AN IMPROVED OPTIMISTIC THREE-STAGE MODEL FOR THE SPREAD OF HIV AMONGST INJECTING INTRAVENOUS DRUG USERS

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ABSTRACT. We start off this paper with a brief introduction to modeling Human Immunodeficiency Virus (HIV) and Acquired Immune Deficiency Syndrome (AIDS) amongst sharing, injecting drug users (IDUs). Then we describe the mathematical model which we shall use which extends an existing model of the spread of HIV and AIDS amongst IDUs by incorporating loss of HIV infectivity over time. This is followed by the derivation of a key epidemiological parameter, the basic reproduction number R_0. Next we give some analytical equilibrium, local and global stability results. We show that if $R_0 \leq 1$ then the disease will always die out. For $R_0 > 1$ there is the disease-free equilibrium (DFE) and a unique endemic equilibrium. The DFE is unstable. An approximation argument shows that we expect the endemic equilibrium to be locally stable. We next discuss a more realistic version of the model, relaxing the assumption that the number of addicts remains constant and obtain some results for this model. The subsequent section gives simulations for both models confirming that if $R_0 \leq 1$ then the disease will die out and if $R_0 > 1$ then if it is initially present the disease will tend to the unique endemic equilibrium. The simulation results are compared with the original model with no loss of HIV infectivity. Next the implications of these results for control strategies are considered. A brief summary concludes the paper.

1. **Introduction.** HIV/AIDS is a viral disease discovered in the 1980's. Untreated infection with HIV eventually leads to AIDS. The main potential transmission routes are: (i) homosexual or heterosexual contact with an infected person; (ii) sharing needles or syringes with an infected person; (iii) blood transfusion and (iv) transmission from mother to child. In the past blood transfusion has been an important transmission route but it is now very rare in countries where blood is screened for HIV antibodies. Transmission from mother to child is still a significant issue even though there are modern day drugs available which can greatly reduce the risk.

In the past when knowledge of how HIV was transmitted was just developing transmission amongst IDUs was a major problem. In many parts of the world HIV prevalence reached 40% and above just one to two years after HIV entered the IDU population [18]. [15] estimated that the proportion of HIV infections caused by injecting drug use is:
• 50 to 90% in Eastern Europe, Central and Eastern Asia and the Pacific;

- 25 to 50% in North America and Western Europe;
- 10 to 25% in Latin America;
- 1 to 10% in Southern and South-Eastern Asia; and
- less than 1% in sub-Saharan Africa (cited in [19]).

Our model is based on an original paper by Kaplan [7] who considers the spread of HIV/AIDS via drug use in "shooting galleries" where addicts meet to inject drugs and share needles. The spread of the disease was modeled using two differential equations:

$$\frac{d\pi}{dt} = (1-\pi)\lambda\beta\alpha - \mu\pi$$

and
$$\frac{d\beta}{dt} = \lambda\gamma\pi - \lambda\gamma\beta(1 - (1-\pi)(1-\theta)).$$

$\beta(t)$ is the fraction of syringes infected and $\pi(t)$ is the fraction of addicts infected at time t. There are m syringes and n addicts in the population. λ is the per addict injection rate, μ is the rate at which addicts leave the sharing, injecting population and $\gamma = n/m$ is the gallery ratio of addicts to needles. α is the infection probability per injection, and θ is the flushing probability, the probability that an initially susceptible addict leaves an infected syringe uninfected after a single use. A key epidemiological parameter is R_0, the basic reproduction number. For $R_0 \leq 1$ we expect the disease to die out, but for $R_0 > 1$ we expect the disease to take off [5].

Kaplan and O'Keefe [10] performed a management science based study of a model loosely based on Kaplan's original model. They developed a syringe tracking and testing system that provided data on HIV transmission. They examined the impact of cleaning and bleaching of infectious needles prior to use and allowing used syringes to be removed and replaced by unused syringes in the needle population. Kaplan and O'Keefe's model suggested that the long-term prevalence of HIV in addicts could be reduced by up to 33% by implementation of a needle exchange. As a result Connecticut legislation was changed to allow needle exchanges to operate on a "one for one" basis. Also legislation was changed in California, New York and Massachusetts to allow needle exchanges to be implemented and developed.

These models assume that all addicts and needles are equally infectious throughout the entire infectious period. In reality addicts pass through three stages of HIV infectivity: an initial highly infectious stage, a second stage of low infectivity and a third stage of medium infectivity before developing clinical symptoms of AIDS. Greenhalgh and Lewis looked at incorporating this into the models. In [6] they split both addicts and needles into three infectious stages. A needle used by an infected or susceptible addict is left in the infectious state of the last person to use it ("The Optimistic Model"). We shall extend this model in the paper. Lewis and Greenhalgh [13] also split addicts and needles into three infectious classes. This time a needle used by an infected or susceptible addict is left in the higher infectious state of its initial infectious state or the state of the last person to use it ("The Pessimistic Model").

2. **The Model.** Consider the "Optimistic Model" of Greenhalgh and Lewis [6]. In reality HIV-infected needles do not remain infected indefinitely but lose infectivity over time. Our target is to examine how addicts and needles interact with each other

under extended hypotheses that an infectious needle in the i'th stage of infectivity becomes virus-free with rate σ_i, $i = 1,2,3$.

The model assumes:

(1) All sharing of drug equipment occurs in shooting galleries. There are m shooting galleries (equivalently m "kits" of drug injection equipment are in circulation) and addicts select shooting galleries or "kits" at random. All addicts inject once per visit to a shooting gallery. There are n addicts and the gallery ratio $\gamma = n/m$.

(2) Each addict visits shooting galleries in accordance with a Poisson process of rate λ, independently of the actions of other addicts.

(3) Injection equipment becomes infected if it is used by an infected addict. Injection equipment always takes on the infectivity characteristics of the last user. Any uninfected addict who uses injection equipment is exposed to HIV.

(4) The random variability in the fraction of infected addicts and needles at time t is sufficiently small to be ignored.

(5) Infectious addicts depart the population for reasons other than developing full-blown AIDS (such as deaths from other causes, treatment or relocation) at per capita rate μ and are immediately replaced by other addicts.

(6) An addict effectively cleans (bleaches) the injection equipment prior to use with probability ϕ.

(7) Each needle is exchanged for an uninfected needle according to a Poisson process with rate τ. This corresponds to needle exchange.

