

# **Report on “The Impact of HIV Testing on the Spread of HIV Infection”**

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# 1 Problem Statement Presented by BC CDC

HIV is a non-curable, infectious disease that affects over 400 new individuals per year in British Columbia. Additionally, it is estimated that 30 % of people with HIV are unaware of their disease. This group of people (the hidden epidemic) is not counted and included in the BC statistics. There are four main phases of HIV infection: acute seroconversion; early HIV illness; established HIV illness; and AIDS defining illness. The spread of any infectious disease can be predicted by using the following equation:

$$R_0 = \beta Dc.$$

$R_0$  is the secondary spread of an agent,  $\beta$  is the efficiency of transmission,  $D$  is the duration of infectiousness, and  $c$  is the number of individuals that are exposed to the infection. The efficiency of transmission ( $\beta$ ) in HIV and the duration of infectiousness ( $D$ ) are directly related to the amount of virus circulating in the blood and the amount of antibody available to combat the virus in the host. HIV antibodies usually develop in individuals within four to six weeks after becoming infected with HIV and the amount of antibody in the host gradually increases until it reaches its maximum point. The amount of antibody and virus in an infected individual provides an indication of which phase of HIV illness the individual is in.

Acute seroconversion (less than 28 days) refers to the stage of infection prior to the development of an antibody response. During acute seroconversion, HIV can be detected in the blood by the use of a nucleic acid amplification test (NAAT) within two days of infection. Standard antibody tests that are used to detect an HIV infection do not differentiate between an established infection (greater than 170 days) and an early HIV infection (less than 170 days). Detuned antibody testing can be done to detect early HIV illness when antibody levels are low. The ability to detect acute and recent HIV infections at a time when they are more infectious, is essential in linking individuals to appropriate care and in preventing the spread of infection. Research studies have found that once individuals are informed of their HIV diagnosis, they will reduce their practice of high-risk sex by about one half. Through mathematical modeling, we would like an algorithm to assist us in answering the following questions:

1. For each acute HIV infection detected by the NAAT, how many HIV infections could be prevented assuming that there is a change in behaviour in the newly infected person?
2. For each early HIV infection detected by the detuned antibody test, how many HIV infections will be prevented assuming additional change in behaviour as a result of enhanced interventions during this stage?

CD4 cells are white blood cells responsible for coordinating much of the immune response and are damaged by HIV. The depletion of CD4 cells results in individuals being susceptible to other types of infections. CD4 cell counts in a healthy non-HIV infected person range between 400–1,400 cells per  $\mu L$ . A CD4 cell count  $< 200$  cells per  $\mu L$  is an indication that the immune system is damaged and disease progression is occurring. Viral loads describe the amount of HIV in an individual's blood. A plasma level of 100,000 copies/mL is considered high and individuals with this viral load are at high risk for transmitting to others. During the acute stage of HIV infection, the viral load is at its highest. Once antibodies begin to develop the viral load gradually decreases. This decrease occurs until approximately six months post transmission when it plateaus, in the absence of treatment, to a set point. Note that this set point varies from person to person. Drugs called antiretrovirals are used to lower the amount of virus in the blood. Currently, the guidelines for treatment state patients may be treated if they are symptomatic or when their CD4 count drops below  $< 200$  cells per  $\mu L$  regardless of viral load levels. In other words, an individual may have a CD4 cell count of over 500 cells per  $\mu L$  and a high viral load and would not be on therapy. There is evidence to suggest that these treatment guidelines have caused a 75 % increase in new HIV infections among men who have sex with men. From a public health perspective, untreated individuals with high viral loads are infectious and will hamper the overall efforts to reduce the burden of HIV/AIDS disease. Recall that not all individuals with a CD4 cell count of over 500 cells/L will have high viral loads since the viral load set point varies from person to person. From a public health perspective, individuals with high viral loads, high CD4 cell counts, and not on antiretroviral therapy, suggests the following question.

3. For each untreated individual with a high viral load and CD4 cell count, how many HIV infections will be transmitted?

## 2 HIV Epidemiology and Control

### 2.1 Basic Description

Since its emergence in the 1980s, the human immunodeficiency virus (HIV), the causative agent of the acquired immune deficiency syndrome (AIDS), continues to pose an unprecedented threat to global health and human development. An estimated 34–46 million people are currently living with the HIV/AIDS pandemic. More than 20 million people have died from HIV-related illnesses during the last 20 years, of which an estimated 3 million deaths occurred in 2003 alone. AIDS is now the leading cause of death in sub-Saharan Africa and the fourth-leading cause of death globally. The pandemic has cut life expectancy significantly in many countries in sub-Saharan Africa. For example, life expectancy in Botswana decreased from 65 years in 1985–1990 to 40 years in 2000–2005 [27].

In addition to being a serious public health menace, HIV/AIDS has far reaching consequences to all social and economic sectors of society. It exacerbates poverty, reduces educational opportunities, devastates the workforce, creates large numbers of orphans, and exerts tremendous pressure on already limited health and social services [26, 24]. For example, HIV/AIDS has cut annual growth rates in Africa by 2–4% per year [7]. The annual economic loss of slower economic growth as a result of HIV/AIDS-related death or disability in 50 countries (US, Russia, 5 in Asia, 8 in Latin America, and 35 in sub-Saharan Africa) during 1992–2000 is estimated at \$25 billion [10].

