INCUBATION PERIODS UNDER VARIOUS ANTI-RETROVIRAL THERAPIES IN HOMOGENEOUS MIXING AND AGE-STRUCTURED DYNAMICAL MODELS: A THEORETICAL APPROACH

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ABSTRACT. With the launch of second line anti-retroviral therapy for HIV infected individuals, there has been an increased expectation of survival for people with HIV. We consider previously well-known models in HIV epidemiology where the parameter for the incubation period is used as one of the important components to explain the dynamics of the variables. Such models are extended here to explain the dynamics with respect to a given therapy that prolongs the life of an HIV infected individual. A deconvolution method is demonstrated for estimation of parameters in the situations when no-therapy and multiple therapies are given to the infected population. The models and deconvolution method are extended in order to study the impact of therapy in age-structured populations. A generalization for a situation when n-types of therapies are available is given. Models are demonstrated using hypothetical data, and sensitivity of the parameters is also computed.

1. Preliminaries, basic ODE model and integro-differential equations models. With the introduction of second line therapy [54] to people living with HIV who were already on first line therapy, there is a further hope for increasing the active life of HIV infected individuals. Revised estimates of the people living with HIV are obtained for some countries to address the impact of second line therapy (see, for example, [40]). Second line theory is provided after failure to respond to the

first line therapy among the infected individuals. Modeling the impact of second line therapy and corresponding extended survival time is complicated because the susceptible population can acquire the virus from two infected classes of populations who are on therapy in addition to the infected population which is without any therapy.

Identifying the first line of individuals who are no more responsive to the first line of therapy through surveillance is still a challenging issue in several countries. Difficulties in monitoring and recording the HIV infected population who are on first and second line therapy will also lead to difficulty in estimating parameters of disease progression and disease related mortalities. Disease progression rate and incubation period are related, and usually both are taken as reciprocal to each other. The incubation period of HIV infected individuals is also expected to increase since the advent of new anti-retroviral therapy policies. The incubation period is generally defined as 'the time duration between the time a virus or bacteria enters the human body and the time at which clinical clinical symptoms occur.' This duration can vary from case to case depending upon the route through which the virus or bacteria enters the immune system of an individual and in some cases depends upon the age of the infected individual. For chickenpox, this duration is 10–21 days, for the common cold 2–5 days, for mumps 12–25 days, for SARS a maximum of up to 10 days, for rubella 14–21 days, for pertussis 7–10 days, and for HIV infection to AIDS 6 months to 10 years or more. The incubation period can be used as a measure of rapidity of the illness after interaction with the virus or bacteria.

It is not easy to collect information on the incubation period of infected individuals unless they are monitored. One of the direct ways of estimating the average incubation period of a given virus in the population is by surveillance and followup of the infected individuals from the time of infection until development of symptoms of the disease. All the infected individuals may not be aware of their infection until symptoms appear, and individuals are available for followup when symptoms do appear. It might not be possible to follow individuals in a typical situation, where time taken for the onset of symptoms from the infection is longer or infected individuals are lost to followup. Due to second line therapy for HIV infected individuals the followup times could be much longer when there is a good adherence for therapy and

systematic health care practices exist among infected cohorts. Hence, there are limitations on directly estimating the average incubation period from prospective cohort studies. Nevertheless, the incubation period occupies an important role, along with other parameters in modeling the disease spread and understanding the basic reproductive rate.

A useful description of various epidemic models, and of estimation of parameters like the incubation period, transmission rates and forces of infections are presented in [3]. The degree of importance of obtaining accurate average incubation periods varies with the type of a disease and impact of available therapies for treating this disease. This degree of variation causes mathematical models to act sensitively in predicting future burden. Models describing dynamics of disease spread where the incubation period is shorter are less subject to produce misleading results than models for the spread with longer and varying incubation periods. Especially for predicting AIDS, the epidemic models developed depend heavily on parameters that determine transmission rates of infection from infected to susceptible and on the parameter which explains the average time to progress to AIDS.

A review of various modeling approaches and quantitative techniques for estimating the incubation period can be found in [9, 12]. The introduction of anti-retroviral therapies and protease inhibitors during the 1990s in several parts of the world resulted in a decline in opportunistic infections related to AIDS [14, 20, 29]. As a result of such intervention, the average incubation period was prolonged. There have been attempts to estimate the incubation period that vary due to drug intervention using statistical density functions [4]. The impact of this variation on the HIV dynamics, stability and on basic reproduction number has been investigated [11, 12, 23].

In this section, we first consider an ODE model that explains the dynamics of HIV spread in a population leading to AIDS (see [26]). We then consider a similar model where incubation period is a variable with respect to a given therapy. We address issues of estimating incubation period to be used in such dynamical models and the impact of the above-mentioned therapies. Various ideas and the outline of this work are given at the end of this section.

Perhaps the most fundamental model for the epidemiology of AIDS

is that given by [**2, 3, 26**], which takes the form

$$\frac{dX}{dt} = \Lambda - (\lambda + \mu)\, X,$$

(1.1)
$$\frac{dY}{dt} = \lambda X - (d + \mu)\, Y,$$

$$\frac{dD_z}{dt} = dY - \gamma D_z.$$

Here the total population (N) is divided into susceptibles (X), infectives (Y) and individuals with the full blown disease (D_z). The parameter Λ is the input into the susceptible class, which can be defined as the number of births in the population, λ is the force of infection, μ is general (non-AIDS related) mortality, γ is disease related mortality and $1/d$ is the average incubation period. Here the incubation period is defined as the duration of time between infection and onset of full blown disease. There are several other constructions of HIV transmission dynamic models.

In the models involving the disease progression parameter, it has been assumed that there is an increase in the mean length of life after HIV infection since the availability of therapies for AIDS [**49, 51**]. There is much work describing the impact of anti-retroviral therapies using data [**1, 8, 15, 16, 17, 19, 22, 24, 25, 27, 28, 29, 31, 34, 35, 42, 45, 46, 47, 50, 52, 53**] and impact is assessed through modeling [**5, 31, 43, 44, 49**].

The time to start ART based on the CD4 count is still debatable, and current WHO (World Health Organization) guidelines (released in 2010 [**54**]) recommend starting ART when CD4 count reaches 350 cell/mm^3. In a recent study on HIV-1 discordant couples [**13**], it was observed that the incidence rates among early ART couples are lower than the incidence rates among couples who were given ART at a standard time.

Drugs are available which cannot eliminate the virus from the body but are helpful in prolonging the life of an individual by slowing the disease progression (in other word, increasing the incubation period). For example, protease inhibitors (say *drug* 1) facilitate in producing non-infectious virus (only infectious virus participates in new virus production), hence slowing the disease progression; anti-retroviral therapy (say *drug* 2) blocks the virus from interacting with the non-infected cells and hence reduces the infection process within the cell population

(see [**30**, Section 5] and [**32**] for fuller details); and a combination of the above two drugs (say *drug* 3) can be more effective by simultaneously combining the functions of *drug* 1 and *drug* 2. Note that, when model (1.1) was developed, the above-described drugs were not available. Information on scale-up of anti-retroviral therapies and related monitoring of individuals can be found elsewhere (for example, see [**7, 21, 31, 48**]. We assume that, once individuals start taking drugs, their average incubation period is prolonged. So, instead of assuming a constant $1/d$, we assume that it varies based on the drug type. Thus, we define $1/d_i = \int_{\mathbb{R}} z_i g(z_i)\, dz_i$, for $i = 0, 1, 2, 3$, where $i = 0$ denotes the "without drug scenario," $i = 1$ for *drug* 1, $i = 2$ for *drug* 2 and $i = 3$ for *drug* 3. Here, g is the probability density function with a certain parameter set (say **B**) and z_i is a continuous random variable representing the incubation period. Here, z_i is a real valued function defined on a standard probability space $(S, \mathbb{A}, P)$, where S is the space of elementary events, $\mathbb{A}$ is called a Borel fields and $P(\mathbb{A})$ is the probability of the event $A \in \mathbb{A}$. So, $z : S \to \mathbb{R}$. We can also denote this integral as a Stieltjes integral $\int_{\mathbb{R}} z_i dG(z_i)$, where $G(z) = P(Z < z)$. We further assume without loss of generality that either of the following two inequalities will hold at a time:

$$(1.2) \qquad \frac{\int_{\mathbb{R}} z_0\, dG(z_0)}{\int_{\mathbb{R}} z_3\, dG(z_3)} < \frac{\int_{\mathbb{R}} z_1\, dG(z_1)}{\int_{\mathbb{R}} z_3\, dG(z_3)} \leq \frac{\int_{\mathbb{R}} z_2\, dG(z_2)}{\int_{\mathbb{R}} z_3\, dG(z_3)} < 1$$

$$(1.3) \qquad \frac{\int_{\mathbb{R}} z_0\, dG(z_0)}{\int_{\mathbb{R}} z_3\, dG(z_3)} < \frac{\int_{\mathbb{R}} z_1\, dG(z_1)}{\int_{\mathbb{R}} z_3\, dG(z_3)} > \frac{\int_{\mathbb{R}} z_2\, dG(z_2)}{\int_{\mathbb{R}} z_3\, dG(z_3)} < 1$$

(In the next section, we will give a detailed estimation procedure for **B**.) Applying these varying incubation periods, model (1.1) is modified as follows:

$$\frac{dX}{dt} = \Lambda - (\lambda_0 + \lambda_1 + \lambda_2 + \lambda_3 + \mu)\, X,$$

$$\frac{dY_0}{dt} = \lambda_0 X - \left\{ \left(\int_{\mathbb{R}} z_0 dG(z_0) \right)^{-1} + \mu \right\} Y_0,$$

$$\frac{dY_1}{dt} = \lambda_1 X - \left\{ \left(\int_{\mathbb{R}} z_1 dG(z_1) \right)^{-1} + \mu \right\} Y_1,$$

$$\frac{dY_2}{dt} = \lambda_2 X - \left\{ \left(\int_{\mathbb{R}} z_2 dG(z_2) \right)^{-1} + \mu \right\} Y_2,$$

$$\frac{dY_3}{dt} = \lambda_3 X - \left\{ \left(\int_{\mathbb{R}} z_3 dG(z_3) \right)^{-1} + \mu \right\} Y_3,$$

$$\frac{dD_{z_0}}{dt} = \left(\int_{\mathbb{R}} z_0 dG(z_0) \right)^{-1} Y_0 - \gamma_0 D_{z_0},$$

$$\frac{dD_{z_1}}{dt} = \left(\int_{\mathbb{R}} z_1 dG(z_1) \right)^{-1} Y_1 - \gamma_1 D_{z_1},$$

$$\frac{dD_{z_2}}{dt} = \left(\int_{\mathbb{R}} z_2 dF(z_2) \right)^{-1} Y_2 - \gamma_2 D_{z_2},$$

(1.4) $$\frac{dD_{z_3}}{dt} = \left(\int_{\mathbb{R}} z_3 dG(z_3) \right)^{-1} Y_3 - \gamma_3 D_{z_3},$$

where Y_0, Y_1, Y_2 and Y_3 are variables for infectives, $D_{z_0}, D_{z_1}, D_{z_2}$ and D_{z_3} are variables for individuals with the full blown disease, $\lambda_0, \lambda_1, \lambda_2$ and λ_3 and $\gamma_0, \gamma_1, \gamma_2$ and γ_3 are variables for disease related mortality for no-drug, *drug* 1, *drug* 2 and *drug* 3, respectively. See Figure 1 which describes the flows in the model (1.4). General mortality and disease-related mortality are incorporated into the model to demonstrate the basic structure of the model, and our aim here is to demonstrate methodology to estimate **B** and thus to estimate $\int_{\mathbb{R}} z_i dG(z_i)$ for all i such that simulations of the model are performed. In model (1.4), the total population $N = X + Y_0 + Y_1 + Y_2 + Y_3 + D_{z_0} + D_{z_1} + D_{z_2} + D_{z_3}$ satisfies

$$\frac{dN}{dt} = \Lambda - \mu X + \mu \sum_{i=0}^{3} Y_i - \sum_{i=0}^{3} \gamma_i D_{z_i}.$$

Estimation of parameters for the varying incubation periods is important for understanding the impact of drugs in prolonging the onset of disease and thus to prolong the survival period of an HIV infected individual. The set **B** will also be useful in obtaining varying basic reproductive rates, R_{0i} for all $i = 0, 1, 2, 3$. This can be computed as $R_{0i} = \lambda \gamma_i \int_{\mathbb{R}} z_i dG(z_i)$ by assuming independence of the impact of various drugs. There is a possibility that β, the probability of infecting a susceptible partner, changes with the activation of a drug in the body. If we assume this as a constant, then $R_{00} \geq R_{01} \geq$ or $< R_{02} \geq R_{03}$. $R_{01} < \{R_{01}, R_{02}, R_{03}\}$, because individuals are assumed to have a longer incubation period due to the effect of drugs. In the absence of clinical evidence, we assume that the impact of *drug*1
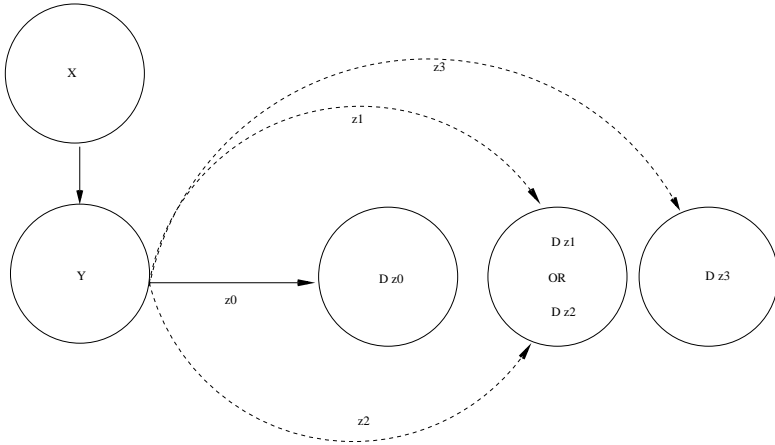
FIGURE 1. Schematic diagram explaining the flow of infected individuals without therapy to individuals who are on therapy.

and *drug*2 follows any one of the following relations: $\int_{\mathbb{R}} z_1 dG(z_1) \leq$ or $> \int_{\mathbb{R}} z_2 dG(z_2)$. Similarly, another important epidemiological measure, the doubling time, t_{di}, is obtained as $t_{di} = \ln(2) \int_{\mathbb{R}} z_i dG(z_i)/[R_{0i} - 1]$. Anti-retroviral therapy helps in blocking the virus from interacting with cells and simultaneously providing protease inhibitors which helps in producing non-infectious virus. So, without loss of generality, it was previously assumed that the impact of double drug therapy is better than a single drug therapy. If we assume disease related mortality is constant for all i, then $\gamma_i = \gamma$. The number of AIDS related deaths in general is high during the latter part of the incubation period due to an increase in opportunistic infections. In general, over all AIDS related mortality rate in a population is assumed to be higher than the general mortality rate in that population. Where there are n types of drugs available, we write the general form for the above dynamical model as follows:

$$\frac{dX}{dt} = \Lambda - \left(\sum_{i=0}^{n} \lambda_i + \mu \right) X,$$

$$\frac{dY_0}{dt} = \lambda_0 X - \left\{ \left(\int_{\mathbb{R}} z_0 dG(z_0) \right)^{-1} + \mu \right\} Y_0,$$

$$\vdots$$

$$\vdots$$

$$\frac{dY_n}{dt} = \lambda_n X - \left\{ \left(\int_{\mathbb{R}} z_n dG(z_n) \right)^{-1} + \mu \right\} Y_n,$$

$$\frac{dD_{z_0}}{dt} = \left(\int_{\mathbb{R}} z_0 dG(z_0) \right)^{-1} Y_0 - \gamma_0 D_{z_0},$$

(1.5)

$$\vdots$$

$$\vdots$$

$$\frac{dD_{z_n}}{dt} = \left(\int_{\mathbb{R}} z_n dG(z_n) \right)^{-1} Y_n - \gamma_n D_{z_n},$$

As a special case, we can consider all the parameters in the above model as Stieltjes integrals, and one can estimate them using the rigorous procedure explained in the next section. For $n = 3$, the model (1.5) becomes the model (1.4) after considering suitable variables. Practically, we do not have a situation where several drugs are available in the market for HIV infected individuals. Hence, model (1.5) should be treated as a theoretical generalization.

This paper is organized as follows. In Section 2, we present contemporary models constructed for understanding the transmission dynamics of HIV for policy formulations and the corresponding modified disease progression component that captures the impact of therapy. In Section 3, we describe in detail the estimation of the set **B** for up to three drugs. Section 4 gives corresponding expressions for the conditional probabilities of N-drugs. We construct theoretical examples using three functions: Gamma, Logistic and Log-normal in Section 5 to demonstrate the method explained in Section 3. In Section 6, analysis for age-structured populations is described in detail. Overall conclusions are given in Section 7. Appendix I gives equations for conditional probability when incubation period for various drug types does not have the monotonicity property. Appendix II gives some more theoretical examples when the incubation period is truncated to the right. Appendix III provides parameter values adopted for numerical simulations and Appendix IV has numerical demonstration of the model

outputs and sensitivity of parameters in projecting HIV and AIDS (see Figures 4–10).