(8) Given exposure to an infectious needle in state i infectivity a susceptible addict becomes infected with probability α_i for $i = 1,2,3$. α_i is the infectiousness of a state i needle. The only way addicts can become infected is through sharing needles.

(9) After initial infection an addict is defined to be acutely infectious and enters the asymptomatic stage according to a Poisson process with rate δ_1.

(10) Asymptomatic addicts enter the pre-AIDS stage according to a Poisson process with per capita rate δ_2.

(11) Pre-AIDS addicts enter the full-blown AIDS stage according to a Poisson process with per capita rate δ_3. At this stage addicts leave the sharing, injecting population. These addicts are immediately replaced by susceptible addicts.

The spread of the disease is given by

$$\frac{d\pi_1}{dt} = \left(1 - \sum_{i=1}^{3} \pi_i\right)\lambda(\alpha_1\beta_1 + \alpha_2\beta_2 + \alpha_3\beta_3)(1 - \phi) - (\mu + \delta_1)\pi_1, \tag{1}$$

$$\frac{d\pi_2}{dt} = \delta_1\pi_1 - (\mu + \delta_2)\pi_2, \qquad \frac{d\pi_3}{dt} = \delta_2\pi_2 - (\mu + \delta_3)\pi_3,$$

and $\dfrac{d\beta_j}{dt} = \lambda\gamma(\pi_j - \beta_j) - \beta_j(\tau + \sigma_j), \quad \text{for} \quad j = 1, 2, 3,$

with suitable initial conditions. Here for $i, j = 1,2,3$, π_i is the fraction of all addicts who are stage i infected addicts and β_j is the fraction of all needles which are infected needles in state j.

3. **Basic Reproduction Number R_0.** R_0 is defined as the expected number of secondary addicts infected by a single newly infected addict entering the DFE (i.e. addicts infected directly via sharing a syringe with the original infected addict).

A newly infected addict infects $\lambda/(\mu + \delta_1)$ syringes in stage 1, and progresses to stage 2 with probability $\delta_1/(\mu + \delta_1)$. A stage 2 infected addict infects $\lambda/(\mu + \delta_2)$

syringes in stage 2 and progresses to stage 3 with probability $\delta_2/(\mu + \delta_2)$. A stage 3 infected addict infects $\lambda/(\mu + \delta_3)$ syringes in stage 3. For $i = 1,2,3$, a state i infected needle is used by susceptible addicts at rate $\lambda\gamma$ (we can assume that all addicts are susceptible as we are near the DFE) and infects

$$\frac{\lambda\gamma\alpha_i(1-\phi)}{\lambda\gamma + \tau + \sigma_i} = \frac{\alpha_i(1-\phi)}{1 + \hat{\tau} + \hat{\sigma}_i}$$

of them, where $\hat{\tau} = \tau/\lambda\gamma$ and $\hat{\sigma} = \sigma_i/\lambda\gamma$. Hence R_0 is given by

$$\frac{\lambda}{\mu + \delta_1}(1-\phi)\left[\frac{\alpha_1}{1 + \hat{\tau} + \hat{\sigma}_1} + \frac{\alpha_2\delta_1}{(1 + \hat{\tau} + \hat{\sigma}_2)(\mu + \delta_2)} + \frac{\alpha_3\delta_1\delta_2}{(1 + \hat{\tau} + \hat{\sigma}_3)(\mu + \delta_2)(\mu + \delta_3)}\right].$$

$$(2)$$

We expect that the disease takes off if $R_0 > 1$ and dies out if $R_0 \leq 1$. We shall explore this in the next two sections.

4. **Equilibrium and Stability Results.** The equilibrium and stability results follow along the lines of [6]. Full details are given in [1].

Theorem 4.1. (i) For $R_0 \leq 1$ the only equilibrium is the DFE $\pi_i = \beta_j = 0$ for $i,j = 1,2,3$. This is globally asymptotically stable (GAS).
(ii) For $R_0 > 1$ the DFE still exists and is unstable. There is also a unique endemic equilibrium $\pi_i = \pi_i^*$ and $\beta_j = \beta_j^*$ for $i,j = 1,2,3$.

Proof. For $i,j = 1,2,3$, let π_i^* denote the equilibrium proportion of addicts who are infected and in infective stage i and β_j^* denote the equilibrium proportion of needles which are infected and in infective state j. We write $\pi^* = \pi_1^* + \pi_2^* + \pi_3^*$, $\beta^* = \beta_1^* + \beta_2^* + \beta_3^*$ and $L = 1 + \frac{\delta_1}{\mu + \delta_2} + \frac{\delta_1\delta_2}{(\mu + \delta_2)(\mu + \delta_3)}$. We can use the equilibrium versions of (1), (1)(ii)-(vi) first to express π_i^* and β_j^* in terms of π^* and then (1)(i) to give an equation for π^*. We deduce that there are two equilibria:

(i) $(\pi^*, \beta^*) = (0,0)$ which is always possible;

(ii) $\pi^* = 1 - \dfrac{1}{R_0}$, $\beta^* = \dfrac{(R_0 - 1)F}{LR_0}$,

where $F = \dfrac{1}{1 + \hat{\tau} + \hat{\sigma}_1} + \dfrac{\delta_1}{(1 + \hat{\tau} + \hat{\sigma}_2)(\mu + \delta_2)} + \dfrac{\delta_1\delta_2}{(1 + \hat{\tau} + \hat{\sigma}_3)(\mu + \delta_2)(\mu + \delta_3)}$,

which is possible if and only if $R_0 > 1$.

Write $f^\infty = \limsup_{t\to\infty} f(t)$. For $R_0 \leq 1$ global stability of the DFE follows from the results:

$$\pi_2^\infty \leq \frac{\delta_1\pi_1^\infty}{\mu + \delta_2}, \quad \pi_3^\infty \leq \frac{\delta_1\delta_2\pi_1^\infty}{(\mu + \delta_2)(\mu + \delta_3)}, \quad \beta_1^\infty \leq \frac{\pi_1^\infty}{1 + \hat{\tau} + \hat{\sigma}_1},$$

$$\beta_2^\infty \leq \frac{\delta_1\pi_1^\infty}{(\mu + \delta_2)(1 + \hat{\tau} + \hat{\sigma}_2)} \quad \text{and} \quad \beta_3^\infty \leq \frac{\delta_1\delta_2\pi_1^\infty}{(\mu + \delta_2)(\mu + \delta_3)(1 + \hat{\tau} + \hat{\sigma}_3)},$$

along the lines of [6].