HIV infects and replicates primarily in CD4<sup>+</sup> T cells. An infected individual typically passes through several infection stages, being highly infectious during the pre-antibody phase (primary infection stage; characterized by high viremia with over 10 million viral copies per ml), maintaining low infectivity during the asymptomatic phase (secondary infection stage), and becoming highly infectious as s/he progresses toward AIDS (AIDS stage) [8, 9, 14, 15, 17, 21]. These stages are sometimes categorized into 4 groups

namely, acute sero-conversion stage (less than 28 days of infection), early infection stage (less than 170 days of infection), established infection stage (after 170 days of infection) and the AIDS (characterized by the presence of clinical symptoms). Studies of HIV RNA in infected individuals show that viral levels vary widely between individuals, where individuals with higher viral loads during the chronic phase tend to develop AIDS more rapidly [20]. Another crucial related fact is that RNA levels are correlated with infectiousness [11, 22]. Thus, models of HIV dynamics need to incorporate the variations in infectiousness and the increase in the average time from primary HIV infection to AIDS stage that goes along with a decreased viral load during the chronic phase of infection [15].

HIV is transmitted from one person to another via numerous modes including sexual, needle sharing amongst IV drug users, vertical transmission from mother to child, blood transfusion. Control measures against the spread of HIV are wide and varied. They include preventive measures such as the use of condoms, education and counselling about safer sex practices, sterilizing needles in health care delivery, voluntary testing and potential use of a vaccine. The currently available therapeutic measure is based on using anti-retroviral therapy, especially highly-active anti-retroviral therapy (HAART), which is known to bring viral load to non-detectable levels. Unfortunately, HAART is not widely accessible in many resource-poor nations where HIV prevalence is the highest.

Over the decades, mathematical models, often of the form of deterministic or stochastic systems of differential equations, have been used to gain insights into the transmission dynamics of HIV and evaluate various intervention strategies both *in vivo* and in a population [1, 2, 3, 4, 5, 8, 12, 13, 15, 16, 17, 19, 21]. This project is focussed on using mathematical model to assess the potential impact of a new HIV testing method, introduced by the British Columbia Centre for Disease Control, known as the Nucleic Acid Amplification Testing (NAAT) in minimizing HIV burden in British Columbia. Unlike standard HIV testing methods (that measure antibody response to the HIV virus), the NAAT test detects newly infected individuals (within two days of acquiring infection). Not much has been done in the modelling literature to ascertain the impact of HIV testing in reducing HIV burden.

Simpson et al. [23] used a decision analysis model to evaluate the impact of acute HIV screening, and applied the model on data from the NC's STAT program. Our approach will be quite different. Unlike the decision analysis model in [23], the dynamic model to be developed in this study takes into account many of the epidemiological and biological features of HIV disease (such as staged-progression, correlation between viral load and infectiousness etc.). Furthermore, we introduced a measure of additional risk reduction in people with an early HIV infection in our model. These adjustments in risk behavior relate to various unspecified interventions aimed at people who were diagnosed in an early stage of their infection. We refer to these additional measures as *detuned* testing. The effect of *detuned* testing on the model parameters is further described in Appendix A.

### 3 Model Formulation

As indicated above, a compartmental deterministic formulation will be used to derive the model for HIV dynamics. To do so, the total population,  $N$ , is subdivided into 9 mutually-exclusive subpopulations (compartments) namely susceptible individuals with low risky behaviour ( $S^l(t)$ ), susceptible individuals with high risky behaviour ( $S^h(t)$ ), newly-infected individuals unaware of their status in the primary stage of infection ( $I_1^u(t)$ ), infected individuals unaware of their status in the (chronic) asymptomatic stage of infection ( $I_2^u(t)$ ), infected individuals unaware of their status in the late HIV and AIDS stage of infection ( $I_3^u(t)$ ), newly-infected individuals aware of their status in the primary stage of infection ( $I_1^k(t)$ ), infected individuals aware of their status in the asymptomatic stage of infection ( $I_2^k(t)$ ), infected individuals aware of their status in the late HIV and AIDS stage of infection ( $I_3^k(t)$ ) and treated individuals that are aware of their status ( $I^T(t)$ ). Thus, the total population is given by

$$N(t) = S^l(t) + S^h(t) + I_1^u(t) + I_2^u(t) + I_3^u(t) + I_1^k(t) + I_2^k(t) + I_3^k(t) + I^T(t).$$

It should be emphasized that once an individual is infected with HIV, he/she undergoes through three stages of infection namely (i) acute/early infection stage ( $I_1$ ), asymptomatic(chronic) stage ( $I_2$ ) and late HIV and AIDS

stage ( $I_3$ ). For all three infection stages, we distinguish between those who are aware of their infection status and those who are not. We use superscript  $k$  (known) and  $u$  (unknown) to denote this difference. Finally, we use a compartment  $I^T$  to denote individuals who receive anti-retroviral therapy.

The high risk class consists of injection drugs users, sexually-active homosexual men, sex workers etc. The low risk susceptible population is increased by the recruitment of individuals (assumed susceptible) into the population at a rate  $\Pi$ . Transitions between low and high risk classes occur at rates  $\alpha_{lh}$  and  $\alpha_{hl}$ . Low risk susceptible individuals acquire infection, following contact with infected individuals in the 3 stages  $I_1, I_2$  and  $I_3$  classes at a rate  $\lambda_l$ , given by

$$\lambda_l = \frac{\beta_{lu_1} I_1^u + \beta_{lu_2} I_2^u + \beta_{lu_3} I_3^u + \beta_{lk_1} I_1^k + \beta_{lk_2} I_2^k + \beta_{lk_3} I_3^k + \beta_{lT} I^T}{N},$$

where  $\beta_{lu_i}$  represents the transmission rate from unknown infected individuals ( $I_i^u; i = 1, 2, 3$ ),  $\beta_{lk_i}$  is the transmission rate from infected individuals who are aware of their status ( $I_i^k, i = 1, 2, 3$ ), and  $\beta_{lT}$  is the transmission rate from treated individuals.