2. Contemporary models and modifications. In this section, we present two contemporary models: the first one [**41**] was developed for understanding the spread of Indian HIV epidemic, and the second one [**40**] was developed to generate the number of people who are eligible for second line ART. These models were found to be practically useful in predicting the HIV numbers in total and those who need second line therapy. For example, the projections of HIV numbers for the year 2011 by running the model [**41**] were 2.08 million, and the actual data released [**33**] by the Ministry of Health and Family Welfare, Government of India, for the number of people living with HIV in India for the year 2011, released in 2012, were 2,088,642 (note that the output of the model was published three years prior to the actual data released).

The HIV model [**41**] has three components: 1) Model for spread in general population, 2) model for spread in homosexual men (MSM), 3) model for spread in intravenous drug users (IDU). We provide a description of this model and then write a corresponding revised model with integro differential equations. The system of differential equations in the three models has incorporated dynamics in 14 compartments: $U(i)$, susceptible population; $V(i)$, sexually transmitted diseases population; $W(i)$, HIV infected; $T(i)$, AIDS in the general population for gender i (say, $i = 1$ for male and $i = 2$ for female), $U(m)$, susceptible MSM; $V(m)$, sexually transmitted infected MSM;, $W(m)$, HIV infected MSM; $T(m)$, MSM population with AIDS; $U(IDU)$, susceptible intravenous drug users; $W(IDU)$, HIV infected intravenous drug users; and $T(IDU)$, intravenous drug users with AIDS. Susceptible males in the general population are eligible to acquire the virus from the jth sub-population ($j = 1$, female married partner; $j = 2$, female casual partner, $j = 3$, commercial sex worker; and $j = 4$, through blood transfusions. All the sub-populations are allowed to contribute for the transmission dynamics of HIV, and each sub-population is also subject to the risk of acquiring the infection from other sub-populations wherever applicable (see [**41**] for a complete description). The differential

equations describing the Indian HIV epidemic model are:

General model

$$
\begin{cases}
\frac{dU(i)}{dt} &= a_i U(i) - U(i)\left(\sum_{j=1}^{4}\frac{b_{ij}V(i)}{N(j)} + \sum_{j=1}^{4}\frac{c_{ij}W(j)}{N(j)}\right) \\
& \quad +\phi V(i) \\
\frac{dV(i)}{dt} &= U(i)\sum_{j=1}^{4}\frac{b_{ij}V(i)}{N(j)} - V(i)\sum_{j=1}^{4}\frac{d_{ij}W(j)}{N(j)} \\
& \quad -\mu V(i) - \phi V(i) \\
\frac{dW(i)}{dt} &= U(i)\sum_{j=1}^{4}\frac{c_{ij}W(j)}{N(j)} + V(i)\sum_{j=1}^{4}\frac{d_{ij}W(j)}{N(j)} \\
& \quad -\delta_i W(i) - \alpha i W(i) \\
\frac{dT(i)}{dt} &= \alpha_i W(i) - \mu_i T(i)
\end{cases}
$$

MSM model

$$
\begin{cases}
\frac{dU(m)}{dt} &= a_m U(m) - U(m)\left(\frac{b_m V(m)}{N(m)} + \frac{c_m W(m)}{N(m)}\right) \\
& \quad +\phi V(m) \\
\frac{dV(m)}{dt} &= U(m)\frac{b_m V(m)}{N(m)} - V(m)\frac{d_m W(m)}{N(m)} - \mu V(m) \\
& \quad -\phi V(m) \\
\frac{dW(m)}{dt} &= U(m)\frac{c_m W(m)}{N(m)} + V(m)\frac{d_m W(m)}{N(m)} \\
& \quad -\delta_m W(m) - \alpha_m W(m) \\
\frac{dT(m)}{dt} &= \alpha_m W(m) - \mu_m T(m)
\end{cases}
$$

IDU model

$$
\begin{cases}
\frac{dU(IDU)}{dt} &= a_{IDU} U(IDU) - U(IDU)\left(\frac{c_{IDU}W(IDU)}{N(IDU)}\right) \\
& \quad +\phi V(IDU) \\
\frac{dW(IDU)}{dt} &= U(IDU)\frac{c_{IDU}W(IDU)}{N(IDU)} - \delta_{IDU}W(IDU) \\
& \quad -\alpha_{IDU}W(IDU) \\
\frac{dT(IDU)}{dt} &= \alpha_{IDU}T(IDU) - \mu_{IDU}T(IDU),
\end{cases}
$$

where $N(j) = V(j) + W(j)$ for $j = 1, 2, 3, 4$ and $N(m) = V(m) + W(m)$. The corresponding models with flexible incubation periods are:

$$
\frac{dU(i)}{dt} = a_i U(i) - U(i)\left(\sum_{j=1}^{4}\frac{b_{ij}V(i)}{N(j)} + \sum_{k=0}^{3}\sum_{j=1}^{4}\frac{c_{ijk}W(j)}{N(j)}\right) + \phi V(i)
$$

$$
\frac{dV(i)}{dt} = U(i)\sum_{j=1}^{4}\frac{b_{ij}V(i)}{N(j)} - V(i)\sum_{k=0}^{3}\sum_{j=1}^{4}\frac{d_{ijk}W(j)}{N(j)} - \mu V(i) - \phi V(i)
$$

$$\frac{dW_0(i)}{dt} = U(i)\sum_{j=1}^{4}\frac{c_{ij0}W(j)}{N(j)} + V(i)\sum_{j=1}^{4}\frac{d_{ij0}W(j)}{N(j)}$$

$$- \left\{\left(\int_{\mathbb{R}} z_0 dG(z_0)\right)^{-1} + \delta_i\right\}W_0(i)$$

$$\frac{dW_1(i)}{dt} = U(i)\sum_{j=1}^{4}\frac{c_{ij1}W(j)}{N(j)} + V(i)\sum_{j=1}^{4}\frac{d_{ij1}W(j)}{N(j)}$$

$$- \left\{\left(\int_{\mathbb{R}} z_1 dG(z_1)\right)^{-1} + \delta_i\right\}W_1(i)$$

$$\frac{dW_2(i)}{dt} = U(i)\sum_{j=1}^{4}\frac{c_{ij2}W(j)}{N(j)} + V(i)\sum_{j=1}^{4}\frac{d_{ij2}W(j)}{N(j)}$$

$$- \left\{\left(\int_{\mathbb{R}} z_2 dG(z_2)\right)^{-1} + \delta_i\right\}W_2(i)$$

$$\frac{dW_3(i)}{dt} = U(i)\sum_{j=1}^{4}\frac{c_{ij3}W(j)}{N(j)} + V(i)\sum_{j=1}^{4}\frac{d_{ij3}W(j)}{N(j)}$$

$$- \left\{\left(\int_{\mathbb{R}} z_3 dG(z_3)\right)^{-1} + \delta_i\right\}W_3(i)$$

$$\frac{dT_{z0}(i)}{dt} = \left(\int_{\mathbb{R}} z_0 dG(z_0)\right)^{-1} W_0(i) - \mu_0 T_{zo}$$

$$\frac{dT_{z1}(i)}{dt} = \left(\int_{\mathbb{R}} z_1 dG(z_1)\right)^{-1} W_1(i) - \mu_1 T_{z1}$$

$$\frac{dT_{z2}(i)}{dt} = \left(\int_{\mathbb{R}} z_2 dG(z_2)\right)^{-1} W_2(i) - \mu_1 T_{z1}$$

$$\frac{dT_{z3}(i)}{dt} = \left(\int_{\mathbb{R}} z_3 dG(z_3)\right)^{-1} W_3(i) - \mu_3 T_{z3}$$

(2.1)

$$\frac{dU(m)}{dt} = a_m U(m) - U(m)\left(\frac{b_m V(m)}{N(m)} + \sum_{k=0}^{3}\frac{c_m W(m)}{N(m)}\right) + \phi V(m)$$

$$\frac{dV(m)}{dt} = U(m)\frac{b_m V(m)}{N(m)} - V(m)\sum_{k=0}^{3}\frac{d_m W(m)}{N(m)} - \mu V(m) - \phi V(m)$$

$$\frac{dW_0(m)}{dt} = U(m)\frac{c_{m0}W(m)}{N(m)} + V(m)\frac{d_{m0}W(m)}{N(m)}$$
$$- \left\{\left(\int_{\mathbb{R}} z_0 dG(z_0)\right)^{-1} + \delta_m\right\}W_0(m)$$

$$\frac{dW_1(m)}{dt} = U(m)\frac{c_{m1}W(m)}{N(m)} + V(m)\frac{d_{m1}W(m)}{N(m)}$$
$$- \left\{\left(\int_{\mathbb{R}} z_1 dG(z_1)\right)^{-1} + \delta_m\right\}W_1(m)$$

$$\frac{dW_2(m)}{dt} = U(m)\frac{c_{m2}W(m)}{N(m)} + V(m)\frac{d_{m2}W(m)}{N(m)}$$
$$- \left\{\left(\int_{\mathbb{R}} z_2 dG(z_2)\right)^{-1} + \delta_m\right\}W_2(m)$$

$$\frac{dW_3(m)}{dt} = U(m)\frac{c_{m3}W(m)}{N(m)} + V(m)\frac{d_{m3}W(m)}{N(m)}$$
$$- \left\{\left(\int_{\mathbb{R}} z_0 dG(z_0)\right)^{-1} + \delta_m\right\}W_3(m)$$

$$\frac{dT_{z0}(m)}{dt} = \left(\int_{\mathbb{R}} z_0 dG(z_0)\right)^{-1} W_0(m) - \mu_m T_{z0}(m)$$

$$\frac{dT_{z1}(m)}{dt} = \left(\int_{\mathbb{R}} z_1 dG(z_1)\right)^{-1} W_1(m) - \mu_m T_{z1}(m)$$

$$\frac{dT_{z2}(m)}{dt} = \left(\int_{\mathbb{R}} z_2 dG(z_2)\right)^{-1} W_2(m) - \mu_m T_{z2}(m)$$

$$\frac{dT_{z3}(m)}{dt} = \left(\int_{\mathbb{R}} z_3 dG(z_3)\right)^{-1} W_3(m) - \mu_m T_{z3}(m)$$

(2.2)

$$\frac{dU(IDU)}{dt} = a_{IDU}U(IDU) - U(IDU)\sum_{k=0}^{3}\left(\frac{c_{IDU,k}W(IDU)}{N(IDU)}\right)$$
$$+ \phi V(IDU)$$

$$\frac{dW_0(IDU)}{dt} = U(IDU)\left(\frac{c_{IDU,0}W(IDU)}{N(IDU)}\right)$$
$$- \left\{\left(\int_{\mathbb{R}} z_0 dG(z_0)\right)^{-1} + \delta_{IDU}\right\}W_0(IDU)$$

$$\frac{dW_1(IDU)}{dt} = U(IDU)\left(\frac{c_{IDU,1}W(IDU)}{N(IDU)}\right)$$
$$- \left\{\left(\int_{\mathbb{R}} z_1 dG(z_1)\right)^{-1} + \delta_{IDU}\right\}W_1(IDU)$$

$$\frac{dW_2(IDU)}{dt} = U(IDU)\left(\frac{c_{IDU,2}W(IDU)}{N(IDU)}\right)$$
$$- \left\{\left(\int_{\mathbb{R}} z_2 dG(z_2)\right)^{-1} + \delta_{IDU}\right\}W_2(IDU)$$

$$\frac{dW_3(IDU)}{dt} = U(IDU)\left(\frac{c_{IDU,3}W(IDU)}{N(IDU)}\right)$$
$$- \left\{\left(\int_{\mathbb{R}} z_3 dG(z_3)\right)^{-1} + \delta_{IDU}\right\}W_3(IDU)$$

$$\frac{dT_{z0}(IDU)}{dt} = \left(\int_{\mathbb{R}} z_0 dG(z_0)\right)^{-1} W_0(IDU) - \mu_{IDU}T_{z0}(IDU)$$

$$\frac{dT_{z1}(IDU)}{dt} = \left(\int_{\mathbb{R}} z_1 dG(z_1)\right)^{-1} W_1(IDU) - \mu_{IDU}T_{z1}(IDU)$$

$$\frac{dT_{z2}(IDU)}{dt} = \left(\int_{\mathbb{R}} z_2 dG(z_2)\right)^{-1} W_2(IDU) - \mu_{IDU}T_{z2}(IDU)$$

$$\frac{dT_{z3}(IDU)}{dt} = \left(\int_{\mathbb{R}} z_3 dG(z_3)\right)^{-1} W_3(IDU) - \mu_{IDU}T_{z3}(IDU)$$

(2.3)

where the variables with suffix z_0, z_1, z_2, z_3 are corresponding to the impact of drug0, drug1, drug2, drug3, respectively. These contemporary models are improvised versions of basic models presented in Section 1 and are tested to accurately predict the epidemic situation during the era of anti-retroviral therapies.

The model [40] was basically developed for predicting the number of HIV infected people on second line ART who have developed resistance for first line ART. It consisted of five variables, namely, X_1, the number

of people with HIV who are yet to develop full-blown AIDS; X_2, the number of people with full-blown AIDS during the scale-up period; X_3, the number of people with full-blown AIDS and not currently on first line ART (after removing the annual number of deaths among people without first line ART); Y_1, the number on first line ART (say, *drug 1*) and Y_2, the number on second line ART (say, *drug 2*). The model equations describing the dynamics in five variables are:

$$\frac{dX_1}{dt} = \Lambda X_1 - \alpha_1 X_1$$

$$\frac{dX_2}{dt} = \alpha_1 X_1 - \beta_1 X_2$$

$$\frac{dX_3}{dt} = \alpha_1 X_1 - p_1 X_3 - \beta_1 X_3$$

$$\frac{dY_1}{dt} = p_1 X_3 - \nu Y_1 - \beta_2 Y_1$$

(2.4)
$$\frac{dY_2}{dt} = \nu Y_1 - \beta_3 Y_2$$

Here, Λ is the annual growth rate in HIV, α_1 is the mean incubation period (without any drugs) (let the corresponding Stieltjes integral variable, as before, be z_0), β_1, β_2 and β_3 are the average survival periods after reaching full-blown AIDS when individuals are without drugs, on first line ART, on second line ART (let the corresponding Stieltjes integral variables be u_1, u_2 and u_3), p_1 is the annual rate of recruitment into first line ART, ν is the annual rate of resistance development for first line ART (for a detailed description, see [**40**]). This model was built with the purpose of projecting the number of people who will be eligible for second line ART, among whom are currently on first line ART. Disease progression after HIV infection, eligibility to first line ART (based on CD4 count definition), developing resistance for first line ART and eligible for second line ART are continuous process, and modeling such phenomena requires information on survival periods for people of ART, rate of resistance development, etc. The model (2.4) is different from standard HIV transmission dynamic models by the fact that only HIV infected individuals are considered in (2.4) rather than both susceptibles and those infected, because we are studying impact of therapy. The data on cohorts of people who are on first line and second therapy could involve variation in terms of the disease progression because the time of initiation of therapy and other biological factors for

each cohort may be different. The integro-differential equations model corresponding to the model (2.4) is

$$\frac{dX_1}{dt} = \Lambda X_1 - \left(\int_{\mathbb{R}} z_0 dG(z_0) \right)^{-1} X_1$$

$$\frac{dX_2}{dt} = \left(\int_{\mathbb{R}} z_0 dG(z_0) \right)^{-1} X_1 - \left(\int_{\mathbb{R}} u_1 dG(u_0) \right)^{-1} X_2$$

$$\frac{dX_3}{dt} = \left(\int_{\mathbb{R}} z_0 dG(z_0) \right)^{-1} X_1 - p_1 X_3 - \left(\int_{\mathbb{R}} u_1 dG(u_1) \right)^{-1} X_3$$

$$\frac{dY_1}{dt} = p_1 X_3 - \nu Y_1 - \left(\int_{\mathbb{R}} u_2 dG(u_2) \right)^{-1} Y_1$$

$$(2.5) \quad \frac{dY_2}{dt} = \nu Y_1 - \left(\int_{\mathbb{R}} u_3 dG(u_3) \right)^{-1} Y_2.$$

3. Conditional probabilities. In this section, we will give a detailed procedure for estimating **B** through a deconvolution technique. Let **B** be split into a collection of four parameter sets, say $\mathbf{B} = \{B_0, B_1, B_2, B_3\}$ for the four types of scenarios described in the previous section. Let H be the time of infection and Z the incubation period. Then the time of onset of the disease can be represented as $D = H + Z$. There have been studies (see, for list of references, [**9**]), in which H and Z were assumed independent and D was estimated through convolution. We outline the general idea of convolution and then give the convolution of H and Z. Suppose (a_n) and (b_n) are two sequences of numbers over the time period. Then

$$(3.1) \qquad\qquad (a_n) * (b_n) = \sum_{k=0}^{n} a_n b_{n-k},$$

where $(a_n)*(b_n)$ is the convolution of these sequences with an operator '∗'. Suppose a and b are mutually independent random variables, and let $A_{\mathcal{L}}(x)$ and $B_{\mathcal{L}}(x)$ be their Laplace transformations. Then $a + b$ has the Laplace transformation $A_{\mathcal{L}} B_{\mathcal{L}}$. Since the multiplication of the Laplace transformation is associative and commutative, it follows that $(a_n)*(b_n)$ is also associative and commutative. Instead of discrete notation, suppose a and b are continuous and independent with probability

density functions h and g. Then the density of $h + g$ is given by

$$f(s) = \int_{-\infty}^{\infty} h(t-s)g(t)dt = \int_{-\infty}^{\infty} h(t)g(t-s)\,ds.$$

Suppose $G(s) = \int_{-\infty}^{s} g(s)\,ds$, and $F(s) = \int_{-\infty}^{s} f(s)\,ds$. Then

$$(3.2) \qquad F(s) = \int_{-\infty}^{\infty} h(t)G(t-s)\,ds.$$

We call F the convolution of h and G. Suppose the above h and G represent the infection density and incubation period distribution functions. Then the convolution of h and G represents the cumulative number of disease cases reported (or observed) and is given by

$$(3.3) \qquad h * G = \int_{-\infty}^{\infty} h(t)G(t-s)\,ds.$$

This kind of convolution in (3.3) was used to estimate the number of AIDS cases for the first time by [10]. Information on G may not be available for some populations. In such situations, G has been estimated through deconvolution from the information available on $h * G$ and h [37, 38]. In this section, we will construct conditional probabilities for each *drug type* and express the function that maximizes **B**. These kinds of conditional probabilities derived for the drug type were not available earlier for the incubation periods when the total number of reported disease cases were considered. Note that $h * G$ is the cumulative number of disease cases.