To show instability of the DFE when $R_0 > 1$ we obtain the characteristic equation of the linearization about this equilibrium in the form

$$\omega^6 + a_1\omega^5 + a_2\omega^4 + a_3\omega^3 + a_4\omega^2 + a_5\omega + a_6 = 0,$$

where

$$a_6 = (\mu + \delta_1)(\mu + \delta_2)(\mu + \delta_3)(\lambda\gamma + \tau + \sigma_1)(\lambda\gamma + \tau + \sigma_2)(\lambda\gamma + \tau + \sigma_3)(1 - R_0),$$

when the result is obvious by the Routh-Hurwitz conditions [14]. □

Let $\pi = \pi_1 + \pi_2 + \pi_3$, the total fraction of infected addicts and $\beta = \beta_1 + \beta_2 + \beta_3$, the total fraction of infected needles at time t.

Theorem 4.2. *If $R_0 > 1$ and either $\pi(0) > 0$ or $\beta(0) > 0$ then there exists $\epsilon > 0$ and $\eta > 0$ such that*

$$\pi_i \geq \epsilon \pi_i^*, \qquad \beta_i \geq \epsilon \beta_i^*, \qquad i = 1,2,3 \quad \forall t \geq \eta.$$

Here ϵ is a fixed positive and small value independent of the initial conditions.

Proof. Define $f_\infty = \liminf_{t \to \infty} f(t)$. The proof proceeds along the lines of the corresponding result in [6]. From the differential equations (1) we show that

$$\pi_{2,\infty} \geq \frac{\delta_1 \pi_{1,\infty}}{\mu + \delta_2}, \quad \pi_{3,\infty} \geq \frac{\delta_1 \delta_2 \pi_{1,\infty}}{(\mu + \delta_2)(\mu + \delta_3)}, \quad \beta_{1,\infty} \geq \frac{\pi_{1,\infty}}{1 + \hat{\tau} + \hat{\sigma}_1},$$

$$\beta_{2,\infty} \geq \frac{\delta_1 \pi_{1,\infty}}{(\mu + \delta_2)(1 + \hat{\tau} + \hat{\sigma}_2)} \quad \text{and} \quad \beta_{3,\infty} \geq \frac{\delta_1 \delta_2 \pi_{1,\infty}}{(\mu + \delta_2)(\mu + \delta_3)(1 + \hat{\tau} + \hat{\sigma}_3)}.$$

Then the result of Theorem 4.2 will follow from showing that $\pi_{1,\infty}$ is bounded strictly away from zero with lower bound dependent only on the model parameters not the initial conditions.

We need the following lemma proved analogously to the corresponding result in [6].

Lemma 4.3. *If at least one of $\pi_1(t)$, $\pi_2(t)$, $\pi_3(t)$, $\beta_1(t)$, $\beta_2(t)$ and $\beta_3(t) > 0$ at $t = 0$ then there exists $\Delta t > 0$ such that*

$$\pi_1(\Delta t), \ \pi_2(\Delta t), \ \pi_3(\Delta t), \ \beta_1(\Delta t), \ \beta_2(\Delta t) \text{ and } \beta_3(\Delta t) > 0.$$

If $\pi_{1,\infty} \geq \frac{1}{2}\epsilon \pi_1^*$ then Theorem 4.2 follows from the lower bounds obtained previously. Suppose from now on that $\pi_{1,\infty} < \frac{1}{2}\epsilon \pi_1^*$. Define $t_0 = \inf\{\eta \geq \Delta t : \pi_1(\eta) < \frac{1}{2}\epsilon \pi_1^*\}$ and $t_1 = \inf\{\eta \geq t_0 : \pi_1(\eta) > \frac{1}{2}\epsilon \pi_1^*\}$. We next show that all components will become small if π_1 becomes small.

Lemma 4.4. *There is a value $\overline{T}_1 > 0$ such that for $t_0 + \overline{T}_1 < t_1$, then $0 < \pi_2 < (\frac{1}{2} + \Delta)\pi_2^*\epsilon$ for every $t \in [t_0 + \overline{T}_1, t_1]$. Here $\overline{T}_1$ depends only on the model parameters and the small parameters $\Delta > 0$ and ϵ, not on the initial conditions.*

Proof. Straightforward from (1)(ii) and the fact that $\pi_1 \leq \frac{1}{2}\epsilon \pi_1^*$ in $[t_0, t_1]$. □

A similar argument shows that there is a value $\overline{T}_2 > 0$ such that for $t_0 + \overline{T}_1 + \overline{T}_2 < t_1$ then $0 < \pi_3 < (\frac{1}{2} + 2\Delta)\pi_3^*\epsilon$ for all $t \in [t_0 + \overline{T}_1 + \overline{T}_2, t_1]$, where $\overline{T}_2$ depends only on the model parameters, Δ and ϵ. Also there exist $\overline{T}_3$, $\overline{T}_4$ and $\overline{T}_5 > 0$ dependent only on the model parameters, Δ and ϵ, such that $0 < \beta_1 < (\frac{1}{2} + \Delta)\epsilon \beta_1^*$, for $t \in [t_0 + \overline{T}_3, t_1]$, $0 < \beta_2 < (\frac{1}{2} + 2\Delta)\epsilon \beta_2^*$, for $t \in [t_0 + \overline{T}_1 + \overline{T}_4, t_1]$, and $0 < \beta_3 < (\frac{1}{2} + 3\Delta)\epsilon \beta_3^*$, for $t \in [t_0 + \overline{T}_1 + \overline{T}_2 + \overline{T}_5, t_1]$.