Similarly, high risk susceptible individuals acquire infection at a rate  $\lambda_h$ , where

$$\lambda_h = \frac{\beta_{hu_1} I_1^u + \beta_{hu_2} I_2^u + \beta_{hu_3} I_3^u + \beta_{hk_1} I_1^k + \beta_{hk_2} I_2^k + \beta_{hk_3} I_3^k + \beta_{hT} I^T}{N}$$

Here,  $\beta_{hu_i}$ ,  $\beta_{hk_i}$  and  $\beta_{hT}$  represent transmission rates from infected individuals who are unaware of their status, aware of their status and treated, respectively. To account for the fact that high risk individuals have a higher probability of getting infected (in comparison to low risk individuals), it is assumed that  $\beta_{lu_i} < \beta_{hu_i}$ ,  $\beta_{lk_i} < \beta_{hk_i}$  for ( $i = 1, 2, 3$ ).

It is also assumed that successfully treated individuals have transmission rates approximately an order of magnitude smaller than stage 2 individuals (owing to the fact that HAART treatment generally brings down viral load noticeably). Individuals unaware of their status progress from the primary stage ( $I_1^u$ ) to the asymptomatic stage ( $I_2^u$ ) at a rate  $\sigma_{u_1 u_2}$ ; progression from the asymptomatic stage to late HIV and AIDS stage ( $I_3^u$ ) occurs at a rate  $\sigma_{u_2 u_3}$ . Individuals in the unknown stages can move to the known stages via

positive diagnosis (with either NAAT or a detuned test). Individuals that are unaware of their status in the primary stage of infection are tested at rate  $\tau_{u_1k_1}$ . Similarly,  $\tau_{u_2k_2}$  and  $\tau_{u_3k_3}$  measure the testing rates for individuals in  $I_2$  and  $I_3$  unknown classes, respectively (the parameter  $\eta$  represents the number of positive case identification; and  $\varepsilon_T$  models the efficacy of NAAT).

Individuals aware of their status progress from the primary stage ( $I_1^k$ ) to the asymptomatic stage ( $I_2^k$ ) at a rate  $\sigma_{k_1k_2}$  and finally progress to late HIV and AIDS stage ( $I_3^k$ ) at a rate  $\sigma_{k_2k_3}$ . Individuals in the known classes are treated at rates  $\psi_{k_i}$ . These (treated) individuals progress to AIDS at a slower rate compared to those in the untreated classes. Further, natural mortality occurs in all classes at a rate  $\mu$  and individuals in the late HIV and AIDS stage suffer an additional disease-induced death at a rate  $\delta$ .

Putting the above discussions and assumptions together leads to the following system of nonlinear ordinary differential equations:



$$\begin{aligned}
\frac{dS^l}{dt} &= \Pi - \alpha_{lh}S^l + \alpha_{hl}S^h - \mu S^l - \frac{\lambda_l S^l}{N}, \\
\frac{dS^h}{dt} &= -\alpha_{hl}S^h + \alpha_{lh}S^l - \mu S^h - \frac{\lambda_h S^h}{N}, \\
\frac{dI_1^u}{dt} &= \frac{\lambda_l S^l}{N} + \frac{\lambda_h S^h}{N} - (\mu + \tau_{u_1 k_1} + \sigma_{u_1 u_2})I_1^u, \\
\frac{dI_2^u}{dt} &= \sigma_{u_1 u_2}I_1^u - (\sigma_{u_2 u_3} + \tau_{u_2 k_2} + \mu)I_2^u, \\
\frac{dI_3^u}{dt} &= \sigma_{u_2 u_3}I_2^u - (\tau_{u_3 k_3} + \mu + \delta_u)I_3^u, \\
\frac{dI_1^k}{dt} &= \tau_{u_1 k_1}I_1^u - (\psi_{k_1} + \sigma_{k_1 k_2} + \mu)I_1^k, \\
\frac{dI_2^k}{dt} &= \tau_{u_2 k_2}I_2^u + \sigma_{k_1 k_2}I_1^k - (\psi_{k_2} + \sigma_{k_2 k_3} + \mu)I_2^k, \\
\frac{dI_3^k}{dt} &= \tau_{u_3 k_3}I_3^u + \sigma_{k_2 k_3}I_2^k + \phi I^T - (\psi_{k_3} + \delta_k + \mu)I_3^k, \\
\frac{dI^T}{dt} &= \psi_{k_1}I_1^k + \psi_{k_2}I_2^k + \psi_{k_3}I_3^k - (\phi + \mu)I^T.
\end{aligned} \tag{1}$$

A flowchart of the model is depicted in Figure 1. Tables 1 and 2 provide further description of the associated parameters together with their estimates using some partial data from the BC CDC.

### 3.1 Basic properties and epidemiological threshold

It is assumed that all the parameters and state variables of the model (1) are non-negative (since the model monitors human populations) for all  $t \geq 0$ . Adding the equations in (1) gives  $dN/dt = \Pi - \mu N - \delta_u I_3^u - \delta_k I_3^k$ . It follows then that, in the absence of HIV infection,  $\lim_{t \rightarrow \infty} I_3^u = 0$  and  $\lim_{t \rightarrow \infty} I_3^k = 0$  so

