood-borne infection. Even as $t \Rightarrow \infty$, it is not optimal to approach zero prevalence in steady state. This result does not reflect posited faults of typical imperfect interventions. It applies to an idealized intervention that completely protects enrolled IDUs. At low sufficiently prevalence, the benefits of intervention do not justify the additional costs.

[Do we know whether this is always true when $a=0$ for all values of b and f ?

Eradication removes the need for further costly prevention interventions. Yet this payoff is not sufficient to justify the accompanying costs.

Like any formal analysis, this study includes important limitations. We use a random-mixing model most appropriate for populations with prevalent random sharing. This random mixing model can be extended to overlapping subgroups or more complex compartmental models. Segregated subgroups tend to depress disease incidence by reducing the proportion of “discordant” needle sharing that matches infected and uninfected IDUs. More sociologically complex models provide a more sophisticated framework to examine the context of needle-sharing and infectious disease spread.^{25, 26} However, mathematical models indicate that the random mixing model provides a good approximation to non-random models when there is even a small degree of overlap across disparate sharing networks.^{27, 28}

Our analysis focuses on an idealized harm reduction intervention. We do not consider many other benefits associated with harm reduction interventions. Methadone maintenance treatment and best-practice syringe exchange include diverse components to shorten drug-using careers and to otherwise halt or to reduce individuals’ injection drug use.²⁹ Including these benefits in the intervention would increase our estimates of program effectiveness and might also alter our analysis of optimal policy.

Variable/Parameter	Empirical values	Definition
$N(t)$	(Since $a=0$, this is θ/δ)	IDU population
$M(t)$		Number of treatment slots
δ	1/(4000 days)	Exit rate from active IDU population
μ	1/(400 days)	Exit rate from treatment
θ	0.5/day	Entry rate of new (uninfected) people into the IDU population
γ	.1	Permanent cure rate of treatment
$I(t)$		Infected IDU population
κ	0.005 for HIV 0.03 for HCV	Infectivity
λ	1/(7 days)	Frequency of needle-sharing
Ω	0.3	Proportion of shooting gallery participants among treatment clients
$G(M)$	In example: $5M+0.00000125M^2$	Amount of money spent on treatment to put M people into a slot
v	\$10,20,50	Daily social cost per infected IDU
ρ	(Irrelevant since $a=0$.)	Daily social cost per IDU independent of infection
π	$I(t)/N$	The proportion of infected individuals-- I/N
U	M/N	The proportion of IDUs receiving the intervention— M/N
A	0	$\mu\gamma-\delta$ The incremental increase in exit per “slot” from the IDU population due to the intervention.
B		$\kappa\lambda$
F		$\kappa\lambda/\Omega$
C	\$5	Cost/day
$\omega=\mu\gamma$	1/(4000 days)	Exit rate from harm reduction intervention. Assumed equal to δ .

Table 1

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