We have the following lemma:

Lemma 4.5. *Let $t_1^\dagger = t_0 + \max[\overline{T}_3, \ \overline{T}_1 + \overline{T}_4, \ \overline{T}_1 + \overline{T}_2 + \overline{T}_5, \ \overline{T}_1 + \overline{T}_2 + \overline{T}_6]$ where $\overline{T}_6$ is defined in the proof of the lemma. If $\pi_1(t)$ goes under $\frac{1}{2}\epsilon \pi_1^*$ at time t_0 then it rises up to $\frac{1}{2}\epsilon \pi_1^*$ by at least time $t_1^\dagger$, where $t_1^\dagger - t_0$ is finite and dependent only on the model parameters, Δ and ϵ, not on the initial conditions.*

Proof. Consider the matrix

$$\mathbf{J_2}(\epsilon) = \begin{bmatrix} -(\mu+\delta_1) & 0 & 0 & \lambda\alpha_1(1-\phi)(1-\epsilon_2) \\ \delta_1 & -(\mu+\delta_2) & 0 & 0 \\ 0 & \delta_2 & -(\mu+\delta_3) & 0 \\ \lambda\gamma & 0 & 0 & -(\lambda\gamma+\tau+\sigma_1) \\ 0 & \lambda\gamma & 0 & 0 \\ 0 & 0 & \lambda\gamma & 0 \end{bmatrix}$$

$$\begin{bmatrix} \lambda\alpha_2(1-\phi)(1-\epsilon_2) & \lambda\alpha_3(1-\phi)(1-\epsilon_2) \\ 0 & 0 \\ 0 & 0 \\ 0 & 0 \\ -(\lambda\gamma+\tau+\sigma_2) & 0 \\ 0 & -(\lambda\gamma+\tau+\sigma_3) \end{bmatrix}.$$

When $\epsilon_2 = 0$ we have the linearized stability matrix at the DFE. If $\omega_1(\epsilon_2)$ is the dominant eigenvalue of $\mathbf{J_2}(\epsilon)$ then $\omega_1(\epsilon_2) \to \omega_1(0)$ as $\epsilon_2 \to 0$ (see [6]). The proof follows along the lines of the corresponding result in [6].

Choose $1 > \epsilon_2 > 0$ such that $\omega_1(\epsilon_2)$ is positive. Then choose ϵ to be small enough so that $\frac{1}{2}\epsilon\pi_1^* + (\frac{1}{2}+\Delta)\epsilon\pi_2^* + (\frac{1}{2}+2\Delta)\epsilon\pi_3^* < \epsilon_2$. The required result of Lemma 4.5 is achieved when $t_0 + \overline{T}_1 + \overline{T}_2 > t_1$, otherwise for $t_1 \geq t \geq t_0 + t_2$ we have

$$\frac{d\mathbf{x}}{dt} \geq \mathbf{J}(\epsilon_2)\mathbf{x}$$

where $\mathbf{x} = (\pi_1, \pi_2, \pi_3, \beta_1, \beta_2, \beta_3)$. Let $\mathbf{e} = (e_1, e_2, e_3, e_4, e_5, e_6)$ be the positive left eigenvector of $\mathbf{J}(\epsilon_2)$ corresponding to the Perron eigenvalue $\omega_1(\epsilon_2)$ [15]. An argument similar to [6] implies that after time $t_0 + t_2 + \overline{T}_6$, $\mathbf{e}.\mathbf{x}(t)$ strictly exceeds $\mathbf{e}.(\frac{1}{2}\epsilon\pi_1^*, (\frac{1}{2}+\Delta)\epsilon\pi_2^*, (\frac{1}{2}+2\Delta)\epsilon\pi_3^*, (\frac{1}{2}+\Delta)\epsilon\beta_1^*, (\frac{1}{2}+2\Delta)\epsilon\beta_2^*, (\frac{1}{2}+3\Delta)\epsilon\beta_3^*)$, where $\overline{T}_6$ is dependent only on the model parameters, ϵ and Δ. This is a contradiction unless $t_1 \leq t_0 + \max[\overline{T}_1, \ \overline{T}_1 + \overline{T}_2, \ \overline{T}_3, \overline{T}_1 + \overline{T}_4, \ \overline{T}_1 + \overline{T}_2 + \overline{T}_5, \ t_2 + \overline{T}_6]$ proving Lemma 4.5. $\square$

A similar argument implies that π_1 must eventually rise above $\frac{1}{2}\epsilon\pi_1^*$ and each subsequent time that π_1 drops under $\frac{1}{2}\epsilon\pi_1^*$ it must tend back to that value by at most time T later where T depends only on the model parameters, Δ, ϵ and ϵ_2. (1)(i) now implies that $\pi_1 \geq \frac{1}{2}\epsilon\pi_1^* \exp[-(\mu+\delta_1)T]$, hence $\pi_{1,\infty} \geq \frac{1}{2}\epsilon\pi_1^* \exp[-(\mu+\delta_1)T] > 0$ and the result of Theorem 4.2 follows from previous comments. $\square$

For $R_0 > 1$ local stability of the endemic equilibrium is too complicated to show directly. However as the timescale on which the β_i change (days) is much faster than that on which the π_i change (years) it is possible to approximate the relationship between the $\beta_i(t)$ and the $\pi_i(t)$ as

$$\beta_i(t) = \frac{\pi_i(t)}{1 + \hat{\tau} + \hat{\sigma}_i} \qquad \text{for} \quad i = 1, 2, 3.$$

With this approximation we have

$$\frac{d\pi_1}{dt} = (1-\pi)\lambda(1-\phi)\left(\frac{\pi_1\alpha_1}{1+\hat{\tau}+\hat{\sigma}_1} + \frac{\pi_2\alpha_2}{1+\hat{\tau}+\hat{\sigma}_2} + \frac{\pi_3\alpha_3}{1+\hat{\tau}+\hat{\sigma}_3}\right) - (\mu+\delta_1)\pi_1,$$

$$\frac{d\pi_2}{dt} = \delta_1\pi_1 - (\mu+\delta_2)\pi_2 \quad \text{and} \quad \frac{d\pi_3}{dt} = \delta_2\pi_2 - (\mu+\delta_3)\pi_3.$$

Theorem 4.6. *The approximate model has the same R_0 and equilibria as the full model. Moreover in the approximate model the unique endemic equilibrium is always locally asymptotically stable (LAS) when it exists.*