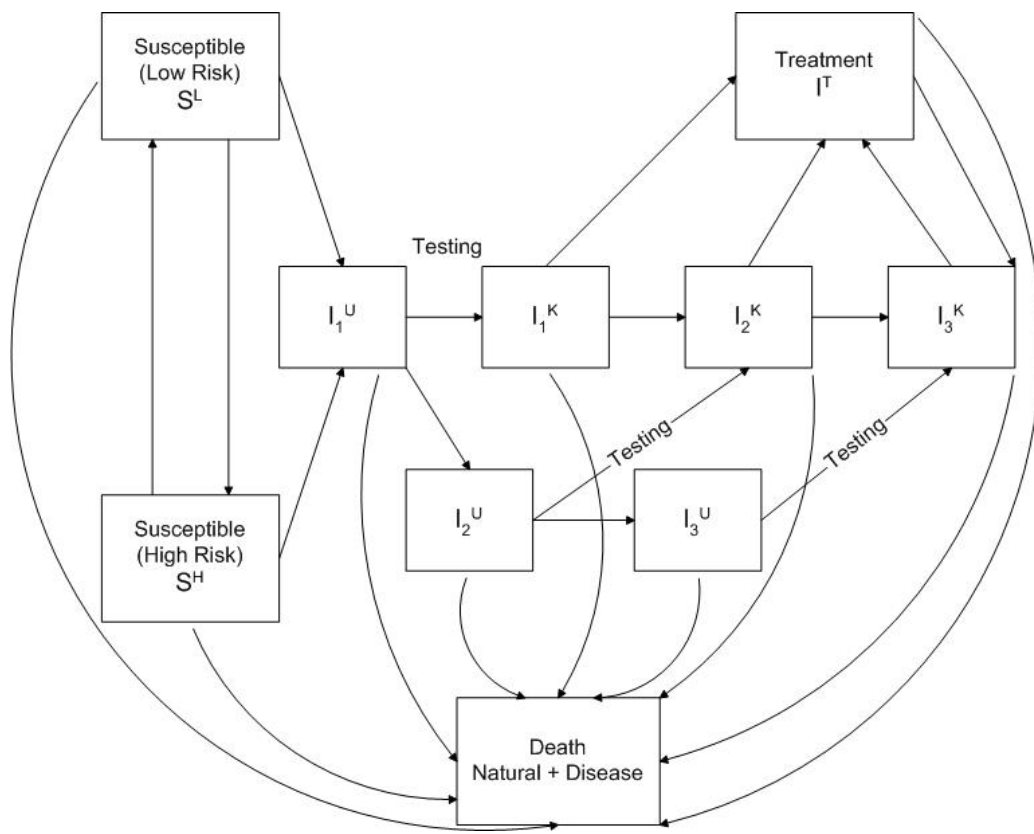


Figure 1: population dynamics chart

that  $N \rightarrow \Pi/\mu$  as  $t \rightarrow \infty$ . Thus,  $\Pi/\mu$  is an upper bound of  $N(t)$  provided  $N(0) \leq \Pi/\mu$ . Consequently, the following feasible region:

$$\mathcal{D} = \left\{ d = (S^l, S^h, I_1^u, I_2^u, I_3^u, I_1^k, I_2^k, I_3^k, I^T) \in \mathbb{R}_+^9 : \sum_i d_i \leq \Pi/\mu \right\}$$

is positively invariant. It is therefore sufficient to consider solutions of the model in  $\mathcal{D}$ . In this region, the usual existence, uniqueness and continuation results hold for the system.

### 3.1.1 Disease-free equilibrium and reproduction number

The equilibrium of the model are obtained by setting the right-hand sides of the equations in (1) to zero. It follows that in the absence of the disease ( $I_1^u = 0, I_2^u = 0, I_3^u = 0, I_1^k = 0, I_2^k = 0, I_3^k = 0, I^T = 0$ ), the model has a disease-free equilibrium given by

$$\begin{aligned} \mathcal{E}_0 &= (S^{l*}, S^{h*}, I_1^{u*}, I_2^{u*}, I_3^{u*}, I_1^{k*}, I_2^{k*}, I_3^{k*}, I^{T*}) \\ &= \left( \frac{\Pi(\mu + \alpha_{hl})}{\mu(\mu + \alpha_{hl} + \alpha_{lh})}, \frac{\Pi\alpha_{lh}}{\mu(\mu + \alpha_{lh} + \alpha_{hl})}, 0, 0, 0, 0, 0, 0, 0 \right) \end{aligned}$$

Using the next generation operator technique in [6, 25], the linear stability of  $\mathcal{E}_0$  can be established. This entails writing the model (1) in terms of the matrices  $F$  and  $V$ , of new infections in each compartment and of transfer rates of individuals between compartments respectively, given by

$$F = \begin{pmatrix} S_1 & S_2 & S_3 & T_1 & T_2 & T_3 & S_t \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix},$$

and

$$V = \begin{pmatrix} t_1 & 0 & 0 & 0 & 0 & 0 & 0 \\ -\sigma_{u_1 u_2} & t_2 & 0 & 0 & 0 & 0 & 0 \\ 0 & -\sigma_{u_2 u_3} & t_3 & 0 & 0 & 0 & 0 \\ -\tau_{u_1 k_1} & 0 & 0 & t_4 & 0 & 0 & 0 \\ 0 & -\tau_{u_2 k_2} & 0 & -\sigma_{k_1 k_2} & t_5 & 0 & 0 \\ 0 & 0 & -\tau_{u_3 k_3} & 0 & -\sigma_{k_2 k_3} & t_6 & -\phi \\ 0 & 0 & 0 & -\psi_{k_1} & -\psi_{k_2} & -\psi_{k_3} & t_7 \end{pmatrix},$$

where

$$S_i = \frac{\beta_{lu_i} S^{l*} + \beta_{hu_i} S^{h*}}{N^*}, \quad T_i = \frac{\beta_{lk_i} S^{l*} + \beta_{hk_i} S^{h*}}{N^*}, \quad S_t = \frac{\beta_{lT} S^{l*} + \beta_{hT} S^{h*}}{N^*}$$

for  $(i = 1, 2, 3)$ . The *effective reproduction number*, denoted by  $\mathcal{R}_T$ , is then given by  $\mathcal{R}_T = \rho(FV^{-1})$ , where  $\rho$  denotes the spectral radius (dominant eigenvalue). It follows that