Let $X_0, X_1, X_2, \ldots, X_{n-k}, \ldots, X_{n-l}, \ldots, X_{n-m}, \ldots, X_n$ be the disease cases available in the time intervals $[U_{i-1}, U_i)$ for $i = 0, 1, 2, \ldots, n-k, \ldots, n-l, \ldots, (n-m)+1, \ldots, n+1$. Suppose **E** is the event of diagnosis of disease after the first infection at T_0. Let $\mathbf{E} = \{E_0, E_1, E_2, E_3\}$, and E_0 occurs in the interval $[U_0, U_{n-k})$, E_1 (or E_2) in $[U_{n-k}, U_{n-l})$ (or $[U_{n-l}, U_{n-m})$) and E_3 in $[U_{n-m}, U_n)$. Now D, the cumulative number of disease cases up to time U_n, can be expressed from (3.3) as follows:

$$D(U_0 \le s \le U_n) = \int_0^{U_{n-k}} h(t)G(t-s)\,ds + \int_{U_{n-k}}^{U_{n-l}} h(t)G(t-s)\,ds$$

$$+ \int_{U_{n-l}}^{U_{n-m}} h(t)G(t-s)\,ds + \int_{U_{n-m}}^{U_n} h(t)G(t-s)\,ds,$$

$$D(\mathbf{A}, \mathbf{B}/U_n) = \int_0^{U_{n-k}} h(t/A_0)G(t - s/B_0)\,ds$$

$$+ \int_{U_{n-k}}^{U_{n-l}} h(t/A_1)G(t - s/B_1)\,ds$$

$$+ \int_{U_{n-l}}^{U_{n-m}} h(t/A_2)G(t - s/B_2)\,ds$$

(3.4)
$$+ \int_{U_{n-m}}^{U_n} h(t/A_3)G(t - s/B_3)\,ds.$$

In the above equation, A_0, A_1, A_2 and A_3 are the parameter sets for the h for drug 0, drug 1, drug 2 and drug 3. An infected individual could fall into any of the intervals described above and, similarly, a full-blown disease diagnosed individual could fall into the same interval. But, for a given individual, the chronological time of infection would be earlier than that of diagnosis of the disease. U_{n-k} is the time of introduction of *drugs* after infection at U_0. Individuals who were diagnosed on or after U_{n-k}, and before U_n, were taking one of the three drugs. If $E_1 \in [U_{n-k}, U_{n-l})$ and $E_2 \in [U_{n-l}, U_{n-m})$, $Z_1 < Z_2$; otherwise, if $E_1 \in [U_{n-l}, U_{n-m})$ and $E_2 \in [U_{n-k}, U_{n-l})$, and if $E_1, E_2 \in [U_{n-k}, U_{n-m})$, then $Z_1 = Z_2$. An individual who was diagnosed with the disease before U_n must have developed symptoms in one of the four intervals $[U_0, U_{n-k})$, $[U_{n-k}, U_{n-l})$, $[U_{n-l}, U_{n-m})$ or $[U_{n-m}, U_n)$. Let $E_j \in [U_{j-1}, U_j) \subseteq [U_0, U_{n-k})$. Then the conditional probability of the occurrence of E_j given E is expressed as

$$P(E_j/E) = P(U_{j-1} \leq D \leq U_j/D \leq U_n)$$

$$= \frac{D(A_0, B_0/U_j) - D(A_0, B_0/U_{j-1})}{D(A_0, B_0/U_n)}$$

$$= \int_0^{U_j} h(t/A_0)G(t - s/B_0)\,ds$$

$$\cdot \left[\int_0^{U_n} h(t/A_0)G(t - s/B_0)\,ds\right]^{-1}$$

$$- \int_0^{U_{j-1}} h(t/A_0)G(t - s/B_0)\,ds$$

(3.5)
$$\cdot \left[\int_0^{U_n} h(t/A_0)G(t - s/B_0)\,ds\right]^{-1}.$$

If drugs were initiated at U_{n-k}, then these conditional probabilities constructed above will change according to the occurrence of E_1, E_2 and E_3. Consider $E_1 \cap E_2 = \emptyset$. Let $E_k \in [U_{k-1}, U_k) \subseteq [U_{n-k}, U_{n-l})$, and $E_1 \in [U_{n-k}, U_{n-l})$. Then

$$
\begin{aligned}
P\left(E_k/E\right) &= P\left(U_{k-1} \leq D \leq U_k / D \leq U_n\right) \\
&= \frac{D(A_1, B_1/U_k) - D(A_1, B_1/U_{k-1})}{D(A_1, B_1/U_n)} \\
&= \int_0^{U_k} h(t/A_1)G(t - s/B_1)\, ds \\
&\quad \cdot \left[\int_0^{U_n} h(t/A_1)G(t - s/B_1)\, ds\right]^{-1} \\
&\quad - \int_0^{U_{k-1}} h(t/A_1)G(t - s/B_1)\, ds \\
&\quad \cdot \left[\int_0^{U_n} h(t/A_1)G(t - s/B_1)\, ds\right]^{-1}.
\end{aligned}
$$
(3.6)

Suppose $E_k \in [U_{k-1}, U_k) \subseteq [U_{n-k}, U_{n-l})$, and $E_2 \in [U_{n-k}, U_{n-l})$, i.e., a situation where $Z_1 > Z_2$. Then

$$
\begin{aligned}
P\left(E_k/E\right) &= \int_0^{U_k} h(t/A_2)G(t - s/B_2)\, ds \\
&\quad \cdot \left[\int_0^{U_n} h(t/A_2)G(t - s/B_2)\, ds\right]^{-1} \\
&\quad - \int_0^{U_{k-1}} h(t/A_2)G(t - s/B_2)\, ds \\
&\quad \cdot \left[\int_0^{U_n} h(t/A_2)G(t - s/B_2)\, ds\right]^{-1}.
\end{aligned}
$$
(3.7)

Letting $E_l \in [U_{l-1}, U_l) \subseteq [U_{n-l}, U_{n-m})$ and $E_2 \in [U_{n-l}, U_{n-m})$, then

$$
\begin{aligned}
P\left(E_l/E\right) &= P\left(U_{l-1} \leq D \leq U_l / D \leq U_n\right) \\
&= \frac{D(A_2, B_2/U_l) - D(A_2, B_2/U_{l-1})}{D(A_2, B_2/U_n)} \\
&= \int_0^{U_l} h(t/A_2)G(t - s/B_2)\, ds
\end{aligned}
$$
(3.8)

$$\cdot \left[\int_0^{U_n} h(t/A_2)G(t-s/B_2)\,ds \right]^{-1}$$

$$- \int_0^{U_{l-1}} h(t/A_2)G(t-s/B_2)\,ds$$

(3.9)
$$\cdot \left[\int_0^{U_n} h(t/A_2)G(t-s/B_2)\,ds \right]^{-1}.$$

Suppose $E_l \in [U_{l-1}, U_l) \subseteq [U_{n-l}, U_{n-m})$, and $E_1 \in [U_{n-l}, U_{n-m})$, i.e., a situation where $Z_1 > Z_2$. Then

$$P\,(E_l/E) = \int_0^{U_l} h(t/A_1)G(t-s/B_1)\,ds$$

$$\cdot \left[\int_0^{U_n} h(t/A_1)G(t-s/B_1)\,ds \right]^{-1}$$

$$- \int_0^{U_{l-1}} h(t/A_1)G(t-s/B_1)\,ds$$

(3.10)
$$\cdot \left[\int_0^{U_n} h(t/A_1)G(t-s/B_1)ds \right]^{-1}.$$

Now consider $E_1 = E_2 \in [U_{p-1}, U_p) \subseteq [U_{n-k}, U_{n-m})$, i.e., $Z_1 = Z_2$. Then the conditional probabilities contain the same parameter sets. In this situation,

$$P\,(E_p/E) = \int_0^{U_p} h(t/A_1)G(t-s/B_1)\,ds$$

$$\cdot \left[\int_0^{U_n} h(t/A_1)G(t-s/B_1)\,ds \right]^{-1}$$

$$- \int_0^{U_{p-1}} h(t/A_1)G(t-s/B_1)\,ds$$

(3.11)
$$\cdot \left[\int_0^{U_n} h(t/A_1)G(t-s/B_1)\,ds \right]^{-1}.$$

Since $Z_3 > Z_0, Z_1, Z_2$, suppose $E_3 \in [U_{m-1}, U_m) \subseteq [U_{n-m}, U_n]$. Then

$$P\,(U_{m-1} \le D \le U_m/D \le U_n) = \frac{D(A_3, B_3/U_m) - D(A_3, B_3/U_{m-1})}{D(A_3, B_3/U_n)}.$$

Therefore,

$$P\left(E_m/E\right) = \int_0^{U_m} h(t/A_3)G(t - s/B_3)\,ds$$

$$\cdot \left[\int_0^{U_n} h(t/A_3)G(t - s/B_3)\,ds\right]^{-1}$$

$$- \int_0^{U_{m-1}} h(t/A_3)G(t - s/B_3)\,ds$$

(3.12)
$$\cdot \left[\int_0^{U_n} h(t/A_3)G(t - s/B_3)\,ds\right]^{-1}.$$

The above conditional probabilities $P(E_j/E)$, $P(E_k/E)$, $P(E_l/E)$, $P(E_p/E)$ and $P(E_m/\mathbf{E})$ are the probabilities associated with the intervals $[U_{j'-1}, U_{j'})$, $[U_{k'-1}, U_{k'})$, $[U_{l'-1}, U_{l'})$, $[U_{p'-1}, U_{p'})$ and $[U_{m'-1}, U_{m'})$ for the ranges of j, k, l, p and m defined above. Since, $X_0, X_1, X_2, \ldots, X_{n-k}, \ldots, X_{n-l}, \ldots, X_{n-m}, \ldots, X_n$ are mutually exclusive, we assume they follow a parametric distribution with the above probabilities. Therefore, we assume they follow the multinomial property of the distribution of values in time intervals and the above conditional probabilities. Then the likelihood functions corresponding to the event set $\mathbf{E}$ are:

$$L_0(\mathbf{A}, \mathbf{B}/P_j) = \prod_{j'=1}^{n-k} P_j(\mathbf{A}, \mathbf{B}/T_{j'}),$$

$$L_{1(2)}(\mathbf{A}, \mathbf{B}/P_k) = \prod_{k'=n-k}^{n-l} P_{k'}(\mathbf{A}, \mathbf{B}/T_{k'}),$$

$$L_{2(1)}(\mathbf{A}, \mathbf{B}/P_{l'}) = \prod_{l'=n-l}^{n-m} P_{l'}(\mathbf{A}, \mathbf{B}/T_{l'}),$$

$$L_{1=2}(\mathbf{A}, \mathbf{B}/P_p) = \prod_{p'=n-k}^{n-m} P_{p'}(\mathbf{A}, \mathbf{B}/T_{p'})$$

and

$$L_3(\mathbf{A}, \mathbf{B}/P_m) = \prod_{m'=n-m}^{n} P_{m'}(\mathbf{A}, \mathbf{B}/T_{m'}).$$

Here $P_\bullet = P(E_\bullet/\mathbf{E})$. We estimate $\mathbf{A}$ by fitting an infection curve from the incidence data, and we then estimate $\mathbf{B}$ by maximizing the likelihood functions expressed above. The best estimate of $\mathbf{A}$ could be information for initial values of X and Y in the model (1.4). Using the corresponding estimate of $\mathbf{B}$, we obtain $\int_{\mathbb{R}} z_i dF(z_i)$. In such situations, the above likelihood functions would be

$$L_0 = \prod_{j'=0}^{n-k} P_j^{T_{j'}}, \qquad L_{1(2)} = \prod_{k'=n-k}^{n-l} P_k^{T_{k'}},$$

$$L_{2(1)} = \prod_{l'=n-l}^{n-m} P_l^{T_{l'}}, \qquad L_{1=2} = \prod_{p'=n-k}^{n-m} P_p^{T_{p'}}$$

and

$$L_3 = \prod_{m'=n-m}^{n} P_m^{T_{m'}}.$$

4. Generalization for multiple drug impact. In this section, expressions for the conditional probabilities are presented when multiple drugs are administered in the population. Refer to Sections 2 and 3 for an introduction on the role of various drugs and refer to Section 4 for basic formulations of conditional probabilities when there are three types of drugs to prolong the incubation period and without any drug situation that would not alter the natural process of disease progression.

Modeling for the situation corresponding to no drug is highly relevant for those countries where surveillance and diagnosis of infections are not complete and several individuals with HIV are not taking drugs.

Let $N = \{N_0, N_1, N_2, \ldots, N_N\}$ be the number of available drugs and $Z = \{Z_0, Z_1, Z_2, \ldots, Z_N\}$ be their corresponding incubation periods. Further, let $Z_0 < Z_1 < Z_2 <, \ldots, < Z_N$ and $\mathbf{A}$ and $\mathbf{B}$ be their parametric sets. Then

$$D\left(\mathbf{A}, \mathbf{B}/U_{N_N}\right) = \int_0^{U_{N_0}} h(t/A_{N_0})G(t - s/B_{N_0})\, ds$$

$$+ \int_{U_{N_0}}^{U_{N_1}} h(t/A_{N_1})G(t - s/B_{N_1})\, ds$$

(4.1) $$\cdots + \int_{U_{N_{N-1}}}^{U_{N_N}} h(t/A_{N_N})G(t-s/B_{N_N})ds.$$

Now, $P(E_{N_i}/E) = P(U_{N_{i-1}} \leq D \leq U_{N_i}/D \leq U_{N_N})$ and L_{N_i} (for some i) can be computed as follows:

$$P(E_{N_i}/E) = \int_0^{U_{N_i}} h(t/A_{N_i})G(t-s/B_{N_i})\,ds \times$$
$$\left[\int_0^{U_{N_N}} h(t/A_{N_N})G(t-s/B_{N_N})\,ds\right]^{-1}$$
$$- \int_0^{U_{N_{i-1}}} h(t/A_{N_{i-1}})G(t-s/B_{N_{i-1}})\,ds \times$$
(4.2) $$\left[\int_0^{U_{N_N}} h(t/A_{N_N})G(t-s/B_{N_N})\,ds\right]^{-1}.$$

$L_{N_i} = \prod_{j=N_{i-1}}^{N_i} P_j^{T_j}$ is maximized for the set $[A_i, B_i]$ by the procedure explained in the previous section. We will obtain N sets of $[\mathbf{A}, \mathbf{B}]$ values, and the corresponding likelihood values are $L_{N_1}, L_{N_2}, L_{N_3}, \ldots, L_{N_N}$. In the above, we have assumed monotonicity of (Z_i) to arrive at (4.2). If the (Z_i) values are not monotonic, then the various conditional probabilities can be constructed as explained in the previous section. There we explained the general expression when there were a finite number of drugs available on the market. For a detailed construction of various conditional probabilities, refer to Appendix I. When the Z_is are not monotonic, and if they follow some order, say for example, $Z_0 > Z_1 < Z_2 > \cdots < Z_N$, then the conditional probabilities can be constructed in the same way as in (3.7)–(3.10). Suppose (Z_p) are equal for each p. Then there will be two scenarios arising: one before drug intervention and one after drug intervention. For this situation, the likelihood equation is $L_{N_p} = \prod_{p=N_{p-1}}^{N_p} P_p^{T_p}$ where $P(E_{N_p}/E)$ is given as follows:

$$P(E_{N_p}/E) = \int_0^{U_{N_p}} h(t/A_{N_p})G(t-s/B_{N_p})\,ds$$
$$\times \left[\int_0^{U_{N_N}} h(t/A_{N_N})G(t-s/B_{N_N})\,ds\right]^{-1}$$

$$-\int_0^{U_{N_{p-1}}} h(t/A_{N_{p-1}})G(t-s/B_{N_{p-1}})]\,ds$$

(4.3)
$$\times\left[\int_0^{U_{N_N}} h(t/A_{N_N})G(t-s/B_{N_N})\,ds\right].$$

5. Theoretical examples. In this section, we show some examples of the likelihood function constructed in the previous section to estimate **A** and **B**. Let $h(s)$ follow a quadratic exponential and **B** follow a) a gamma function and b) a logistic function.