Proof. It is straightforward to show that the approximate model has the same R_0 and equilibria as the full model. For $R_0 > 1$ we linearize the approximate model about the unique endemic equilibrium $(\pi_1^*, \pi_2^*, \pi_3^*)$. We find that the characteristic equation is

$$\omega^3 + a_1\omega^2 + a_2\omega + a_3 = 0,$$

where $\quad a_1 = (\mu+\delta_2+\mu+\delta_3) + \frac{\mu+\delta_1}{L}(R_0-1)$

$$+\frac{\mu+\delta_1}{E}\left(\frac{\alpha_2\delta_1}{(1+\hat{\tau}+\hat{\sigma}_2)(\mu+\delta_2)} + \frac{\alpha_3\delta_1\delta_2}{(1+\hat{\tau}+\hat{\sigma}_3)(\mu+\delta_2)(\mu+\delta_3)}\right),$$

$$a_2 = (\mu+\delta_2)(\mu+\delta_3) + \frac{\mu+\delta_1}{L}(R_0-1)(\delta_1+\mu+\delta_2+\mu+\delta_3)$$

$$+\frac{\mu+\delta_1}{E}\left(\frac{\alpha_2\delta_1(\mu+\delta_3)}{(1+\hat{\tau}+\hat{\sigma}_2)(\mu+\delta_2)} + \frac{\alpha_3\delta_1\delta_2}{(1+\hat{\tau}+\hat{\sigma}_3)(\mu+\delta_2)}\right.$$

$$\left.+\frac{\alpha_3\delta_1\delta_2}{(1+\hat{\tau}+\hat{\sigma}_3)(\mu+\delta_3)}\right),$$

and $\quad a_3 = \frac{\mu+\delta_1}{L}(\delta_1\delta_2 + \delta_1(\mu+\delta_3) + (\mu+\delta_2)(\mu+\delta_3))(R_0-1).$

Here $\quad E = \frac{\alpha_1}{1+\hat{\tau}+\hat{\sigma}_1} + \frac{\alpha_2\delta_1}{(1+\hat{\tau}+\hat{\sigma}_2)(\mu+\delta_2)} + \frac{\alpha_3\delta_1\delta_2}{(1+\hat{\tau}+\hat{\sigma}_3)(\mu+\delta_2)(\mu+\delta_3)}.$

It follows that $a_1 > 0$, $a_3 > 0$ and $a_1a_2 > a_3$, therefore the Routh-Hurwitz conditions are satisfied and the unique endemic equilibrium is LAS when it exists. $\quad\square$

4.1. Global Stability of the Endemic Equilibrium. We now return to the full model. We suspect that if $R_0 > 1$ and disease is initially present then the system will approach the unique endemic equilibrium. We have not been able to show this analytically, although in the next section we shall see that simulation suggests it. However we can show the following result:

We define $\mathbf{M}^{\dagger}$ to be the matrix:

$$\begin{bmatrix} \mu + \lambda\epsilon(1-\phi) & -\delta_1 & 0 & -\lambda\gamma & 0 & 0 \\ 0 & \mu+\delta_1+\delta_2 & -\delta_2 & -\lambda\gamma & -\lambda\gamma & 0 \\ -\delta_3 & -\delta_1 & \mu+\delta_3 & -\lambda\gamma & 0 & -\lambda\gamma \\ -(1-\pi^*)\lambda\alpha_1(1-\phi) & 0 & 0 & M_{44}^+ & 0 & 0 \\ -(1-\pi^*)\lambda\alpha_2(1-\phi) & 0 & 0 & 0 & M_{55}^+ & 0 \\ -(1-\pi^*)\lambda\alpha_3(1-\phi) & 0 & 0 & 0 & 0 & M_{66}^+ \end{bmatrix},$$

where $M_{44}^+ = \lambda\gamma + \tau + \sigma_1$, $M_{55}^+ = \lambda\gamma + \tau + \sigma_2$ and $M_{66}^+ = \lambda\gamma + \tau + \sigma_3$.

Theorem 4.7. *If $R_0 > 1$, $(\mu+\delta_2+\delta_1)(\mu+\delta_3) > \delta_1\delta_2$, $\det(\mathbf{M}^\dagger) > 0$ and disease is initially present then at large times the disease approaches the endemic equilibrium.*

Proof. Along the lines of the corresponding result in [6]. Full details are given in [1]. □

5. **Model with a Variable Population Size.** One of the drawbacks of the model just discussed is that it assumes that the addict population size is constant for mathematical simplicity and it would be more realistic to model new addicts entering the population and dying from AIDS by using a variable population size. This is discussed by [12] for a simpler model. We follow [4] and assume that new addicts come into the sharing injecting population at rate cn^ν, where $0 \le \nu \le 1$ and c is positive. If $\nu = 1$ then there is feedback from the current users who recruit new naive users into the sharing injecting population. If $\nu = 0$ then we have constant recruitment of new addicts as discussed for HIV/AIDS amongst gay men by [2] and [3].

Addicts in stage 3 may develop full-blown AIDS (at per capita rate δ_3) when they are assumed to cease sharing syringes. All addicts may stop sharing syringes for other reasons (i.e. giving up drugs, going to prison, entering treatment) at per capita rate μ. We also assume that the gallery ratio is constant so that the total number of addicts at time t, $n(t)$, is equal to $\gamma m(t)$ where $m(t)$ is the total number of syringes at time t. With these modified assumptions the differential equations which describe the progress of the disease are:

$$\frac{d\pi_1}{dt} = \left(1 - \sum_{i=1}^3 \pi_i\right)\lambda(\alpha_1\beta_1 + \alpha_2\beta_2 + \alpha_3\beta_3)(1-\phi) - (\mu+\delta_1)\pi_1 - \frac{\pi_1}{n}\frac{dn}{dt}, \quad (3)$$

$$\frac{d\pi_2}{dt} = \delta_1\pi_1 - (\mu+\delta_2)\pi_2 - \frac{\pi_2}{n}\frac{dn}{dt}, \qquad \frac{d\pi_3}{dt} = \delta_2\pi_2 - (\mu+\delta_3)\pi_3 - \frac{\pi_3}{n}\frac{dn}{dt},$$

$$\frac{d\beta_j}{dt} = \lambda\gamma(\pi_j - \beta_j) - \beta_j(\tau+\sigma_j) - \frac{\beta_j}{n}\frac{dn}{dt}, \quad \text{for} \quad j=1,2,3,$$

and $\dfrac{dn}{dt} = cn^\nu - \mu n - \delta_3\pi_3 n.$

The initial conditions are $\pi_i(0)$, $\beta_j(0)$, $n(0) \ge 0$ for $i,j = 1,2,3$, $\pi_1(0) + \pi_2(0) + \pi_3(0) \le 1$ and $\beta_1(0) + \beta_2(0) + \beta_3(0) \le 1$. We take $0 < \nu < 1$.