$$\mathcal{R}_T = \frac{AS^{l*} + BS^{h*}}{N^*} = \frac{A(\mu + \alpha_{hl}) + B\alpha_{lh}}{\mu + \alpha_{hl} + \alpha_{lh}}$$

where,

$$\begin{aligned}
A &= \frac{\beta_{lu_2}\sigma_{u_1u_2}}{t_1t_2} + \frac{\beta_{lu_3}\sigma_{u_2u_3}\sigma_{u_1u_2}}{t_1t_2t_3} + \frac{\tau_{u_3k_3}\sigma_{u_2u_3}(\beta_{lk_3}t_7 + \beta_{lT}\psi_{k_3})\sigma_{u_1u_2}}{Ct_1t_2t_3} \\
&+ \frac{\beta_{lk_1}\tau_{u_1k_1}}{t_1t_4} + \frac{\beta_{lu_1}}{t_1} + \frac{(\beta_{lT}t_6 + \beta_{lk_3}\phi)\psi_{k_1}\tau_{u_1k_1}}{Ct_1t_4} \\
&+ \frac{\beta_{lk_3}(\phi\psi_{k_2} + \sigma_{k_2k_3}t_7)\sigma_{k_1k_2}\tau_{u_1k_1}}{Ct_1t_4t_5} + \frac{\beta_{lk_2}\sigma_{u_1u_2}\tau_{u_2k_2}}{t_1t_2t_5} + \frac{\beta_{lk_2}\sigma_{k_1k_2}\tau_{u_1k_1}}{t_1t_4t_5} \\
&+ \frac{\beta_{lT}(\psi_{k_2}t_6 + \psi_{k_3}\sigma_{k_2k_3})\sigma_{k_1k_2}\tau_{u_1k_1}}{Ct_1t_4t_5} + \frac{\beta_{lk_3}(\phi\psi_{k_2} + \sigma_{k_2k_3}t_7)\sigma_{u_1u_2}\tau_{u_2k_2}}{Ct_1t_2t_5} \\
&+ \frac{\beta_{lT}(\psi_{k_2}t_6 + \psi_{k_3}\sigma_{k_2k_3})\sigma_{u_1u_2}\tau_{u_2k_2}}{Ct_1t_2t_5} \\
B &= \frac{\beta_{hu_1}}{t_1} + \frac{\beta_{hu_2}\sigma_{u_1u_2}}{t_1t_2} + \frac{\beta_{hu_3}\sigma_{u_2u_3}\sigma_{u_1u_2}}{t_1t_2t_3} + \frac{\beta_{hk_1}\tau_{u_1k_1}}{t_1t_4} \\
&+ \frac{\beta_{hk_2}(\tau_{u_2k_2}\sigma_{u_1u_2}t_4 + \sigma_{k_1k_2}\tau_{u_1k_1}t_2)}{t_1t_2t_4t_5} + \frac{\sigma_{u_2u_3}\sigma_{u_1u_2}(\beta_{hk_3}t_7 + \beta_{hT}\psi_{k_3})\tau_{u_3k_3}}{Ct_1t_2t_3} \\
&+ \frac{\sigma_{u_1u_2}\beta_{hk_3}(\sigma_{k_2k_3}t_7 + \phi\psi_{k_2})\tau_{u_2k_2}}{Ct_1t_2t_5} + \frac{\sigma_{u_1u_2}\beta_{hT}(\psi_{k_2}t_6 + \psi_{k_3}\sigma_{k_2k_3})\tau_{u_2k_2}}{Ct_1t_2t_5} \\
&+ \frac{\beta_{hT}(\psi_{k_1}t_6t_5 + \psi_{k_3}\sigma_{k_2k_3}\sigma_{k_1k_2} + \psi_{k_2}t_6\sigma_{k_1k_2})\tau_{u_1k_1}}{Ct_1t_4t_5} \\
&+ \frac{\beta_{hk_3}(\phi\psi_{k_2}\sigma_{k_1k_2} + \sigma_{k_2k_3}\sigma_{k_1k_2}t_7 + \phi\psi_{k_1}t_5)\tau_{u_1k_1}}{Ct_1t_4t_5} \\
C &= t_7t_6 - \psi_{k_3}\phi = (\mu + \delta_k)t_7 + \mu\psi_{k_3}
\end{aligned}$$

with

$$\begin{aligned}
t_1 &= \mu + \tau_{u_1k_1} + \sigma_{u_1u_2}, & t_2 &= \mu + \tau_{u_2k_2} + \sigma_{u_2u_3}, & t_3 &= \mu + \tau_{u_3k_3} + \delta_u, \\
t_4 &= \mu + \psi_{k_1} + \sigma_{k_1k_2}, & t_5 &= \mu + \psi_{k_2} + \sigma_{k_2k_3}, & t_6 &= \mu + \psi_{k_3} + \delta_k, \\
t_7 &= \mu + \phi.
\end{aligned}$$

Using Theorem 2 of [25], the following result is obtained.

**Lemma 1** *The disease-free equilibrium  $\mathcal{E}_0$  is locally-asymptotically stable if  $\mathcal{R}_T < 1$  and unstable if  $\mathcal{R}_T > 1$ .*

This threshold quantity,  $\mathcal{R}_T$ , measures the average number of new cases generated by a single infected individual in a population where HAART and

HIV testing programs are implemented. Note that this threshold differs from the regular *basic reproduction number*, which represents the average number of cases generated by an index case in a completely susceptible population. The result above (Lemma (1)) shows that if HIV testing and HAART can make  $\mathcal{R}_T$  less than unity, then HIV can be eliminated from the community provided the initial sizes of the sub-populations of the model are in the basin of attraction of  $\mathcal{E}_0$ . In other words, a small influx of infected individuals will not generate large outbreaks if  $\mathcal{R}_T < 1$ . On the other hand, the disease will persist (establish) itself if  $\mathcal{R}_T > 1$ . It can be shown, using a suitable Lyapunov function (not presented here), that the disease-free equilibrium is in fact globally-stable for  $\mathcal{R}_T < 1$  (guaranteeing disease elimination whenever  $\mathcal{R}_T < 1$  regardless of the initial sizes of the sub-populations of the model). Simulations, using the parameter and initial values in Tables 1-3, show that  $\mathcal{R}_T$  is approximately equal to 0.22 for British Columbia. This indicates that the combined use of HIV testing and administration of anti-retroviral therapies can lead to the theoretical elimination of HIV in British Columbia (asymptotically).