Infections in most of the countries started declining after the availability of antiretroviral therapies [**14, 20**], and incidence in the recent period was found to be stable in some countries like India [**41**]. This motivated us to choose a quadratic exponential to represent $h(s)$, namely, $h(s) = \exp(\alpha_1 s^2 + \alpha_2 s + \alpha_3)$ for all $-\infty < \alpha_1, \alpha_2, \alpha_3 < \infty$. A quadratic exponential function has been shown to be a good model for representing the above declines in the incidence rates [**38**].

The incubation period for AIDS is large as well as variable; therefore, functions like the gamma, Weibull and logistic can mimic several shapes to fit the incubation period data depending on their parameter values. Such well-known functions were used by many researchers for modeling the incubation period of AIDS.

We now demonstrate the application of such functions for the theory explained in Section 2.

5.1. Example 1: Gamma function. If $\omega > 0$ is the parameter and $\Gamma(\omega)$ is the complete distribution function, then the incomplete gamma distribution is

$$G(\omega; t_j) = \frac{1}{\Gamma(\omega)}\int_0^{t_j} e^{-x}x^{\omega-1}dx,$$
$$\text{for } a \geq 0, t_j \geq 0 \text{ and } a + t_j \neq 0.$$

From the conditional probability equations (3.5)–(3.12) and the likelihood equations explained in the latter part of Section 3, the following are the likelihood equations without a drug and with three

types of drugs:

$$(5.1) \quad L_0\left(\alpha_1, \alpha_2, \alpha_3; \omega/P_j\right) = \prod_j a_1(j)a_2(j) - \prod_j a_1(j-1)a_2(j),$$

where

$$a_1(j) = \left[\int_0^{u_j} e^{\alpha_1 s^2 + \alpha_2 s + \alpha_3} \left\{\frac{1}{\Gamma(\omega)} \int_0^{t_j} e^{-(u_j - s)} (u_j - s)^{\omega - 1} du_j\right\} ds\right]^{T_j}$$

$$a_1(j-1) = \left[\int_0^{u_{j-1}} e^{\alpha_1 s^2 + \alpha_2 s + \alpha_3}\right.$$

$$\left. \times \left\{\frac{1}{\Gamma(\omega)} \int_0^{t_{j-1}} e^{-(u_{j-1} - s)} (u_{j-1} - s)^{\omega - 1} du_{j-1}\right\} ds\right]^{T_j}$$

$$a_2(j) = \left[\int_0^{u_n} e^{\alpha_1 s^2 + \alpha_2 s + \alpha_3} \left\{\frac{1}{\Gamma(\omega)} \int_0^{t_n} e^{-(u_n - s)} (u_n - s)^{\omega - 1} du_n\right\} ds\right]^{-T_j}$$

$$(5.2) \quad L_{1(2)}\left(\alpha_1, \alpha_2, \alpha_3; \omega/P_k\right) = \prod_k a_1(k)a_2(k) - \prod_k a_1(k-1)a_2(k),$$

where

$$a_1(k) = \left[\int_0^{u_k} e^{\alpha_1 s^2 + \alpha_2 s + \alpha_3} \left\{\frac{1}{\Gamma(\omega)} \int_0^{t_k} e^{-(u_k - s)} (u_k - s)^{\omega - 1} du_k\right\} ds\right]^{T_k}$$

$$a_1(k-1) = \left[\int_0^{u_{k-1}} e^{\alpha_1 s^2 + \alpha_2 s + \alpha_3}\right.$$

$$\left. \times \left\{\frac{1}{\Gamma(\omega)} \int_0^{t_{k-1}} e^{-(u_{k-1} - s)} (u_{k-1} - s)^{\omega - 1} du_{k-1}\right\} ds\right]^{T_k}$$

$$a_2(k) = \left[\int_0^{u_n} e^{\alpha_1 s^2 + \alpha_2 s + \alpha_3} \left\{\frac{1}{\Gamma(\omega)} \int_0^{t_n} e^{-(u_n - s)} (u_n - s)^{\omega - 1} du_n\right\} ds\right]^{-T_k}$$

$$(5.3) \quad L_{2(1)}\left(\alpha_1, \alpha_2, \alpha_3; \omega/P_l\right) = \prod_l a_1(l)a_2(l) - \prod_l a_1(l-1)a_2(l),$$

where

$$a_1(l) = \left[\int_0^{u_l} e^{\alpha_1 s^2 + \alpha_2 s + \alpha_3} \left\{\frac{1}{\Gamma(\omega)} \int_0^{t_l} e^{-(u_l - s)} (u_l - s)^{\omega - 1} du_l\right\} ds\right]^{T_l}$$

$$a_1(l-1) = \left[\int_0^{u_{l-1}} e^{\alpha_1 s^2 + \alpha_2 s + \alpha_3}\right.$$

$$\times \left\{ \frac{1}{\Gamma(\omega)} \int_0^{t_{l-1}} e^{-(u_{l-1}-s)} (u_{l-1}-s)^{\omega-1} du_{l-1} \right\} ds \right]^{T_l}$$

$$a_2(l) = \left[\int_0^{u_n} e^{\alpha_1 s^2 + \alpha_2 s + \alpha_3} \left\{ \frac{1}{\Gamma(\omega)} \int_0^{t_n} e^{-(u_n-s)} (u_n-s)^{\omega-1} du_n \right\} ds \right]^{-T_l}$$

(5.4) $\quad L_{1=2}(\alpha_1, \alpha_2, \alpha_3; \omega/P_p) = \prod_p a_1(p) a_2(p) - \prod_p a_1(p-1) a_2(p),$

where

$$a_1(p) = \left[\int_0^{u_p} e^{\alpha_1 s^2 + \alpha_2 s + \alpha_3} \left\{ \frac{1}{\Gamma(\omega)} \int_0^{t_p} e^{-(u_p-s)} (u_p-s)^{\omega-1} du_p \right\} ds \right]^{T_p}$$

$$a_1(p-1) = \left[\int_0^{u_{p-1}} e^{\alpha_1 s^2 + \alpha_2 s + \alpha_3} \right.$$

$$\times \left\{ \frac{1}{\Gamma(\omega)} \int_0^{t_{p-1}} e^{-(u_{p-1}-s)} (u_{p-1}-s)^{\omega-1} du_{p-1} \right\} ds \right]^{T_p}$$

$$a_2(p) = \left[\int_0^{u_n} e^{\alpha_1 s^2 + \alpha_2 s + \alpha_3} \left\{ \frac{1}{\Gamma(\omega)} \int_0^{t_n} e^{-(u_n-s)} (u_n-s)^{\omega-1} du_n \right\} ds \right]^{-T_p}$$

(5.5) $\quad L_3(\alpha_1, \alpha_2, \alpha_3; \omega/P_m) = \prod_m a_1(m) a_2(m) - \prod_m a_1(m-1) a_2(m),$

where

$$a_1(m) = \left[\int_0^{u_m} e^{\alpha_1 s^2 + \alpha_2 s + \alpha_3} \left\{ \frac{1}{\Gamma(\omega)} \int_0^{t_m} e^{-(u_m-s)} (u_m-s)^{\omega-1} du_m \right\} ds \right]^{T_m}$$

$$a_1(m-1) = \left[\int_0^{u_{m-1}} e^{\alpha_1 s^2 + \alpha_2 s + \alpha_3} \right.$$

$$\times \left\{ \frac{1}{\Gamma(\omega)} \int_0^{t_{m-1}} e^{-(u_{m-1}-s)} (u_{m-1}-s)^{\omega-1} du_{m-1} \right\} ds \right]^{T_m}$$

$$a_2(m) = \left[\int_0^{u_n} e^{\alpha_1 s^2 + \alpha_2 s + \alpha_3} \left\{ \frac{1}{\Gamma(\omega)} \int_0^{t_n} e^{-(u_n-s)} (u_n-s)^{\omega-1} du_n \right\} ds \right]^{-T_m}.$$

5.2. Example 2: Logistic function. Suppose θ_1 and θ_2 are parameters and

$$F(\theta_1, \theta_2; t_j) = \left\{ 1 + e^{-(t_j - \theta_1/\theta_2)} \right\}^{-1}, \quad \text{for } \theta_1, \theta_2 > 0,$$

is the distribution function. The likelihood equations to obtain the parameters of logistic distribution without drugs and for three types of drugs are as follows:

$$(5.6) \quad L_0\left(\alpha_1, \alpha_2, \alpha_3; \theta_1, \theta_2/P_j\right) = \prod_j a_1'(j)a_2'(j) - \prod_j a_1'(j-1)a_2'(j)$$

where

$$a_1'(j) = \left[\int_0^{u_j} e^{\alpha_1 s^2 + \alpha_2 s + \alpha_3}\left\{\left\{1 + e^{-\left(\frac{u_j - \theta_1}{\theta_2}\right)}\right\}^{-1}\right\}ds\right]^{T_j}$$

$$a_1'(j-1) = \left[\int_0^{u_{j-1}} e^{\alpha_1 s^2 + \alpha_2 s + \alpha_3}\left\{\left\{1 + e^{-\left(\frac{u_{j-1} - \theta_1}{\theta_2}\right)}\right\}^{-1}\right\}ds\right]^{T_j}$$

$$a_2'(j) = \left[\int_0^{u_n} e^{\alpha_1 s^2 + \alpha_2 s + \alpha_3}\left\{\left\{1 + e^{-\left(\frac{u_n - \theta_1}{\theta_2}\right)}\right\}^{-1}\right\}ds\right]^{-T_j}$$

$$(5.7) \quad L_{1(2)}\left(\alpha_1, \alpha_2, \alpha_3; \theta_1, \theta_2/P_k\right) = \prod_k a_1'(k)a_2'(k) - \prod_k a_1'(k-1)a_2'(k),$$

where

$$a_1'(k) = \left[\int_0^{u_k} e^{\alpha_1 s^2 + \alpha_2 s + \alpha_3}\left\{\left\{1 + e^{-\left(\frac{u_k - \theta_1}{\theta_2}\right)}\right\}^{-1}\right\}ds\right]^{T_k}$$

$$a_1'(k-1) = \left[\int_0^{u_{k-1}} e^{\alpha_1 s^2 + \alpha_2 s + \alpha_3}\left\{\left\{1 + e^{-\left(\frac{u_{k-1} - \theta_1}{\theta_2}\right)}\right\}^{-1}\right\}ds\right]^{T_k}$$

$$a_2'(k) = \left[\int_0^{u_n} e^{\alpha_1 s^2 + \alpha_2 s + \alpha_3}\left\{\left\{1 + e^{-\left(\frac{u_n - \theta_1}{\theta_2}\right)}\right\}^{-1}\right\}ds\right]^{-T_k}$$

$$(5.8) \quad L_{2(1)}\left(\alpha_1, \alpha_2, \alpha_3; \theta_1, \theta_2/P_l\right) = \prod_l a_1'(l)a_2'(l) - \prod_l a_1'(l-1)a_2'(l),$$

where

$$a_1'(l) = \left[\int_0^{u_l} e^{\alpha_1 s^2 + \alpha_2 s + \alpha_3}\left\{\left\{1 + e^{-\left(\frac{u_l - \theta_1}{\theta_2}\right)}\right\}^{-1}\right\}ds\right]^{T_l}$$

$$a_1'(l-1) = \left[\int_0^{u_{l-1}} e^{\alpha_1 s^2 + \alpha_2 s + \alpha_3}\left\{\left\{1 + e^{-\left(\frac{u_{l-1} - \theta_1}{\theta_2}\right)}\right\}^{-1}\right\}ds\right]^{T_l}$$

$$a_2'(l) = \left[\int_0^{u_n} e^{\alpha_1 s^2 + \alpha_2 s + \alpha_3}\left\{\left\{1 + e^{-\left(\frac{u_n - \theta_1}{\theta_2}\right)}\right\}^{-1}\right\}ds\right]^{-T_l}$$

$$(5.9)\ \ L_{1=2}\left(\alpha_1,\alpha_2,\alpha_3;\theta_1,\theta_2/P_p\right)=\prod_p a_1'(p)a_2'(p)-\prod_p a_1'(p-1)a_2'(p),$$

where

$$a_1'(p)=\left[\int_0^{u_p}e^{\alpha_1 s^2+\alpha_2 s+\alpha_3}\left\{\left\{1+e^{-\left(\frac{u_p-\theta_1}{\theta_2}\right)}\right\}^{-1}\right\}ds\right]^{T_p}$$

$$a_1'(p-1)=\left[\int_0^{u_{p-1}}e^{\alpha_1 s^2+\alpha_2 s+\alpha_3}\left\{\left\{1+e^{-\left(\frac{u_{p-1}-\theta_1}{\theta_2}\right)}\right\}^{-1}\right\}ds\right]^{T_p}$$

$$a_2'(p)=\left[\int_0^{u_n}e^{\alpha_1 s^2+\alpha_2 s+\alpha_3}\left\{\left\{1+e^{-\left(\frac{u_n-\theta_1}{\theta_2}\right)}\right\}^{-1}\right\}ds\right]^{-T_p}$$

(5.10)
$$L_3\left(\alpha_1,\alpha_2,\alpha_3;\theta_1,\theta_2/P_m\right)=\prod_m a_1'(m)a_2'(m)-\prod_m a_1'(m-1)a_2(m),$$

where

$$a_1'(m)=\left[\int_0^{u_m}e^{\alpha_1 s^2+\alpha_2 s+\alpha_3}\left\{\left\{1+e^{-\left(\frac{u_m-\theta_1}{\theta_2}\right)}\right\}^{-1}\right\}ds\right]^{T_m}$$

$$a_1'(m-1)=\left[\int_0^{u_{m-1}}e^{\alpha_1 s^2+\alpha_2 s+\alpha_3}\left\{\left\{1+e^{-\left(\frac{u_{m-1}-\theta_1}{\theta_2}\right)}\right\}^{-1}\right\}ds\right]^{T_m}$$

$$a_2'(m)=\left[\int_0^{u_n}e^{\alpha_1 s^2+\alpha_2 s+\alpha_3}\left\{\left\{1+e^{-\left(\frac{u_n-\theta_1}{\theta_2}\right)}\right\}^{-1}\right\}ds\right]^{-T_m}.$$

5.3. Example 3: Log-normal function. Suppose μ and σ are parameters and $LNF(\mu,\sigma;t_j)=\{1+\mathrm{erf}(\frac{\ln x-\mu}{\sigma\sqrt{2}})\}/2$, for $\mu,\sigma>0$, is the distribution function. (Here, $\mathrm{erf}\{\cdot\}$ is the error function of the Gaussian function).