For this model there is a unique DFE given by

$$(\pi_1, \pi_2, \pi_3, \beta_1, \beta_2, \beta_3, n) = (0, 0, 0, 0, 0, 0, n_0^*)$$

where $n_0^* = (\frac{\mu}{c})^{\frac{1}{\nu-1}}$. R_0 is the same as in the constant population size model. We have the following results:

Theorem 5.1. *For the model given by (3):*
(i)   If $R_0 \leq 1$ then the only possible equilibrium is the DFE which is GAS.
(ii) If $R_0 > 1$ then the DFE exists and is unstable, but there is also a unique endemic equilibrium given by

$$(\pi_1, \pi_2, \pi_3, \beta_1, \beta_2, \beta_3, n) = (\pi_1^*, \pi_2^*, \pi_3^*, \beta_1^*, \beta_2^*, \beta_3^*, n_e^*)$$

where $\pi_1^*, \pi_2^*, \pi_3^*, \beta_1^*, \beta_2^*$ and β_3^* are the equilibrium values discussed in Section 4 and $n_e^* = (\frac{\mu + \delta_3 \pi_3^*}{c})^{\frac{1}{\nu-1}}$.

Proof. The equilibrium results are straightforward. For $R_0 \leq 1$ we can express equations (3) in terms of the absolute numbers of infected addicts and infected needles and show that the DFE is GAS using the same methods as in Theorem 4.1, i.e. the proof of the corresponding result in [6].

For $R_0 > 1$ we proceed as in [12]. The roots of the characteristic equation are $\omega_1 = \nu c n_0^{*\nu-1} - \mu = \mu(\nu - 1) < 0$ and the roots of the characteristic equation of the linearization of system (1) about the DFE of that model. Theorem 5.1 follows. □

6. **Simulations.** We performed simulations to illustrate our analytical results. The parameter values were estimated from the literature and real data. The simulations suggest that for $R_0 > 1$ if the disease is initially present then it will tend to the unique endemic equilibrium. They also confirm that if $R_0 \leq 1$ then the disease will eventually die out.

We use the value $100 : 1 : 10$ for $\alpha_1 : \alpha_2 : \alpha_3$ suggested by [13]. Other papers use different values for this ratio (i.e. [17]) but the ratios $100 : 1 : 10$ are better supported by the data. We also have that σ^{-1}, the average time until a needle becomes virus-free, is a weighted average of the mean time until an infectious needle becomes virus-free over the three types of infectious needles

$$\sigma^{-1} = \frac{\beta_1^*}{\beta^*}\sigma_1^{-1} + \frac{\beta_2^*}{\beta^*}\sigma_2^{-1} + \frac{\beta_3^*}{\beta^*}\sigma_3^{-1}. \tag{4}$$

If we also make the reasonable assumption that the average time until an infectious needle becomes virus-free is proportional to its viral load we have that

$$\sigma_i^{-1} = K\alpha_i \tag{5}$$

for $i = 1,2,3$, for some constant K.

To estimate σ_1, σ_2 and σ_3 we use a simple approximation argument. From [7] we know that an average infected needle becomes virus-free in about a week, so σ^{-1} = 52 per year. From [10] we have that $\beta^* = 0.675$. From [13] we have that $\alpha_2 = 0.0011$, $\alpha_1 = 0.11$, $\alpha_3 = 0.011$, $\beta_1^* = 0.024$, $\beta_2^* = 0.562$ and $\beta_3^* = 0.088$. It is then straightforward from (4) that $\sigma_1 = 2.9569$ per year, $\sigma_2 = 295.69$ per year and $\sigma_3 = 29.569$ per year. Note that this is only an approximate method as the estimate of α_2 in [13] assumes that $\sigma_1 = \sigma_2 = \sigma_3 = 0$ per year and it would ideally have been better to estimate α_2 and K simultaneously from (4) and (5) although this would have been extremely complicated.

Having an initial approximate estimate of σ_1, σ_2 and σ_3 if we were then to perform simulations with the same values of α_1, α_2 and α_3 as in [13] looking at equation (2)

we see that we would automatically decrease R_0. So instead we increase α_2 to compensate for this so that with our new parameter estimates of σ_1, σ_2 and σ_3 we have $R_0 = 2.92$ as in [13], using the parameter values in that paper. When we do this we find that $\alpha_2 = 0.00133$ so $\alpha_1 = 0.133$ and $\alpha_3 = 0.0133$, only a small difference from the original values.

[9] estimate $n_0^* = 2,300$ for New Haven, USA, but this will vary from location to location. ν is difficult to estimate as we have no data. We take $n(0) = n_0^* = 5,000$ and $\nu = 0.05$ to give reasonably large sizes in all subpopulations. This implies that $c = \mu n_0^{*1-\nu} = 435.36$ per year.

We start with the constant population size model (1). For our first simulation the remaining parameter values based on realistic estimates from the literature are $\lambda = 246.22$ per year [10], $\gamma = 0.908$ [11], $\mu = 0.1333$ per year [4], $\phi = 0.64$ [6], $\tau = 15.53$ per year [8], $\delta_1 = 8.0$ per year, $\delta_2 = 0.1154$ per year and $\delta_3 = 0.8276$ per year [13]. These parameters give $R_0 = 2.001$. Figure 1 shows a typical simulation over 15 years. The starting values are $\pi_1(0) = 0.0791$, $\pi_2(0) = 0.249$, $\pi_3(0) = 0.022$, $\beta_1(0) = 0.092$, $\beta_2(0) = 0.100$ and $\beta_3(0) = 0.020$. We see that both the fractions of infected addicts and needles tend to their unique endemic equilibrium values as time becomes large. The simulation was repeated with several sets of parameter values giving $R_0 > 1$ and several different starting values. In each case provided that the disease was initially present in either addicts or needles the disease eventually approaches the unique endemic equilibrium.
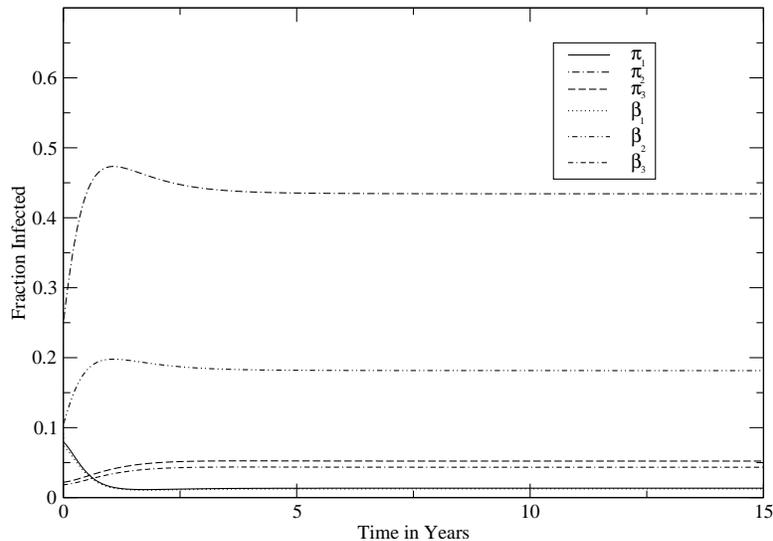

FIGURE 1. Typical simulation when $R_0 > 1$.