## 4 Numerical Simulations

In order to monitor the potential impact of the NAAT and detuned testing in the HIV transmission dynamics in British Columbia, the model is simulated using the parameter estimates (for British Columbia) given in Appendix A (see see Tables 1 and 2 for a brief overview of these parameter values) and the initial values in Table 3. Further, the transmission rates  $\beta_{h,u_i} = (0.6, 0.06, 0.5)$  and the risk adjustment parameter is fixed at  $r = 0.43$ . It is assumed that the implementation of NAAT can result in 30 additionally detected infected individuals per year.

Figure 2 depicts the number of new cases that can be prevented (within a year) as a result of using NAAT for varying values of the *tune strength* parameter. The number of cases cases averted are plotted on the  $y$ -axis, while the number of additional cases discovered by NAAT is depicted on the  $x$ -axis. It should be stated that a tune strength of 1 corresponds to no added interventions other than informing those detected people of the fact

that they are in the acute/early stage of HIV disease. A tune strength of 100 corresponds to a reduction of risk behavior to 1% of what it would have been without extra intervention (i.e.,  $\beta_{,k_1}$  would be  $0.01 \cdot \beta_{,k_1}$ ). These simulations show the following.

- (i) The use of combined NAAT and detuned testing, with a tune strength of 1.333 (that is, a reduction of risk behavior to 75% of what it would have been without added intervention) can result in **three** averted cases in the first year of testing (with the assumption of 30 new cases detected in the first year through the implementation of NAAT);
- (ii) The simple application of NAAT without any added intervention can still prevent approximately **one** new infection in the first year.

Although these figures seem promising, it should be cautioned that making long-term predictions (longer than a year) is problematic largely due to the quality of data we have.