The likelihood equations for obtaining the parameters of logistic distribution without drugs and for three types of drugs are as follows:

$$(5.11)\ \ \ L_0\left(\alpha_1,\alpha_2,\alpha_3;\mu,\sigma/P_j\right)=\prod_j a_1''(j)a_2''(j)-\prod_j a_1''(j-1)a_2''(j),$$

where

$$a_1''(j)=\left[\frac{1}{2}\int_0^{u_j}e^{\alpha_1 s^2+\alpha_2 s+\alpha_3}\left\{1+\mathrm{erf}\left(\frac{\ln x-\mu}{\sigma\sqrt{2}}\right)\right\}ds\right]^{T_j}$$

$$a_1''(j-1) = \left[\frac{1}{2}\int_0^{u_{j-1}} e^{\alpha_1 s^2 + \alpha_2 s + \alpha_3}\left\{1 + \mathrm{erf}\left(\frac{\ln x - \mu}{\sigma\sqrt{2}}\right)\right\}ds\right]^{T_j}$$

$$a_2''(j) = \left[\frac{1}{2}\int_0^{u_n} e^{\alpha_1 s^2 + \alpha_2 s + \alpha_3}\left\{1 + \mathrm{erf}\left(\frac{\ln x - \mu}{\sigma\sqrt{2}}\right)\right\}ds\right]^{-T_j}$$

(5.12)
$$L_{1(2)}\left(\alpha_1, \alpha_2, \alpha_3; \mu, \sigma/P_k\right) = \prod_k a_1''(k)a_2''(k) - \prod_k a_1''(k-1)a_2''(k),$$

where

$$a_1''(k) = \left[\frac{1}{2}\int_0^{u_k} e^{\alpha_1 s^2 + \alpha_2 s + \alpha_3}\left\{1 + \mathrm{erf}\left(\frac{\ln x - \mu}{\sigma\sqrt{2}}\right)\right\}ds\right]^{T_k}$$

$$a_1''(k-1) = \left[\frac{1}{2}\int_0^{u_{k-1}} e^{\alpha_1 s^2 + \alpha_2 s + \alpha_3}\left\{1 + \mathrm{erf}\left(\frac{\ln x - \mu}{\sigma\sqrt{2}}\right)\right\}ds\right]^{T_k}$$

$$a_2''(k) = \left[\frac{1}{2}\int_0^{u_n} e^{\alpha_1 s^2 + \alpha_2 s + \alpha_3}\left\{1 + \mathrm{erf}\left(\frac{\ln x - \mu}{\sigma\sqrt{2}}\right)\right\}ds\right]^{-T_k}$$

(5.13) $$L_{2(1)}\left(\alpha_1, \alpha_2, \alpha_3; \mu, \sigma/P_l\right) = \prod_l a_1''(l)a_2''(l) - \prod_l a_1''(l-1)a_2''(l),$$

where

$$a_1''(l) = \left[\frac{1}{2}\int_0^{u_l} e^{\alpha_1 s^2 + \alpha_2 s + \alpha_3}\left\{1 + \mathrm{erf}\left(\frac{\ln x - \mu}{\sigma\sqrt{2}}\right)\right\}ds\right]^{T_l}$$

$$a_1''(l-1) = \left[\frac{1}{2}\int_0^{u_{l-1}} e^{\alpha_1 s^2 + \alpha_2 s + \alpha_3}\left\{1 + \mathrm{erf}\left(\frac{\ln x - \mu}{\sigma\sqrt{2}}\right)\right\}ds\right]^{T_l}$$

$$a_2''(l) = \left[\frac{1}{2}\int_0^{u_n} e^{\alpha_1 s^2 + \alpha_2 s + \alpha_3}\left\{1 + \mathrm{erf}\left(\frac{\ln x - \mu}{\sigma\sqrt{2}}\right)\right\}ds\right]^{-T_l}$$

(5.14)
$$L_{1=2}\left(\alpha_1, \alpha_2, \alpha_3; \mu, \sigma/P_p\right) = \prod_p a_1''(p)a_2''(p) - \prod_p a_1''(p-1)a_2''(p),$$

where

$$a_1''(p) = \left[\frac{1}{2}\int_0^{u_p} e^{\alpha_1 s^2 + \alpha_2 s + \alpha_3}\left\{1 + \mathrm{erf}\left(\frac{\ln x - \mu}{\sigma\sqrt{2}}\right)\right\}ds\right]^{T_p}$$

$$a_1''(p-1) = \left[\frac{1}{2}\int_0^{u_{p-1}} e^{\alpha_1 s^2+\alpha_2 s+\alpha_3}\left\{1+\mathrm{erf}\left(\frac{\ln x-\mu}{\sigma\sqrt{2}}\right)\right\}ds\right]^{T_p}$$

$$a_2''(p) = \left[\frac{1}{2}\int_0^{u_n} e^{\alpha_1 s^2+\alpha_2 s+\alpha_3}\left\{1+\mathrm{erf}\left(\frac{\ln x-\mu}{\sigma\sqrt{2}}\right)\right\}ds\right]^{-T_p}$$

(5.15)
$$L_3\left(\alpha_1,\alpha_2,\alpha_3;\mu,\sigma/P_m\right) = \prod_m a_1'(m)a_2'(m) - \prod_m a_1'(m-1)a_2(m),$$

where

$$a_1''(m) = \left[\frac{1}{2}\int_0^{u_m} e^{\alpha_1 s^2+\alpha_2 s+\alpha_3}\left\{1+\mathrm{erf}\left(\frac{\ln x-\mu}{\sigma\sqrt{2}}\right)\right\}ds\right]^{T_m}$$

$$a_1''(m-1) = \left[\frac{1}{2}\int_0^{u_{m-1}} e^{\alpha_1 s^2+\alpha_2 s+\alpha_3}\left\{1+\mathrm{erf}\left(\frac{\ln x-\mu}{\sigma\sqrt{2}}\right)\right\}ds\right]^{T_m}$$

$$a_2''(m) = \left[\frac{1}{2}\int_0^{u_n} e^{\alpha_1 s^2+\alpha_2 s+\alpha_3}\left\{1+\mathrm{erf}\left(\frac{\ln x-\mu}{\sigma\sqrt{2}}\right)\right\}ds\right]^{-T_m}.$$

6. Age-structured populations. In this section, we extend models 1.4 and 1.5 to accommodate age structure into the population mixing and epidemiology parameters. The incubation period for children is shorter than that for adults. Within the adult population, there could be variability due to age at the time of infection. There are studies that analyze the HIV data collected on age at the time of infection in order to study parameters like incubation period [6], and some studies incorporate age structure in the models to explain the impact of an age-dependent incubation period [18].

Information on population age structure is an important source of data in countries with a severe AIDS epidemic. Countries with a high number of young adults with high-risk behavior need special interventions in terms of behavioral counseling, treatment with drugs, monitoring and evaluation of the epidemic. For most of the countries with high numbers of HIV infected individuals, age-related data for measuring impact of drugs are not available. Virus transmission rates, disease progression rates and mortality rates could be highly age-dependent. Improving surveillance activities by age-structure of the HIV infected and susceptible populations would benefit the overall disease control programs in a country.

In the absence of availability of cohort data, the methods explained in Section 2 could be of great use to estimate the incubation period. The analysis and method explained there could be carried out based on the data available for individuals of every age (rounded to the closest integer). We describe the age-structure model and the method for obtaining the incubation period in this section by considering j age groups. In a hospital set-up it is relatively easy to follow cohorts of age groups compared to following cohorts of individuals for each age group.

Suppose the population in the jth age group is divided into X_j susceptible, $Y_{0,j}$, $Y_{1,j}$, $Y_{2,j}$ and $Y_{3,j}$ are infected and $D_{z_0,j}$, $D_{z_1,j}$, $D_{z_2,j}$ and $D_{z_3,j}$ are individuals with the disease without drugs, for $drug1$, $drug2$ and $drug3$, respectively. The differential equations explaining these variables are:

$$\frac{dX_j}{dt} = \Lambda_j - \left(\lambda_{jk}^0 + \lambda_{jk}^1 + \lambda_{jk}^2 + \lambda_{jk}^3 + \mu_j \right) X_j,$$

$$\frac{dY_{0,j}}{dt} = \lambda_{jk}^0 X_j - \left\{ \left(\int_{\mathbb{R}} z_{0,j} dG(z_{0,j}) \right)^{-1} + \mu_j \right\} Y_{0,j},$$

$$\frac{dY_{1,j}}{dt} = \lambda_{jk}^1 X_j - \left\{ \left(\int_{\mathbb{R}} z_{1,j} dG(z_{1,j}) \right)^{-1} + \mu_j \right\} Y_{1,j},$$

$$\frac{dY_{2,j}}{dt} = \lambda_{jk}^2 X_j - \left\{ \left(\int_{\mathbb{R}} z_{2,j} dG(z_{2,j}) \right)^{-1} + \mu_j \right\} Y_{2,j},$$

(6.1) $\quad\dfrac{dY_{3,j}}{dt} = \lambda_{jk}^3 X_j - \left\{ \left(\int_{\mathbb{R}} z_{3,j} dG(z_{3,j}) \right)^{-1} + \mu_j \right\} Y_{3,j},$

$$\frac{dD_{z_0,j}}{dt} = \left(\int_{\mathbb{R}} z_{0,j} dG(z_{0,j}) \right)^{-1} Y_{0,j} - \gamma_{0,j} D_{z_0,j},$$

$$\frac{dD_{z_1,j}}{dt} = \left(\int_{\mathbb{R}} z_{1,j} dG(z_{1,j}) \right)^{-1} Y_{1,j} - \gamma_{1,j} D_{z_1,j},$$

$$\frac{dD_{z_2,j}}{dt} = \left(\int_{\mathbb{R}} z_{2,j} dF(z_{2,j}) \right)^{-1} Y_{2,j} - \gamma_{2,j} D_{z_2,j},$$

$$\frac{dD_{z_3,j}}{dt} = \left(\int_{\mathbb{R}} z_{3,j} dG(z_{3,j}) \right)^{-1} Y_{3,j} - \gamma_{3,j} D_{z_3,j}.$$

Here, Λ_j is the input of susceptibles for the individuals in the age group j, μ_j is the mortality rate, λ_{jk}^0, λ_{jk}^1, λ_{jk}^2 and λ_{jk}^3 are the forces of infection at which a susceptible in the age group j is infected by

an infected individual in the age group k, and $\gamma_{0,j}$, $\gamma_{1,j}$, $\gamma_{2,j}$ and $\gamma_{3,j}$ are disease related mortality rates for the infected individuals in the age group j without drugs, and with $drug1$, $drug2$ and $drug3$ for the individuals. $\left(\int_{\mathbb{R}} z_{i,j} dG(z_{i,j})\right)^{-1}$ is the rate of disease progression for the infected individual for the age group j for the drug type i. Special attention is necessary in data collection for understanding the forces of infection by age group.

If there are n drug types available, then the general model describing the dynamics of various variables described above is as follows:

$$\frac{dX_j}{dt} = \Lambda_j - \left(\lambda_{jk}^0 + \lambda_{jk}^1 + \lambda_{jk}^2 + \lambda_{jk}^3 + \mu_j\right) X_j,$$

$$\frac{dY_{0,j}}{dt} = \lambda_{jk}^0 X_j - \left\{\left(\int_{\mathbb{R}} z_{0,j} dG(z_{0,j})\right)^{-1} + \mu_j\right\} Y_{0,j},$$

$$\vdots$$

$$\vdots$$

$$(6.2) \qquad \frac{dY_{n,j}}{dt} = \lambda_{jk}^n X_j - \left\{\left(\int_{\mathbb{R}} z_{n,j} dG(z_{n,j})\right)^{-1} + \mu_j\right\} Y_{n,j},$$

$$\frac{dD_{z_0,j}}{dt} = \left(\int_{\mathbb{R}} z_{0,j} dG(z_{0,j})\right)^{-1} Y_{0,j} - \gamma_{0,j} D_{z_0,j},$$

$$\vdots$$

$$\vdots$$

$$\frac{dD_{z_n,j}}{dt} = \left(\int_{\mathbb{R}} z_{n,j} dG(z_{n,j})\right)^{-1} Y_{n,j} - \gamma_{n,j} D_{z_n,j},$$

where $\alpha_{i,j}$ is the mortality rate of infected individuals of drug type i in the age group j.

6.1. Varying incubation periods for age-structured populations.
We are interested in the average incubation period for a group of individuals in the age group j. If $H(j)$ is the time of infection and $Z(j)$ is the incubation period for the jth age group, then the time of onset of the disease for this age group is $D(j) = H(j) + Z(j)$. This is the time of onset of the disease for an individual who acquired the infection

$$D(j)$$

H(j)	0	1	...	j	j+1	...	j+ω
0	(0,0)	(0,1)	...	(0,j)	(0,j+1)	...	(0,j+ω)
1		(1,1)	...	(1,j)	(1,j+1)	...	(1,j+ω)
⋮				⋮	⋮		⋮
j				(j,j)	(j,j+1)	...	(j,j+ω)
j+1					(j+1,j+1)	...	(j+1,j+ω)
⋮							⋮
j+ω							(j+ω,j+ω)

FIGURE 2. Age-structured infection and disease development matrix. Here row values indicate infection age group ($H(j)$) and column values for age group in which infected individual developed disease ($D(j)$). An individual who acquired the infection in j, and developed disease in $j + \omega$, is indicated by the cell $(j, j + \omega)$.

while in the jth age group. Development of the disease will be some time units (for example: months, years) after infection at age j. An individual who acquired the infection at age j is assumed to develop the full disease before completion of the same age j or $> j$. Given $H(j)$, for some j, then $D(j)$ is allowed to occur at age $j'(j' = j, j+1, \cdots, j+\omega$, where $j+\omega$ is the last age group for the possibility of infection). Clearly, $H(j) \leq D(j)$. $H(j) = D(j)$ is possible if an individual acquired infection and attains disease before completion of age j. One can do an analysis using a bi-annual (or half-yearly) aging process.

Consider an infection and disease development matrix (see Figure 2) where each cell (j, j') denotes the (infection age groups, disease onset age groups) for $j = 0, 1, 2, \ldots, j+\omega$; $j' = 0, 1, 2, \ldots, j+\omega$. Only those cells for which $j \leq j'$ are provided, and other cells are left blank for which the incubation period is not defined. In the matrix, all the eligible cells are denoted, so obviously there are more cells present where the condition $j \leq j'$ is satisfied, and also j is very low. (In fact, the average incubation period is not beyond a certain duration. It is not intended in the matrix to suggest that the lower the value of j, the larger the value of the incubation period). If the age of infection is higher, for some j, and towards the last few possible age groups, then it is possible that $j' - j$ is shorter because individuals die naturally in old age. At the same time, the chance of infection in the very higher age groups (say 60+) is negligible for HIV (unless there are some rare causes). In the absence of age specific cohorts of infected individuals and follow-up data, it is not feasible to calculate disease progression rates and survival

probabilities using direct cohort methods.

In this section, we extend the method given in Section 2 to estimate the average disease progression rates (or average incubation periods) for infections in age group j. This method is dependent on infection densities and data on disease occurrences for the age group j.

Let $p(t,j)$ and $q(t,j)$ be the probability density functions of infection density and incubation period for the age group j. If $Q(t,j)$ is the distribution function of the incubation period, then $Q(t,j) = \int_{-\infty}^{t} q(t,j)\, dt$. Now, the convolution of $p(t,j)$ and $Q(t,j)$ is given by

$$C(s,t) = \int_{-\infty}^{\infty} p(t,j)Q(t-s,j)\, ds.$$

We call C the convolution of p and Q (i.e. $p * Q$, where $*$ is the convolution operator). Therefore,

$$p * Q = \int_{-\infty}^{\infty} p(t,j)Q(t-s,j)\, ds.$$

Suppose an individual is diagnosed with a disease at age j in the year U_k. Then there is a possibility that this individual acquired the infection in any of the years prior to U_k (provided this individual was born in the year $\geq U_0$). Similarly, all those individuals who are diagnosed with the disease at age $j + w$ in the year U_n have actually acquired infection in any of the years from U_0 to U_n. In the same way, an individual infected at age j will be diagnosed with the disease in an age group $\geq j$. We consider model (6.1), where four types of drugs were considered in Section 2.