To verify that the disease does indeed die out if $R_0 < 1$ several other simulations were performed with different starting values and parameter sets with $R_0 < 1$ and in each case the disease died out. This confirms the results of Theorem 4.1.

We may ask whether the introduction of loss of HIV infectivity over time makes any practical difference to the results of our model. The answer seems to be that it makes a small but practically significant difference to the results. For the model parameters above we find that $\pi_1^* = 0.01350$, $\pi_2^* = 0.4340$, $\pi_3^* = 0.05215$, $\beta_1^* = 0.01247$, $\beta_2^* = 0.1815$, $\beta_3^* = 0.04340$ and $R_0 = 2.001$. With the same parameter values except that $\sigma_1 = \sigma_2 = \sigma_3 = 0$ per year, $\alpha_2 = 0.0011$, $\alpha_1 = 0.11$ and $\alpha_3 = 0.011$, see above discussion, we find that $\pi_1^* = 0.01290$, $\pi_2^* = 0.4150$, $\pi_3^* = 0.04983$, $\beta_1^* = 0.01206$, $\beta_2^* = 0.3880$, $\beta_3^* = 0.04660$ and $R_0 = 1.9146$. Hence we see that there is a small but significant difference in the equilibrium number of infected addicts and R_0 (R_0 differs by about 5%) but there is a big difference between the numbers of stage 2 infected syringes. Figure 2 shows the simulation of the model with those parameter values and the same starting values as in Figure 1.
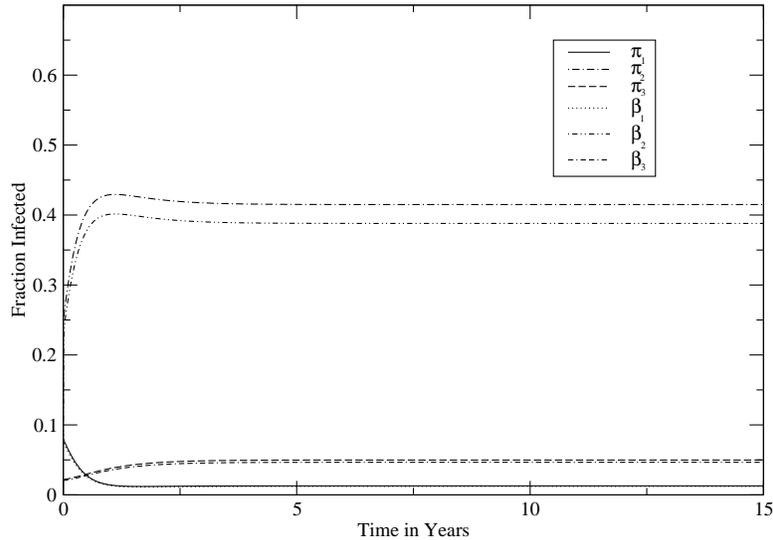

FIGURE 2. Corresponding simulation with $\sigma_1 = \sigma_2 = \sigma_3 = 0$ and $R_0 > 1$.

We now move on to simulation for the variable population size model. Figure 3 shows a simulation with parameter values as discussed above, starting values for $\beta_1, \beta_2, \beta_3, \pi_1, \pi_2$ and π_3 as in the other two simulations, and $n(0) = n_0^* = 5,000$. In this figure for $j = 1,2,3$, I_j and i_j denote respectively the number of addicts and needles in infectious state j. Note that the simulation tends to the unique endemic equilibrium values but that the time taken for it to do this is larger than in the constant population size model. This is similar to the corresponding result discussed in [12]. We performed simulations with various parameter values and initial conditions for the variable population size model and the results were as expected. Provided that $R_0 \leq 1$ the system ultimately tended to the unique DFE

but if $R_0 > 1$ and HIV was initially present, either in addicts or needles, the system tended to the unique endemic equilibrium as time became large.
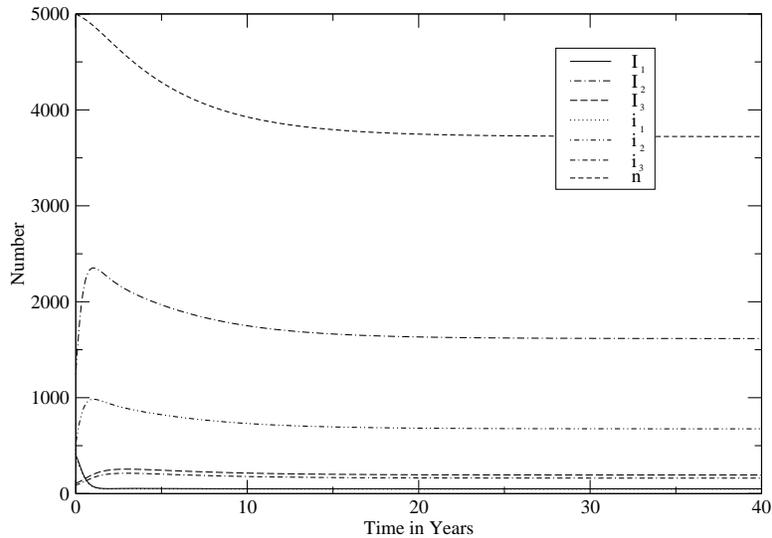

FIGURE 3. Simulation for variable population size model.

7. **Implications for Control Strategies.** Part of the power of Kaplan's original model was that it gave us the ability to explore how interventions or control levers might affect certain parameters and would or would not be effective at bringing R_0 beneath one and eradicating the disease. This is explored in [12] for a simpler model.

For example using the expression for R_0 in (2) and writing $R_0 \equiv R_0(\lambda, \phi, \tau)$ with the other parameters held fixed we can eliminate disease in the population (for both models) either by:

(i) using health education to decrease the per capita needle-sharing rate λ beneath the critical value λ_0 given by the unique root of $R_0(\lambda_0, \phi, \tau) = 1$. This gives $\lambda_0 = 136.44$ per year if the σ_i are non-zero and 135.44 per year if the σ_i are zero.