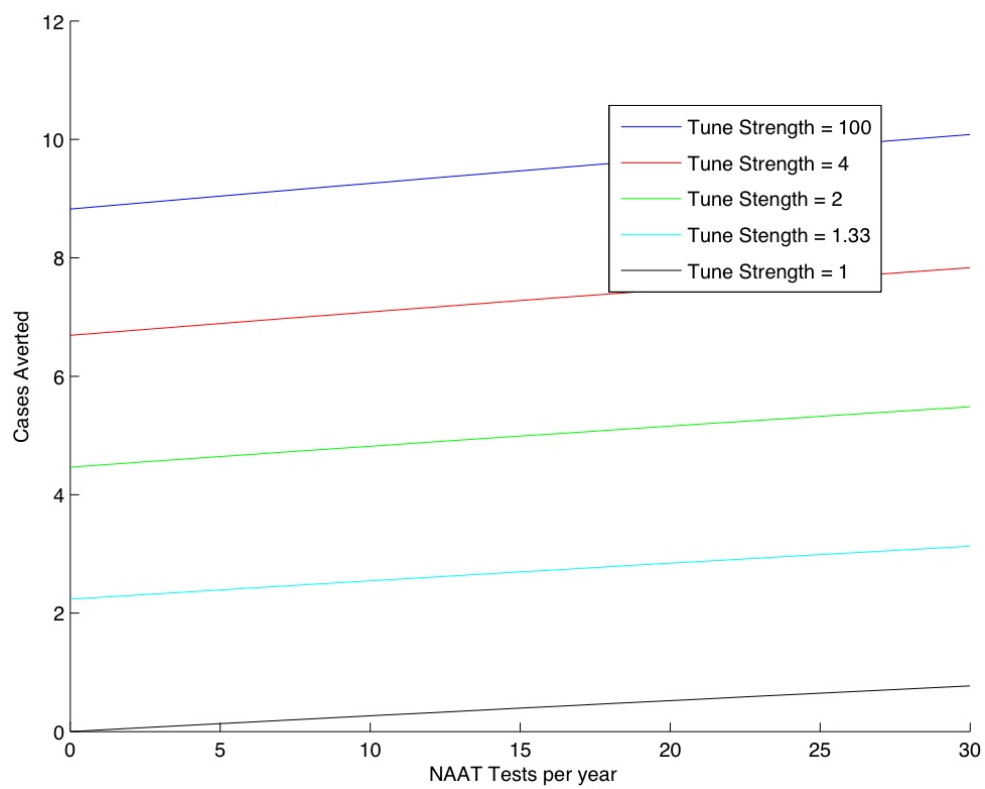


Figure 2: efficacy of NAAT and detuned testing



Variables	Meaning	Estimates (per week)
$\pi$	population increase (births & arrivals)	$\frac{40000}{52}$
$\alpha_{l,h}$	movement from low to high risk susceptible class	$10^{-7}$
$\alpha_{h,l}$	movement from high to low risk susceptible class	0
$\beta_{l,u_i}$	transmission rate from $I_i^u$ to low risk susceptible class for $i = 1, 2, 3$ .	$\frac{1}{3} \cdot \beta_{h,u_i}$
$\beta_{l,k_i}$	transmission rate from $I_i^k$ to low risk susceptible class for $i = 1, 2, 3$ .	$r \cdot \beta_{l,u_i}$
$\beta_{l,T}$	transmission rate from $I^T$ to low risk susceptible class	$r \cdot \beta_{l,k_2}$
$\beta_{h,u_i}$	transmission rate from $I_i^u$ to high risk susceptible class for $i = 1, 2, 3$	$\frac{1}{52} \cdot \{0.3 - 0.6, 0.03 - 0.06, 0.2 - 0.5\}$
$\beta_{h,k_i}$	transmission rate from $I_i^k$ to high risk susceptible class for $i = 1, 2, 3$ .	$r \cdot \beta_{h,u_i}$
$\beta_{h,T}$	transmission rate from $I^T$ to high risk susceptible class	$r \cdot \beta_{h,u_2}$
$\sigma_{u_1,u_1}$	progression rate from $I_1^u$ to $I_2^u$	$\frac{1}{24}$
$\sigma_{u_2,u_3}$	progression rate from $I_2^u$ to $I_3^u$	$\frac{1}{6 \cdot 52}$
$\sigma_{k_1,k_2}$	progression rate from $I_1^k$ to $I_2^k$	$\frac{1}{24}$
$\sigma_{k_2,k_3}$	progression rate from $I_2^k$ to $I_3^k$	$\frac{1}{6 \cdot 52}$
$\tau_{u_1,k_1}$	testing rate from $I_1^u$ to $I_1^k$	$\{1.55 + \varepsilon_T \eta\} / I_1^u(0)$
$\tau_{u_2,k_2}$	testing rate from $I_2^u$ to $I_2^k$	$6.39 / I_2^u(0)$
$\tau_{u_3,k_3}$	testing rate from $I_3^u$ to $I_3^k$	$0.69 / I_3^u(0)$
$\psi_{k_i}$	treatment rate from known stage $i$ to treated $i$ for $i = 1, 2, 3$ .	$\{0, 0, 10 / I_3^u(0)\}$
$\phi$	progression from treated to known 3	0.001
$\mu$	natural death rate	$\frac{1}{60 \cdot 52}$
$\delta_u$	death rate due to undetected AIDS	$\frac{1}{2 \cdot 52}$
$\delta_k$	death rate due to AIDS after treatment stops to be effective	$\frac{1}{2 \cdot 52}$

Table 1: Dynamical Parameters and their Estimates

<b>Variables</b>	<b>Meaning</b>	<b>Estimates (per week)</b>
$\varepsilon_T$	efficacy of testing (sensitivity)	91%
$\eta$	desirable increase in no. detected	0 – 30
$r$	measure of adjusted behavior due to awareness of disease	0.43
$tune$	measure of adjusted behavior due to add. counselling in stage 1	0.01 – 1
$tune\ strength$	$1/tune$	1 – 100

Table 2: **Testing Parameters and their Estimates**

## Conclusions

A deterministic compartmental model is designed and used to evaluate the impact of NAAT and detuned testing in combatting the spread of HIV in British Columbia. The model is, first of all, analyzed rigorously to gain insights into its dynamical features and to determine important epidemiological thresholds, such as the effective reproduction number. Using data for British Columbia (supplied by the BC CDC), and assuming NAAT testing detects 30 infected people per year in addition to plausible level of risk modification amongst those aware of their HIV status, this study shows that using NAAT and detuned test could avert up to 3 new cases per year. Further, even without any additional intervention, using NAAT is still beneficial (can avert approximately one case in the first year). Overall, this study suggests that the combined use of NAAT and detuned testing offers a promising approach for halting the spread of HIV in British Columbia. Having said all these, it is worth emphasizing that more refinements of the model are necessary, as more quality data becomes available, in order to make a more definitive evaluation of these tests.

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## Appendix A: Description and Estimation of Parameters

$\pi$  population increase – births and arrivals

Census data shows that approximately 40000 children are born in the province of British Columbia every year. We assume the additional net influx such as immigration, migration, etc. to be negligible. Using this figure, the parameter  $\pi$  is estimated to be  $\pi \approx \frac{40000}{52}$  per week.

$\alpha_{l,h}$  transition from low to high risk susceptible class

$\alpha_{h,l}$  transition from high to low risk susceptible class

It is assumed, plausibly, that transitions between the low risk and high risk susceptible classes is rather limited. Hence, the values of  $\alpha_{l,h}$  and  $\alpha_{h,l}$  are small.

$\beta_{l,u_i}$  transmission rate from  $I_i^u$  to low risk susceptibles ( $i = 1, 2, 3$ )

$\beta_{l,k_i}$  transmission rate from  $I_i^k$  to low risk susceptibles ( $i = 1, 2, 3$ )

$\beta_{l,T}$  transmission rate from  $I^T$  to low risk susceptibles

$\beta_{h,u_i}$  transmission rate from  $I_i^u$  to high risk susceptibles ( $i = 1, 2, 3$ )

$\beta_{h,k_i}$  transmission rate from  $I_i^k$  to high risk susceptibles ( $i = 1, 2, 3$ )

$\beta_{h,T}$  transmission rate from  $I^T$  to high risk susceptibles

Estimates for transmission rates between unknown stages and high risk susceptible individuals seem to be standard in literature. They can for example be found in [8, 15] and the references therein. We use the rates  $\{\beta_{h,u_1}, \beta_{h,u_2}, \beta_{h,u_3}\} \approx \{5.8 \times 10^{-3} - 1.2 \times 10^{-2}, 5.8 \times 10^{-4} - 1.2 \times 10^{-3}, 3.8 \times 10^{-3} - 9.6 \times 10^{-2}\}$  per week. We assume the corresponding transmission rates for the low risk susceptibles to be significantly smaller; setting  $\beta_{l,u_i} = \frac{1}{3}\beta_{h,u_i}$ . A crucial assumption in this study is that infected individuals do (positively) change (reduce) their risk behavior once they are aware of their status (through using condoms during sex; not sharing needles; informing their part-

ners of their HIV status etc.). Data from the CDC Atlanta [18] supports this assumption, and estimates the risk reduction parameter ( $r$ ) to be  $r = 0,43$ . Therefore, we assume that the transmission rates between known stages and low and high risk susceptible classes are the same as the ones above, scaled by the risk-reduction factor  $r$ . That is,  $\beta_{l,k_i} = r\beta_{l,u_i}$  and  $\beta_{h,k_i} = r\beta_{h,u_i}$ . We further assume that treated individuals transmit infection at a (small) rate comparable to that of infected individuals in the chronic stage who are aware of their infection status.