Let $A_0(j)$, $A_1(j)$, $A_2(j)$ and $A_3(j)$ be the parameter sets in age group j for the four kinds of drugs. Let $B_0(j)$, $B_1(j)$, $B_2(j)$ and $B_3(j)$ be the parameter sets C and $E_0(j)$, $E_1(j)$, $E_2(j)$ and $E_3(j)$ be the corresponding events of diagnosis of disease in the age group j for the four types of drugs. The cumulative number of diagnosed disease cases up to U_n for individuals who are diagnosed in the age group j is

$$J(U_0 < s < U_n, j) = \sum_{j^*=0}^{j} I(j^*,j),$$

where $I(0,j), I(1,j), \ldots, I(j,j)$ are the numbers of disease cases di-

agnosed in age group j and acquired the infection in the age group $0, 1, \ldots, j$.

$$I(0, j) = \int_0^{U_{n-k}} p(t, 0)Q(t - s, j)\, ds$$

$$+ \int_{U_{n-k}}^{U_{n-l}} p(t, 0)Q(t - s, j)\, ds$$

$$+ \int_{U_{n-l}}^{U_{n-m}} p(t, 0)Q(t - s, j)\, ds$$

$$+ \int_{U_{n-m}}^{U_n} p(t, 0)Q(t - s, j)\, ds$$

$$= \int_0^{U_{n-k}} p(t, 0/A_0)Q(t - s, j/B_0)\, ds$$

$$+ \int_{U_{n-k}}^{U_{n-l}} p(t, 0/A_1)Q(t - s, j/B_1)\, ds$$

$$+ \int_{U_{n-l}}^{U_{n-m}} p(t, 0/A_2)Q(t - s, j/B_2)\, ds$$

$$+ \int_{U_{n-m}}^{U_n} p(t, 0/A_3)Q(t - s, j/B_3)\, ds$$

$$I(1, j) = \int_0^{U_{n-k}} p(t, 1)Q(t - s, j)\, ds$$

$$+ \int_{U_{n-k}}^{U_{n-l}} p(t, 1)Q(t - s, j)\, ds$$

$$+ \int_{U_{n-l}}^{U_{n-m}} p(t, 1)Q(t - s, j)\, ds$$

$$+ \int_{U_{n-m}}^{U_n} p(t, 1)Q(t - s, j)\, ds$$

$$= \int_0^{U_{n-k}} p(t, 1/A_0)Q(t - s, j/B_0)\, ds$$

$$+ \int_{U_{n-k}}^{U_{n-l}} p(t, 1/A_1)Q(t - s, j/B_1)\, ds$$

$$+ \int_{U_{n-l}}^{U_{n-m}} p(t, 1/A_2) Q(t - s, j/B_2) \, ds$$

$$+ \int_{U_{n-m}}^{U_n} p(t, 1/A_3) Q(t - s, j/B_3) \, ds$$

$$\vdots$$

$$I(j, j) = \int_0^{U_{n-k}} p(t, j) Q(t - s, j) \, ds$$

$$+ \int_{U_{n-k}}^{U_{n-l}} p(t, j) Q(t - s, j) \, ds$$

$$+ \int_{U_{n-l}}^{U_{n-m}} p(t, j) Q(t - s, j) \, ds$$

$$+ \int_{U_{n-m}}^{U_n} p(t, j) Q(t - s, j) \, ds$$

$$= \int_0^{U_{n-k}} p(t, j/A_0) Q(t - s, j/B_0) \, ds$$

$$+ \int_{U_{n-k}}^{U_{n-l}} p(t, j/A_1) Q(t - s, j/B_1) \, ds$$

$$+ \int_{U_{n-l}}^{U_{n-m}} p(t, j/A_2) Q(t - s, j/B_2) \, ds$$

$$+ \int_{U_{n-m}}^{U_n} p(t, j/A_3) Q(t - s, j/B_3) \, ds.$$

Similar to unstructured populations, we assume that U_{n-k} is the time of the introduction of drugs after the first year of detection of the disease in U_0. If $E_1(j) \in [U_{n-k}, U_{n-l})$ and $E_2(j) \in [U_{n-l}, U_{n-m})$, then $Z_1(j) < Z_2(j)$; otherwise, if $E_2(j) \in [U_{n-k}, U_{n-l})$ and $E_1(j) \in [U_{n-l}, U_{n-m})$, then $Z_2(j) < Z_1(j)$. If $E_1(j), E_2(j) \in [U_{n-k}, U_{n-m})$, then $Z_1(j) = Z_2(j)$. An individual who was diagnosed with the disease in the age group j before U_n is already developed in one of the four intervals $[U_0, U_{n-k})$, $[U_{n-k}, U_{n-l})$, $[U_{n-l}, U_{n-m})$ and $[U_{n-m}, U_n)$ is assumed. If $E_0(j) \in [U_{i'-1}, U_{i'}) \subseteq [U_0, U_{n-k})$, (for drug type i'), then the conditional probability of occurrence of $E_0(j)$ given $E(j)$ is:

$$Pr\left[E_0(j)/E(j)\right] = Pr\left[U_{i'-1} \le J \le U_{i'}, j/J \le U_n\right]$$

$$= \frac{J\left[A_0(j), B_0(j)/U_{i'}, j\right] - J\left[A_0(j), B_0(j)/u_{i'-1}, j\right]}{J\left[A_0(j), B_0(j)/U_n, j\right]},$$

where J values for $E_0(j)$ are given by:

$$J\left[A_0(j), B_0(j)/U_{i'}, j\right] = \int_0^{U_{i'}} p(t, 0/A_0)Q(t - s, j/B_0)\, ds$$

$$+ \int_0^{U_{i'}} p(t, 1/A_0)Q(t - s, j/B_0)\, ds \cdots$$

$$+ \int_0^{U_{i'}} p(t, j/A_0)Q(t - s, j/B_0)\, ds$$

$$J\left[A_0(j), B_0(j)/U_{i'-1}, j\right] = \int_0^{U_{i'-1}} p(t, 0/A_0)Q(t - s, j/B_0)\, ds$$

$$+ \int_0^{U_{i'-1}} p(t, 1/A_0)Q(t - s, j/B_0)\, ds \cdots$$

$$+ \int_0^{U_{i'-1}} p(t, j/A_0)Q(t - s, j/B_0)\, ds$$

$$J\left[A_1(j), B_1(j)/U_n, j\right] = \int_0^{U_n} p(t, 0/A_0)Q(t - s, j/B_0)\, ds$$

$$+ \int_0^{U_n} p(t, 1/A_0)Q(t - s, j/B_0)\, ds \cdots$$

$$+ \int_0^{U_n} p(t, j/A_0)Q(t - s, j/B_0)\, ds.$$

The above probability expressions are for the case without drug interventions. When *drugs* were initiated at U_{n-k}, then these probabilities changed according to the occurrence of $E_1(j)$, $E_2(j)$ and $E_3(j)$. Suppose $E_1(j) \cap E_2(j) = \emptyset$. If $[U_{k'-1}, U_{k'}) \subseteq [U_{n-k}, U_{n-l})$ and $E_1 \in [U_{n-k}, U_{n-l})$, then

$$Pr\left[E_1(j)/E(j)\right] = Pr\left[U_{k'-1} \le J \le U_{k'}, j/J \le U_n\right]$$

$$= \frac{J\left[A_1(j), B_1(j)/U_{k'}, j\right] - J\left[A_1(j), B_1(j)/u_{k'-1}, j\right]}{J\left[A_1(j), B_1(j)/U_n, j\right]},$$

where J values for $E_1(j)$ are given by

$$J\left[A_1(j), B_1(j)/U_{k'}, j\right] = \int_0^{U_{k'}} p(t, 0/A_1)Q(t - s, j/B_1)\, ds$$

$$+ \int_0^{U_{k'}} p(t, 1/A_1) Q(t - s, j/B_1)\, ds \cdots$$

$$+ \int_0^{U_{k'}} p(t, j/A_1) Q(t - s, j/B_1)\, ds$$

$$J\left[A_1(j), B_1(j)/U_{k'-1}, j\right] = \int_0^{U_{k'-1}} p(t, 0/A_1) Q(t - s, j/B_1)\, ds$$

$$+ \int_0^{U_{k'-1}} p(t, 1/A_1) Q(t - s, j/B_1)\, ds \cdots$$

$$+ \int_0^{U_{k'-1}} p(t, j/A_1) Q(t - s, j/B_1)\, ds$$

$$J\left[A_1(j), B_1(j)/U_n, j\right] = \int_0^{U_n} p(t, 0/A_1) Q(t - s, j/B_1)\, ds$$

$$+ \int_0^{U_n} p(t, 1/A_1) Q(t - s, j/B_1)\, ds \cdots$$

$$+ \int_0^{U_n} p(t, j/A_1) Q(t - s, j/B_1)\, ds.$$

In the above, instead of $E_1(j)$, if $E_2 \in [U_{n-k}, U_{n-l})$, then the probabilities would be:

$$Pr\left[E_2(j)/E(j)\right] = Pr\left[U_{k'-1} \leq J \leq U_{k'}, j/J \leq U_n\right]$$
$$= \frac{J\left[A_2(j), B_2(j)/U_{k'}, j\right] - J\left[A_2(j), B_2(j)/u_{k'-1}, j\right]}{J\left[A_2(j), B_2(j)/U_n, j\right]},$$

where J values for $E_1(j)$ are given by

$$J\left[A_2(j), B_2(j)/U_{k'}, j\right] = \int_0^{U_{k'}} p(t, 0/A_2) Q(t - s, j/B_2)\, ds$$

$$+ \int_0^{U_{k'}} p(t, 1/A_2) Q(t - s, j/B_2)\, ds \cdots$$

$$+ \int_0^{U_{k'}} p(t, j/A_2) Q(t - s, j/B_2)\, ds$$

$$J\left[A_2(j), B_2(j)/U_{k'-1}, j\right] = \int_0^{U_{k'-1}} p(t, 0/A_2) Q(t - s, j/B_2)\, ds$$

$$+ \int_0^{U_{k'-1}} p(t, 1/A_2) Q(t - s, j/B_2)\, ds \cdots$$

$$+ \int_0^{U_{k'-1}} p(t, j/A_2)Q(t - s, j/B_2)\, ds$$

$$J\left[A_2(j), B_2(j)/U_n, j\right] = \int_0^{U_n} p(t, 0/A_2)Q(t - s, j/B_2)\, ds$$

$$+ \int_0^{U_n} p(t, 1/A_2)Q(t - s, j/B_2)\, ds$$

$$+ \int_0^{U_n} p(t, j/A_2)Q(t - s, j/B_2)\, ds.$$

If $[U_{l-1}, U_l) \subseteq [U_{n-l}, U_{n-m})$ and $E_1 \in [U_{n-l}, U_{n-m})$, then

$$Pr\left[E_1(j)/E(j)\right] = Pr\left[U_{l'-1} \leq J \leq U_{l'}, j/J \leq U_n\right]$$

$$= \frac{J\left[A_1(j), B_1(j)/U_{l'}, j\right] - J\left[A_1(j), B_1(j)/u_{l'-1}, j\right]}{J\left[A_1(j), B_1(j)/U_n, j\right]},$$

where J values for $E_1(j)$ are given by

$$J\left[A_1(j), B_1(j)/U_{l'}, j\right] = \int_0^{U_{l'}} p(t, 0/A_1)Q(t - s, j/B_1)\, ds$$

$$+ \int_0^{U_{l'}} p(t, 1/A_1)Q(t - s, j/B_1)\, ds \cdots$$

$$+ \int_0^{U_{l'}} p(t, j/A_1)Q(t - s, j/B_1)\, ds$$

$$J\left[A_1(j), B_1(j)/U_{l'-1}, j\right] = \int_0^{U_{l'-1}} p(t, 0/A_1)Q(t - s, j/B_1)\, ds$$

$$+ \int_0^{U_{l'-1}} p(t, 1/A_1)Q(t - s, j/B_1)\, ds \cdots$$

$$+ \int_0^{U_{l'-1}} p(t, j/A_1)Q(t - s, j/B_1)\, ds$$

$$J\left[A_1(j), B_1(j)/U_n, j\right] = \int_0^{U_n} p(t, 0/A_1)Q(t - s, j/B_1)\, ds$$

$$+ \int_0^{U_n} p(t, 1/A_1)Q(t - s, j/B_1)\, ds \cdots$$

$$+ \int_0^{U_n} p(t, j/A_1)Q(t - s, j/B_1)\, ds.$$

Suppose $[U_{l-1}, U_l) \subseteq [U_{n-l}, U_{n-m})$ and $E_2 \in [U_{n-l}, U_{n-m})$. Then

$$Pr\left[E_2(j)/E(j)\right] = Pr\left[U_{l'-1} \leq J \leq U_{l'}, j/J \leq U_n\right]$$
$$= \frac{J\left[A_2(j), B_2(j)/U_{l'}, j\right] - J\left[A_2(j), B_2(j)/u_{l'-1}, j\right]}{J\left[A_2(j), B_2(j)/U_n, j\right]},$$

where J values for $E_2(j)$ are given as below:

$$J\left[A_2(j), B_2(j)/U_{l'}, j\right] = \int_0^{U_{l'}} p(t, 0/A_2)Q(t-s, j/B_2)\, ds$$
$$+ \int_0^{U_{l'}} p(t, 1/A_2)Q(t-s, j/B_2)\, ds \cdots$$
$$+ \int_0^{U_{l'}} p(t, j/A_2)Q(t-s, j/B_2)\, ds$$

$$J\left[A_2(j), B_2(j)/U_{l'-1}, j\right] = \int_0^{U_{l'-1}} p(t, 0/A_2)Q(t-s, j/B_2)\, ds$$
$$+ \int_0^{U_{l'-1}} p(t, 1/A_2)Q(t-s, j/B_2)\, ds \cdots$$
$$+ \int_0^{U_{l'-1}} p(t, j/A_2)Q(t-s, j/B_2)\, ds$$

$$J\left[A_2(j), B_2(j)/U_n, j\right] = \int_0^{U_n} p(t, 0/A_2)Q(t-s, j/B_2)\, ds$$
$$+ \int_0^{U_n} p(t, 1/A_2)Q(t-s, j/B_2)\, ds \cdots$$
$$+ \int_0^{U_n} p(t, j/A_2)Q(t-s, j/B_2)\, ds.$$

If $E_1(j) = E_2(j) \in [U_{p'-1}, U_{p'}) \subseteq [U_{n-k}, U_{n-m})$ i.e., $Z_1(j) = Z_2(j)$, then the conditional probabilities contain the same parameter sets. The probabilities for this situation are:

$$Pr[E_1(j) = E_2(j)/E(j)] = Pr\left[U_{p'-1} \leq J \leq U_{p'}, j/J \leq U_n\right]$$
$$= \frac{J\left[A_2(j), B_2(j)/U_{p'}, j\right] - J\left[A_2(j), B_2(j)/u_{p'-1}, j\right]}{J\left[A_2(j), B_2(j)/U_n, j\right]},$$

where J values for $E_2(j)$ are given by

$$J\left[A_2(j), B_2(j)/U_{p'}, j\right] = \int_0^{U_{p'}} p(t, 0/A_2)Q(t-s, j/B_2)\, ds$$

$$+ \int_0^{U_{p'}} p(t, 1/A_2)Q(t-s, j/B_2)\, ds \cdots$$

$$+ \int_0^{U_{p'}} p(t, j/A_2)Q(t-s, j/B_2)\, ds$$

$$J\left[A_2(j), B_2(j)/U_{p'-1}, j\right] = \int_0^{U_{p'-1}} p(t, 0/A_2)Q(t-s, j/B_2)\, ds$$

$$+ \int_0^{U_{p'-1}} p(t, 1/A_2)Q(t-s, j/B_2)\, ds \cdots$$

$$+ \int_0^{U_{p'-1}} p(t, j/A_2)Q(t-s, j/B_2)\, ds$$

$$J\left[A_2(j), B_2(j)/U_n, j\right] = \int_0^{U_n} p(t, 0/A_2)Q(t-s, j/B_2)\, ds$$

$$+ \int_0^{U_n} p(t, 1/A_2)Q(t-s, j/B_2)\, ds \cdots$$

$$+ \int_0^{U_n} p(t, j/A_2)Q(t-s, j/B_2)\, ds.$$

Since $Z_3(j) > \{Z_0(j), Z_1(j), Z_2(j)\}$, suppose $E_3(j) \in [U_{m'-1}, U_{m'}) \subseteq [U_{n-m}, U_n]$. Now the above probabilities are:

$$Pr\left[E_3(j)/E(j)\right] = Pr\left[U_{m'-1} \le J \le U_{m'}, j/J \le U_n\right]$$

$$= \frac{J\left[A_3(j), B_3(j)/U_{m'}, j\right] - J\left[A_3(j), B_3(j)/u_{m'-1}, j\right]}{J\left[A_3(j), B_3(j)/U_n, j\right]},$$

where the J values for $E_3(j)$ are given by

$$J\left[A_3(j), B_3(j)/U_{m'}, j\right] = \int_0^{U_{m'}} p(t, 0/A_3)Q(t-s, j/B_3)\, ds$$

$$+ \int_0^{U_{m'}} p(t, 1/A_3)Q(t-s, j/B_3)\, ds \cdots$$

$$+ \int_0^{U_{m'}} p(t, j/A_3)Q(t-s, j/B_3)\, ds$$

$$J\left[A_3(j), B_3(j)/U_{m'-1}, j\right] = \int_0^{U_{m'-1}} p(t, 0/A_3)Q(t-s, j/B_3)\, ds$$

$$+ \int_0^{U_{m'-1}} p(t, 1/A_3)Q(t-s, j/B_3)\, ds \cdots$$

$$+ \int_0^{U_{m'-1}} p(t, j/A_3)Q(t-s, j/B_3)\, ds$$

$$J\left[A_3(j), B_3(j)/U_n, j\right] = \int_0^{U_n} p(t, 0/A_3)Q(t-s, j/B_3)\, ds$$

$$+ \int_0^{U_n} p(t, 1/A_3)Q(t-s, j/B_3)\, ds \cdots$$

$$+ \int_0^{U_n} p(t, j/A_3)Q(t-s, j/B_3)\, ds.$$

Using the above conditional probabilities, likelihood functions can be constructed by assuming some parametric form for the diagnosed disease cases. For each age group above, an analysis is conducted to estimate the incubation periods.

7. Conclusions. The methods and models developed support further biological and epidemiological experiments in the HIV infected population. As per the current WHO guidelines, ART is prescribed only when CD4 count reaches 350 $cells/mm^3$ [**54**]. Experiments indicate the mortality rate among the HIV infected population drops after individuals are on ART, and hence the expected life years remaining once an individual reaches $CD4 = 350$ is different for those individuals who are on ART and those who are not on ART. After providing ART for all the eligible people, the length of life gained by individuals can be measured, and the resultant functional form can be modeled. Similarly, models can be built for lengths of lives for those individuals who reach $CD4 = 350$ and are not on ART. However, modeling on the data for those who are not on ART and having lower levels of CD4 is practically not feasible, because most countries have ART guidelines which will be effective as soon as an individual is found HIV positive and the CD4 count reaches a certain lower level such that ART is initiated. With a careful collection of published literature, a comparison of disease progression rates obtained during pre-ART and ART years can provide useful statistics on the mean incubation period.

Until recently, the WHO recommended starting ART when the CD4 count reaches 250 or lower. Guidelines for introducing ART have been evolving over the years. Improved monitoring of cohorts of infected individuals and improvements in medical technology will help to improve the life of infected people.