(ii) using health education to increase the effective syringe cleaning efficacy above the unique root ϕ_0 of the equation $R_0(\lambda, \phi_0, \tau) = 1$. This gives $\phi_0 = 0.820$ if the σ_i are non-zero and 0.812 if the σ_i are zero.

or (iii) increasing the needle exchange rate τ above τ_0 given by the unique root of $R_0(\lambda, \phi, \tau_0) = 1$. This gives $\tau_0 = 283.13$ per year if the σ_i are non-zero and 234.21 per year if the σ_i are zero.

Of course in practice we would probably aim to use a combination of these strategies to reduce R_0 beneath one. We see that with the parameter values chosen it looks as though introducing loss of HIV infectivity over time makes a small difference to the amount of control effort need to eliminate the disease for decreasing

needle sharing and increasing needle cleaning, but a larger significant difference for needle exchange.

8. **Summary.** In this paper we have looked at an improved model for the spread of HIV/AIDS amongst sharing IDUs. The infected needles and infected addicts were each split into three groups representing the three levels of differential infectivity amongst addicts. The key difference between this and previous work was that infected needles did not remain infected indefinitely. Instead they lost infectivity at rate depending on their infectious class.

We derived a differential equation model for the spread of the disease. We found that there was a key threshold parameter R_0, the basic reproduction number. For $R_0 \leq 1$ there was a unique DFE which was GAS. For $R_0 > 1$ the DFE was unstable. There was a unique endemic equilibrium. For an approximation to this model this unique endemic equilibrium was LAS when it existed. We discussed introducing recruitment of new addicts and deaths from AIDS into the model and obtained similar although less complete results (we did not show analytic stability of the endemic equilibrium in this case). Simulations with realistic parameter values confirmed global asymptotic stability of the DFE for $R_0 \leq 1$ and suggested that for $R_0 > 1$ the system would always tend to the unique endemic equilibrium provided that disease was initially present. Hence the qualitative behavior of the model with or without differential loss of HIV infectivity over time included is the same. Finally we used our theoretical results to determine the minimum control policies to just eliminate HIV in the population by reducing needle sharing, or increasing needle cleaning or exchange. The inclusion of loss of HIV infectivity over time makes a small but possibly significant difference to quantities such as R_0, the equilibrium fraction of addicts infected and the critical education and needle cleaning control strategies. There was a much larger difference in the equilibrium number of infected needles and critical needle exchange rate.

REFERENCES

[1] Wafa Al-Fwzan, "Modelling the Spread of HIV/AIDS through Three Stages amongst Injecting Drug Users," Ph.D thesis, University of Strathclyde, Glasgow, U.K., 2007.

[2] R.M. Anderson and R.M. May, "Infectious Diseases of Humans: Dynamics and Control," Oxford University Press, Oxford, 1991.

[3] S.P. Blythe and R.M. Anderson, Heterogeneous sexual activity models of HIV transmission in male homosexual populations, *AIDS impact on the number of intravenous drug users*, IMA J. Math. Appl. Med. Biol., **5** (1998), 237–260.

[4] J.P. Caulkins and E.H. Kaplan, *AIDS impact on the number of intravenous drug users*, Interfaces, **21** (1991), 50–63.

[5] D. Greenhalgh and G. Hay, *Mathematical modelling of the spread of HIV/AIDS amongst injecting drug users*, IMA J. Math. Appl. Med. Biol., **14** (1997), 11–38.

[6] D. Greenhalgh and F.I. Lewis, *Three-stage AIDS incubation period: a best case scenario using addict-needle interaction assumptions*, IMA J. Math. Appl. Med. Biol., **17** (2000), 95–118.

[7] E.H. Kaplan, *Needles that kill: Modeling human immunodeficiency virus transmission via shared drug injection equipment in shooting galleries*, Rev. Inf. Diseases, **11** (1989), 289–298.

[8] E.H. Kaplan, *Probability models of needle exchange*, Operations Research, **43** (1995), 558–568.

[9] E.H. Kaplan and R. Heimer, *A circulation theory of needle exchange*, AIDS, **8** (1994), 567–574.

[10] E.H. Kaplan and E. O'Keefe, *Let the needles do the talking! Evaluating the New Haven needle exchange*, Interfaces, **23** (1993), 7–26.

[11] Fraser I. Lewis, "Assessing the Impact of Variable Infectivity on the Transmission of HIV among Intravenous Drug Users," Ph.D thesis, University of Strathclyde, Glasgow, U.K., 2000.

[12] F.I. Lewis and D. Greenhalgh, *Effects of variable infectivity on the spread of HIV/AIDS among intravenous drug users*, J. Biol. Systems, **9** (1991), 13–40.

[13] F.I. Lewis and D. Greenhalgh, *Three stage AIDS incubation period: a worst case scenario using addict-needle interaction assumptions*, Math. Biosci, **169** (2001), 53–87.

[14] R.M. May, "Stability and Complexity in Model Ecosystems," 2nd edition, Princeton University Press, Princeton, 1974.

[15] R. Needle, A. Ball, D. des Jarlais, C. Whitmore and E. Lambert, *The global research network on HIV prevention in drug using populations (GRN) 1998-2000: trends in the epidemiology, ethnography, and prevention of HIV/AIDS in injecting drug users*, in "2000 Global Research Network Meeting on HIV Prevention in Drug Using Populations, Third Annual Meeting Report, Durban, South Africa," National Institute on Drug Abuse, (2000), 9–17.

[16] A. Nold, *Heterogeneity in disease transmission modelling*, Math. Biosci, **52** (1980), 227–240.

[17] D. Peterson, K. Willard, M. Altmann, L. Gatewood and G. Davidson, *Monte-Carlo simulation of HIV infection in an intravenous drug user community*, J.A.I.D.S., **3** (1990), 1086–1095.

[18] T. Rhodes, G.V. Stimson, N. Grofts, A. Ball, K. Dehne and L. Khodkevich, *Drug injecting, rapid HIV spread and the risk environment: implications for assessment and response*, AIDS, **13**(SupplA) (1999), S259–S269.

[19] UNAIDS, "Joint United Nations Programme on HIV/AIDS (UNAIDS) Advocacy Guide: HIV/AIDS Prevention Among Injecting Drug Users," UNAIDS, Geneva, Switzerland, 2005.

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