$\sigma_{u_1,u_1}$	progression rate from $I_1^u$ to $I_2^u$
$\sigma_{u_2,u_3}$	progression rate from $I_2^u$ to $I_3^u$
$\sigma_{k_1,k_2}$	progression rate from $I_1^k$ to $I_2^k$
$\sigma_{k_2,k_3}$	progression rate from $I_2^k$ to $I_3^k$

We assume the duration of the acute/early HIV illness stage to be approximately 24 weeks and the duration of the asymptomatic stage to be six years. Current HIV treatment guidelines in BC are to apply anti-retroviral therapy only when CD4 count drops below 200 cells per micro-liters of blood or upon onset of symptoms. In our model, this guideline is reflected in the low/negligible treatment rates for infected individuals in stages 1 and 2. This leads to the estimates on  $\sigma_{u_1,u_2} = \sigma_{k_1,k_2} \approx \frac{1}{24}$  per week as well as  $\sigma_{u_2,u_3} = \sigma_{k_2,k_3} \approx \frac{1}{6 \times 52}$  per week.

$\tau_{u_1,k_1}$	testing rate from $I_1^u$ to $I_1^k$
$\tau_{u_2,k_2}$	testing rate from $I_2^u$ to $I_2^k$
$\tau_{u_3,k_3}$	testing rate from $I_3^u$ to $I_3^k$

Data from the BC CDC database shows that 152440 HIV tests have been conducted during a 12 month period. Out of these, 445 cases came back positive. Thus, on average,  $\frac{445}{52} = 8.6$  tests per week are positive. Furthermore, an estimated 18% of reportable cases are tested as recently infected (i.e., during the first 5 – 6 months after infection). Hence, approximately  $8.6 \cdot 0.18 = 1.55$  positive tests of recently-infected people are conducted per week. Also, an estimated 8% of all new positive tests correspond to people who already are symptomatic and/or have AIDS (third stage). This means that approxi-



mately  $8.6 \cdot 0.08 = 0.69$  new positive tests of stage 3 cases are conducted per week. Combining all these, it follows that there are  $8.6 - 0.69 - 1.55 = 6.36$  new cases per week in stage 2.

- $\psi_{k_i}$  treatment rate from known stage  $i$  to stage of treated individuals
- $\phi$  progression from treated to known 3

Again, treatment guidelines in BC lead us to the assumption that treatment rates in stages 1 and 2 are negligible. We also believe that the progression from the treated class to full AIDS is small and calculated it according to the number of years spent in the treated class which we expect to be around 15 (which gives a total life span from infection to death of  $\approx 22 - 25$  years).

- $\mu$  natural death rate
- $\delta_u$  death rate due to undetected AIDS
- $\delta_k$  death rate due to AIDS after treatment stops to be effective

We assume an average time span of sexual activity of 60 years, which then leads to a natural death rate  $\mu = \frac{1}{60 \cdot 52}$  per week. For both death rates due to AIDS we assume the same values. An average life span of 2 years with AIDS (after HAART treatment fails to be effective or in the absence of HAART treatment) leads to the rate  $\delta = \frac{1}{2 \cdot 52}$ .

## Testing-related Parameters

- $\varepsilon_T$  efficacy of testing (sensitivity)
- $\eta$  desirable increase in number of cases detected
- $r$  measure of adjusted behavior due to knowledge of infection
- $tune$  measure of additional adjusted behavior in stage 1 due to various interventions
- $tune\ strength$   $1/tune$

We added another means to measure additional risk reduction in peo-

Variables	Meaning	Initial Estimates
$S_l$	initial low risk susceptible population	$3 \cdot 10^6$
$S_h$	initial high risk susceptible population	63000
$I_i^u$	initial unknown infected population	{100, 2000, 900}
$I_i^k$	initial known infected population	{200, 3080, 1180}
$I^T$	initial treated population	3540

Table 3: **Initial Values and Their Estimates**

ple with an early HIV infection. These adjustments in risk behavior relate to various unspecified interventions aimed at people who were diagnosed in an early stage of their infection. We use the variables  $tune$  and  $tune\ strength = 1/tune$  to indicate how effective these adjustments are, i.e. the values for  $\beta_{l,k_1}$  and  $\beta_{h,k_1}$  drop by a factor of  $tune$ . We let the value for the parameter  $tune$  range from 0.01 to 1, where  $tune = 1$  corresponds to no added intervention other than informing people earlier in their illness by identifying them through NAAT.

It is an assumption that the application of NAAT will lead to the detection of  $\eta$  additional cases per year. Together with the efficacy rate of the testing procedure  $\varepsilon_T$  this influences the testing rate as follows:  $\tau_{u_1,k_1} = \{1.55 + \varepsilon_T \eta\} / I_1^u(0)$ . Here, we assume an efficacy of our testing procedure of 91%. This is based on results from a study conducted in North Carolina. As mentioned before we use an improvement rate in risk behavior  $r = 0.43$  for infected individuals who are aware of their status. In the process of validating the effectiveness of NAAT we let  $\eta$  vary between 0 and 30 people per year. These numbers are in compliance with CDC data given to us for reasonable testing.

A brief overview of the parameters is summarized in Tables 1 and 2.