There are debates regarding the introduction of ART to people who have a CD4 count of 500 or above. A change in the guidelines for initiating ART will lead to the formation of different study populations for key parameters estimation and formation of cohorts of people with differential drug exposure. The relation between the CD4 count and time of initiation of therapy is important for disease progression rates and mortality rates, and generation of such data requires scientific planning and inference.

There could be several limitations in studies which capture the impact of ART interventions using inaccurate experimental designs to evaluate drug efficacy in the population. For example, survival patterns of a cohort of people recruited for ART in the early 2000s based on a CD4 count around 200 need not be same as the survival pattern of a different cohort of people who were recruited in 2010s based on a CD4 count around 350. Analyzing the population data on ART which was collected by mixing various cohorts formulated at various time points requires allocation of weights for obtaining efficient descriptive statistics on treatment efficacy. Careful planning of cohort based studies on treatment for meaningful conclusions is necessary for population based policies and guidelines. Simultaneous efforts of up to date statistical data analysis and mathematical modeling of the impacts of ART are necessary formulation of better guidelines for treatment.

Revised models that address the impacts of anti-retroviral therapy, protease inhibitors and a combination of the drugs presented in Section 1 are useful in understanding the dynamics of variables for individuals with the full blown disease for no-drug, $drug1$, $drug2$ and $drug3$, i.e., $D_{z_0}, D_{z_1}, D_{z_2}$ and D_{z_3}. Using the methodologies in Sections 2 to 4, one is able to estimate the parameters for the incubation period for each drug type by the deconvolution method. We have demonstrated this method for three types of drugs, and one can obtain **B** for as many drugs as possible from the formulas for n-types of drugs in Section 3. There is evidence of drugs being useful in prevention programs (for example, see [13]). Drugs may be useful for avoiding opportunistic in-

fections for some specific periods of time. Eventually, an individual will succumb to AIDS, whether or not that individual takes drugs (which is also demonstrated in the truncation effect in Figure 3). The truncation effect formulas can be used to obtain the parameter set (say, $\mathbf{B}^T$), but we did not demonstrate this numerically. There were other types of methods for obtaining incubation periods (see [36] when data is censored and see [39] when data is from a hospital based cohort).

We did not introduce intracellular delay that might arise due to drug interventions. There are not many quantitative results available on the relationship between the dose of a drug and the resultant delay in the development of the disease. Suppose $s_1, s_2, s_3, \ldots, s_k$ are k levels of doses of a single drug, and $\tau_1, \tau_2, \tau_3, \ldots, \tau_k$ are the respective delays obtained in producing a new infected cell. Then we can write the relation $R^2(s, \tau)$ between s and τ as

$$\frac{\left\{\sum_{i=1}^{k} (s_i - \overline{s}) (\tau_i - \overline{\tau})\right\}^2}{\left\{\sum_{i=1}^{k} (s_i - \overline{s})\right\}^2 \left\{\sum_{i=1}^{k} (\tau_i - \overline{\tau})\right\}^2}.$$

$R^2(s, \tau)$ is called the correlation coefficient of dose-delay. $\overline{s}$ is the mean dose-level and $\overline{\tau}$ is the mean delay. This experiment can be conducted for various doses s_{ij} (say) for drug type $j = 1, 2, 3, \ldots, n$. Each drug will produce a delay depending upon the dose level. From this, the average delay can be statistically compared to understand the mean dose effect due to a particular drug and hence the drug efficacy. However, this does not give dynamics over the time period, but it is very useful in preparing the baseline parameters for simulation studies, and also for the models explained in Sections 1, 2 and 5.

Our work may be interesting for people working on developing computational techniques for solving integro-differential equations, algorithms to solve convolution type equations in epidemiology, and EM-type algorithms. The age-structure analysis presented is more complicated than the analysis presented for the non-age structured populations, and we provide a new kind of analysis for the incubation period. When reported disease cases and densities of the infection are available for a period of several years in the population, then this kind of analysis offers a reliable method to estimate the incubation period distribution.

Second line therapy is further expected to raise the length of survival

of people with HIV. There is a need to estimate parameters of the survival period, disease related mortality rates, rate of development of resistance among people on first line therapy such that models that project the number of people eligible for second line therapy are utilized for ART planning.

Existing transmission dynamics models for HIV (built without the ART component) can be updated with compartments of people who are on ART and who are without ART, because there could be differential rates of transmissions of HIV by the level adherence to second line therapy. The possibility of eligible people for second line therapy while still on first line therapy due to non availability or lesser availability of diagnostic centers for detecting resistance levels for first line therapy cannot be ruled out. The difficulty of identifying all HIV infected individuals at the population level still remains high as all susceptible individuals with risk behavior towards HIV are not diagnosed on a regular basis (unless they are recruited for a specific cohort base followup study). With the invention of new therapies and new guidelines there is an increasing need for continued efforts for modeling and data analysis to strengthen the public health gains of ART.

8. Appendix I: Conditional probabilities for generalized multiple drug impact. Here we derive expressions for conditional probabilities when several drugs are available and the incubation period is non-monotonic. When such a situation arises there will be several combinations of orders of Zs. We take one such situation and write corresponding Ls for the purpose of demonstration.

Suppose $Z_0 < \cdots < Z_k = \cdots = Z_{k+n+1} < \cdots < Z_N$. Let us divide this into the following two inequalities and an equality: $Z_0 < \cdots < Z_k$, $Z_{k+1} = \cdots = Z_{k+n}$ and $Z_{k+n+1} < \cdots < Z_N$. If we consider the first

and third inequalities, then

$$\mathcal{D}\left(\mathbf{A},\mathbf{B}/U_{N_k}\right) = \int_0^{U_{N_0}} h(t/A_{N_0})G(t-s/B_{N_0})\,ds$$

$$+ \int_{U_{N_0}}^{U_{N_1}} h(t/A_{N_1})G(t-s/B_{N_1})\,ds$$

$$\cdots + \int_{U_{N_{k-1}}}^{U_{N_k}} h(t/A_{N_k})G(t-s/B_{N_k})\,ds$$

$$\mathcal{D}\left(\mathbf{A},\mathbf{B}/U_{N_N}\right) = \int_0^{U_{N_{n+k+1}}} h(t/A_{N_{n+k+1}})G(t-s/B_{N_{n+k+1}})\,ds$$

$$+ \int_{U_{N_0}}^{U_{N_{n+k+2}}} h(t/A_{N_{n+k+2}})G(t-s/B_{N_{n+k+2}})\,ds$$

$$\cdots + \int_{U_{N_{N-1}}}^{U_{N_N}} h(t/A_{N_N})G(t-s/B_{N_N})\,ds.$$

We can express $\{P(E_{N_\theta}/E)\}_{\theta=0}^{\theta=k}$, $\{P(E_{N_\theta}/E)\}_{\theta=n+k+1}^{\theta=N}$ and the corresponding $\{L_{N_\theta}\}_\theta$ as shown in Section 3. Then L_{N_θ} is maximized for the set $[A_\theta, B_\theta]$. We obtain $N-n-k$ sets of $[\mathbf{A},\mathbf{B}]$ values, and the corresponding likelihood functions $\{L_{N_\theta}\}_{\theta=0}^k$ and $\{L_{N_\theta}\}_{\theta=n+k+1}^N$.

9. Appendix II: Truncated incubation period. Suppose there is an upper bound for the impact of drugs on the incubation period, that is, the incubation period cannot be increased after a certain time point after the drug use. Then the likelihood equations explained in Section 4 would change accordingly. There was an earlier attempt to truncate the incubation period with the help of the truncated Weibull distribution [**38**]. The impact of drugs using such functions has not been seen. If Z is the length of the incubation period and if Z_c is the truncation point, then

$$G(Z) = 1 - \exp\left\{-\left(\frac{z}{\delta_1}\right)^{\delta_2}\right\}, \quad \text{for } 0 < Z < Z_c,$$

and

$$G(\mathcal{Z}) = 1 - \exp\left\{-\left(\frac{z}{\delta_1}\right)^{\delta_2}\right\} \exp\left\{-\left(\frac{\delta_2}{\delta_1}\right)\left(\frac{t_c}{\delta_1}\right)^{(\delta_2-1)(z-z_c)}\right\},$$
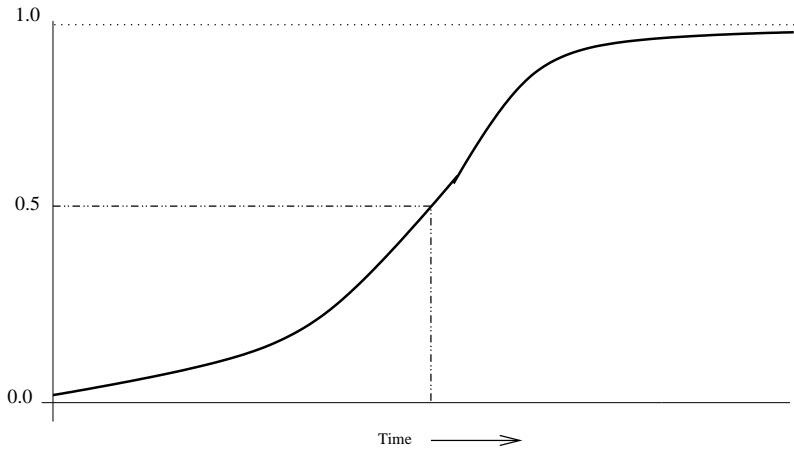
FIGURE 3. Truncated incubation period. The idea of truncated cumulative distribution of the incubation period is plotted. After a certain time duration, there will not be any gain due to therapy. Median incubation period is represented by the line cutting the curve at 0.5, corresponding to the Y-axis.

for $Z \geq Z_c$. Here, δ_1 and δ_2 are scale and shape parameters. One can construct a likelihood function for each drug type using such functions as follows:

$$(9.1) \qquad L\left(\mathbf{A}, \mathbf{B}/P_j\right) = L_{<Z_c} + L_{\geq Z_c},$$

where

$$L_{<Z_c} = \prod_j b_1(j) b_2(j) - \prod_j b_1(j-1) b_2(j)$$

$$L_{\geq Z_c} = \prod_j b_1^t(j) b_2^t(j) - \prod_j b_1^t(j-1) b_2^t(j)$$

and

$$b_1(j) = \left\{ \int_0^{u_j} e^{\alpha_1 s^2 + \alpha_2 s + \alpha_3} \left\{ 1 - \exp\left\{ -\left(\frac{t}{\delta_1}\right)^{\delta_2} \right\} \right\} ds \right\}^{T_j}$$

$$b_1(j-1) = \left\{ \int_0^{u_{j-1}} e^{\alpha_1 s^2 + \alpha_2 s + \alpha_3} \left\{ 1 - \exp\left\{ -\left(\frac{t}{\delta_1}\right)^{\delta_2} \right\} \right\} ds \right\}^{T_j}$$

$$b_2(j) = \left\{ \int_0^{u_n} e^{\alpha_1 s^2 + \alpha_2 s + \alpha_3} \left\{ 1 - \exp\left\{ -\left(\frac{t}{\delta_1}\right)^{\delta_2} \right\} \right\} ds \right\}^{-T_j}$$

$$b_1^t(j) = \left[\int_0^{u_j} e^{\alpha_1 s^2 + \alpha_2 s + \alpha_3} 1 - \exp\left\{ -\left(\frac{z}{\delta_1}\right)^{\delta_2} \right\} \right.$$
$$\left. \times \exp\left\{ -\left(\frac{\delta_2}{\delta_1}\right) \left(\frac{t_c}{\delta_1}\right)^{(\delta_2-1)(z-z_c)} \right\} ds \right]^{T_j}$$

$$b_1^t(j-1) = \left[\int_0^{u_{j-1}} e^{\alpha_1 s^2 + \alpha_2 s + \alpha_3} 1 - \exp\left\{ -\left(\frac{z}{\delta_1}\right)^{\delta_2} \right\} \right.$$
$$\left. \times \exp\left\{ -\left(\frac{\delta_2}{\delta_1}\right) \left(\frac{t_c}{\delta_1}\right)^{(\delta_2-1)(z-z_c)} \right\} ds \right]^{T_j}$$

$$b_2^t(j) = \left[\int_0^{u_n} e^{\alpha_1 s^2 + \alpha_2 s + \alpha_3} 1 - \exp\left\{ -\left(\frac{z}{\delta_1}\right)^{\delta_2} \right\} \right.$$
$$\left. \times \exp\left\{ -\left(\frac{\delta_2}{\delta_1}\right) \left(\frac{t_c}{\delta_1}\right)^{(\delta_2-1)(z-z_c)} \right\} ds \right]^{-T_j}.$$

For each drug type, an expression of the type in (9.1) can be derived. Despite the assumption on truncation as mentioned above, the incubation period could vary according to the type of the drug.

10. APPENDIX III: Parameters.

TABLE 1. Parameters

Parameter	Description	Value	Reference(s)
λ	Force of infection (before introduction of any therapy)	0.003	Based on 19, we assumed.
μ	General mortality (non-AIDS)	0.014	Assumption
γ	Disease related mortality (before introduction of therapy)	0.5	47, 48, 49
d	Reciprocal of the average incubation period (before introduction of therapy)	0.125	19
λ_0	Force of infection (without therapy after introduction)	0.003	Based on 19, we assumed.
λ_1	Force of infection with drug 1	0.0009	49
λ_2	Force of infection with drug 2	0.0009	49
λ_3	Force of infection with drug 3 (combination therapy)	0.0003	49
γ_0	Disease related mortality without any therapy	0.5	48
γ_1	Disease related mortality with drug 1	0.25	Assumption
γ_2	Disease related mortality with drug 2	0.25	Assumption
γ_3	Disease related mortality with drug 3 (combination therapy)	0.15	48
d_0	Reciprocal of the average incubation period (without therapy)	0.125	48,49
d_1	Reciprocal of the average incubation period with drug 1	0.067	48, 49
d_2	Reciprocal of the average incubation period with drug 2	0.067	19, 49
d_3	Reciprocal of the average incubation period with drug 3	0.053	19, 48, 49

APPENDIX IV: Figures. In this section, using the parameters in Appendix III, output of the models for hypothetical population sizes and sensitivity of the parameters in projecting HIV and AIDS are shown in Figures 4–10. The impact of $drug1$ and $drug2$ on Y_1, Y_2, D_{z1} and D_{z2} is assumed to be equal when administered independently in the population, and hence $Y_1 = Y_2$ and $D_{z1} = D_{z2}$ in all the simulations presented. Initial and final values for the parameters are: d_0 : $(0.1, 0.15)$, d_1, d_2 : $(0.06, 0.075)$, d_3 : $(0.045, 0.058)$, λ_0 : $(0.001, 0.006)$, λ_1, λ_2 : $(0.0006, 0.0012)$, λ_3 : $(0.00002, 0.0005)$, γ_0 : $(0.4, 0.6)$, γ_1, γ_2 : $(0.1, 0.4)$, γ_3 : $(0.2, 0.3)$, μ : $(0.012, 0.016)$.
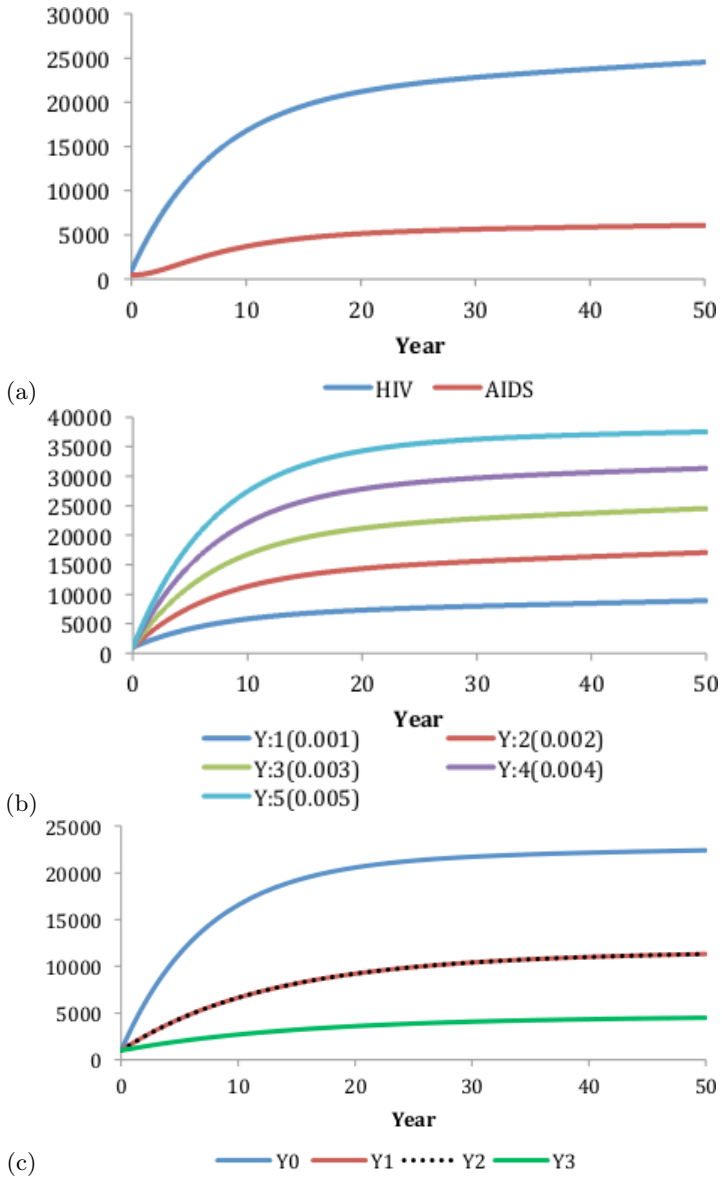
FIGURE 4. (a) Number of HIV and AIDS (before therapy), (b) Number of HIV infected (before therapy), (c) Number of HIV (after therapy)
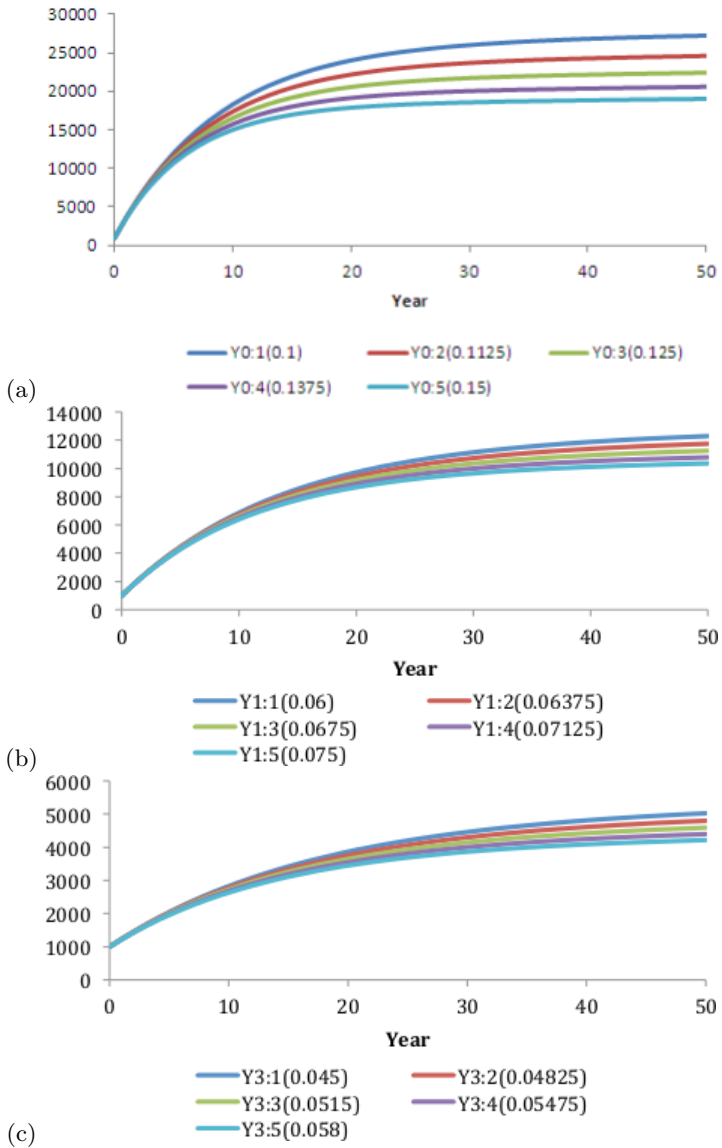
FIGURE 5. (a) Sensitivity of d_0 on Y_0, (b) Sensitivity of d_1 and d_2 on Y_1 and Y_2, (c) Sensitivity of d_3 on Y_3.
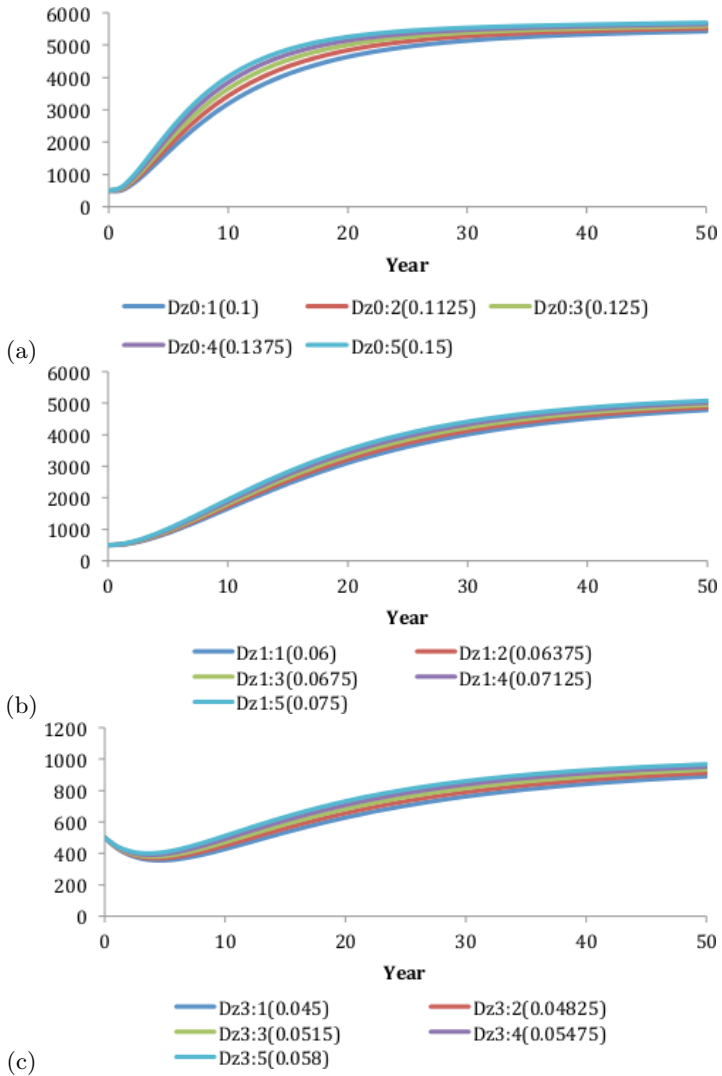
FIGURE 6. (a) Sensitivity of d_0 on D_{z0}, (b) Sensitivity of d_1 and d_2 on D_{z1} and D_{z2}, (c) Sensitivity of d_3 on D_{z3}.
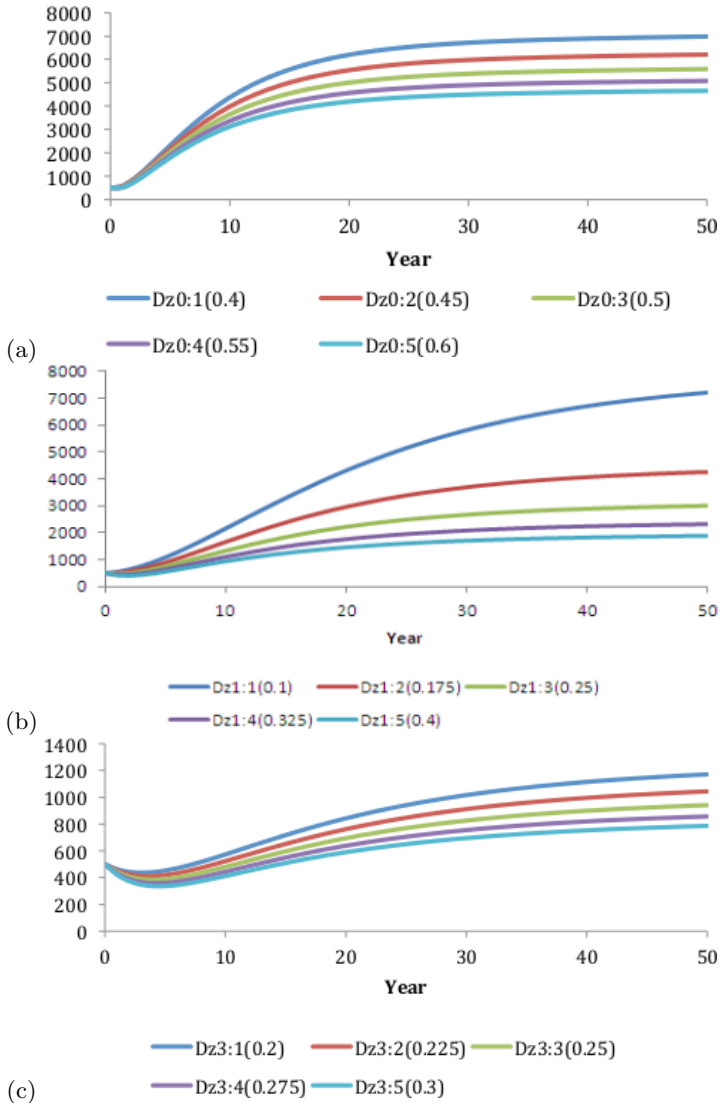
(a)

(b)

(c)

FIGURE 7. (a) Sensitivity of γ_0 on D_{z0}, (b) Sensitivity of γ_1 and γ_2 on D_{z1} and D_{z2}, (c) Sensitivity of γ_3 on D_{z3}.
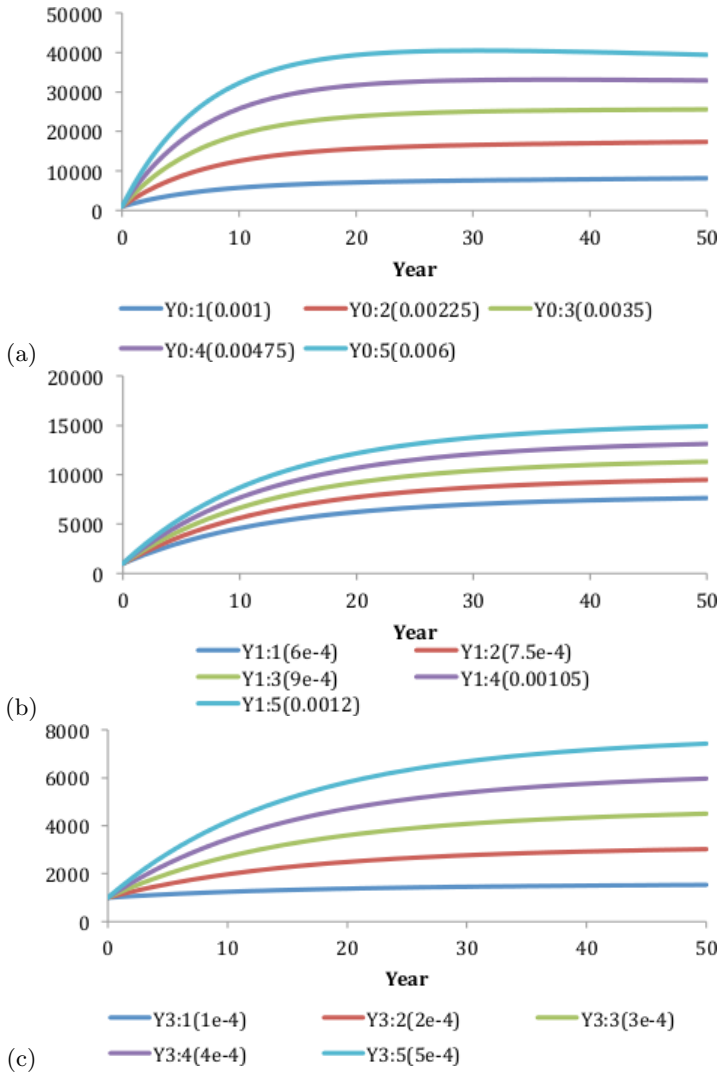
FIGURE 8. (a) Sensitivity of λ_0 on Y_0, (b) Sensitivity of λ_1 and λ_2 on Y_1 and Y_2, (c) Sensitivity of λ_3 on Y_3.
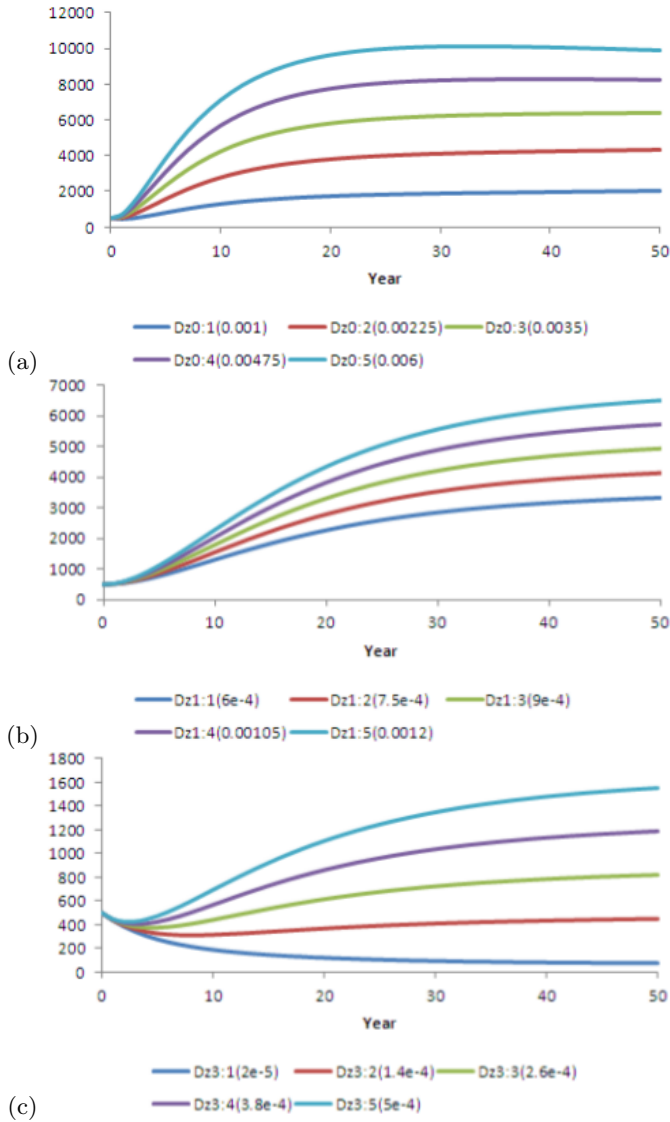
FIGURE 9. (a) Sensitivity of λ_0 on D_{z0}, (b) Sensitivity of λ_1 and λ_2 on D_{z1} and D_{z2}, (c) Sensitivity of λ_3 on D_{z3}.

(a)

(b)

(c)
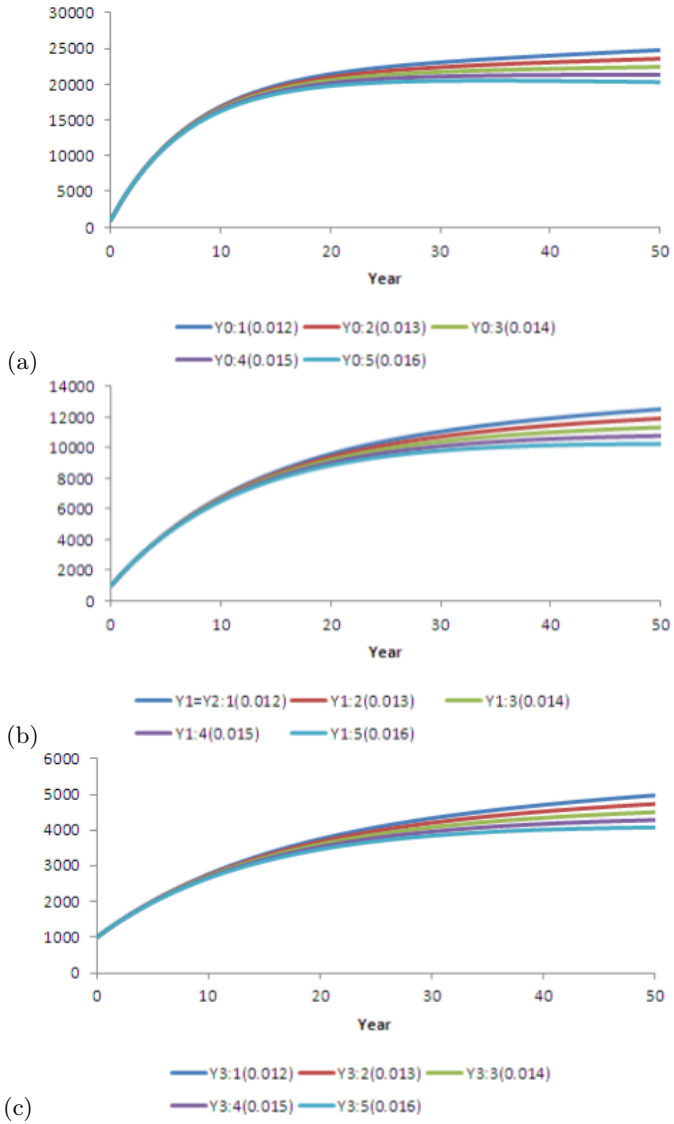
FIGURE 10. (a) Sensitivity of μ on Y_0, (b) Sensitivity of μ on Y_1 and Y_2, (c) Sensitivity of μ on Y_3.

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