

博士論文

Forecasting HIV in Japan

(日本における HIV の予想に関する研究)

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Abstract

Background: Although HIV prevalence in Japan is low, new HIV notifications are increasing rapidly amongst men who have sex with men (MSM). Little is known about the dynamics of the HIV epidemic in Japan, but understanding how the disease is spreading and future trends in prevalence is essential to planning interventions and setting priorities for the health system.

Objectives: This study used a deterministic compartmental mathematical model of HIV to understand the dynamics of the HIV epidemic in Japan, to project trends 30 years into the future, and to identify interventions that may be effective in controlling the epidemic.

Methods: I developed a deterministic compartmental model of HIV/AIDS that divides the population into ten compartments based on HIV serostatus, CD4 count, knowledge of HIV serostatus and treatment activity. This model was applied to three risk groups: MSM, low-risk women and low-risk men. I derived an analytical expression for the basic reproduction number of this model in a simplified MSM-only population, and analyzed the effect on the basic reproduction number of key parameters related to behavioral and biomedical interventions. I used data on numbers of MSM, HIV/AIDS cases, and disease transmission parameters to develop forecasts of HIV prevalence in the three risk groups over the next 30 years for two scenarios: a high HIV risk scenario that models what is known about Japanese risk and treatment-seeking behavior now, and a lower HIV risk scenario that models reasonable and achievable improvements in this behavior. Results from the models were analyzed statistically to identify determinants of epidemic spread.

Results: In the base case high HIV risk scenario, HIV prevalence amongst MSM increased over 30 years from a baseline value of 2.1% to 10.4% (sensitivity range: 7.4—18.7%). Prevalence decreased amongst low-risk men women, but in a minority of models prevalence amongst women began to increase again after 20 years, probably because of limited sexual contact with MSM. With moderate changes to sexual risk and treatment-seeking behavior

proposed in the lower HIV risk scenario, prevalence at 30 years amongst MSM was 1.1%, with a sensitivity range between 0.2% and 4.1%. In the lower HIV risk scenario there was no risk of epidemic growth amongst low-risk men and women in any model run. Mathematical analysis of the model equations showed that the progress of the epidemic is highly dependent on testing rates, that small increases in testing rates can have a large effect on epidemic size in communities with low testing rates, and that current Japanese sexual and treatment-seeking behaviors are on the edge of the parameter space required to contain the epidemic.

Conclusion: Both projections and mathematical analysis suggested that small changes in sexual risk and treatment-seeking behavior would be sufficient to contain the epidemic in Japanese MSM. However, if these changes do not occur, the projections in this study show that the HIV epidemic amongst MSM will grow rapidly in scale over the next 30 years. Urgent improvements in testing rates, changes to treatment guidelines to encourage early entry into treatment, and scaling up of current interventions to a more coherent and intensive, community-wide program are essential if the epidemic is to be contained in Japan.

Keywords: HIV/AIDS, Japan, mathematical model, epidemiology, HAART, sexual behavior

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List of abbreviations

WHO	World Health Organization
HAART	Highly-Active Antiretroviral Therapy
MSM	Men who have sex with men
HIV	Human immunodeficiency virus
AIDS	Acquired immunodeficiency syndrome
NGO	Non-government organization
ART	Anti-retroviral treatment
ODE	Ordinary differential equation
DFE	Disease free equilibrium
LHS	Latin hypercube sampling
EF	Efficiency factor
PLWH	People living with HIV
RR	Rate Ratio
VCT	Voluntary counseling and testing

1. INTRODUCTION

1.1. HIV/AIDS in Japan

Although HIV prevalence remains low in Japan[1], new HIV infections are at an all-time high, and have been increasing rapidly for the past 10 years. The majority of new infections in Japan are among men who have sex with men (MSM), and of these the vast majority are Japanese nationals[1]. This suggests a dynamic of increasing prevalence of the illness amongst a hard-to-reach, poorly-researched minority[1, 2], and the HIV epidemic among Japanese MSM may be following the same path it followed in MSM in other countries 20 years ago[3-5], with the same risk of reaching a high prevalence in Japanese MSM.

Japan commenced surveillance of HIV/AIDS in 1984, and the first cases of HIV in MSM were notified in 1985^[6]. The epidemic initially developed slowly among MSM, and Japanese concerns focused on the epidemic among hemophiliacs, due to the use of blood contaminated with HIV between 1983 and 1985[7]. Until the early 1990s the majority of notified HIV cases in Japan remained recipients of blood products, and as late as 1995 the primary driver of the future of the epidemic was believed to be heterosexual contact[8]. Court cases and an advocacy movement for those infected by tainted blood focused public attention on this group of people living with HIV (PLWH), and some researchers have suggested that the resolution of these cases in the late 1980s and early 1990s gave the Japanese public a sense of resolution of the challenges of HIV/AIDS[7]. The early focus of journalists on recipients of tainted blood as donors often counter-posed them with “reckless” or “immoral” MSM or sex

workers[9], and these men and women may have experienced the stigmatization and marginalization common at this time in other countries[10]. Against this backdrop of medically-acquired HIV, representative organizations for MSM did not become publicly active until the 1990s[11], and government-supported non-government organizations (NGOs) only began widespread anti-HIV activities from 1998[12]. This delay in activism and the focus on victims of tainted blood products has restricted the awareness of HIV amongst MSM in Japan.

The HIV epidemic changed rapidly, however. While in 1997 only 14% of new HIV/AIDS cases were attributable to homosexual contact[13], by 2012 this proportion had changed to 66%[14]. Figure 1 shows the trend in HIV and AIDS notifications to 2010, clearly showing the recent rapid rise in HIV and AIDS notifications amongst MSM. In contrast to the epidemic amongst MSM, the number of notifications of HIV and AIDS cases due to heterosexual contact has plateaued.

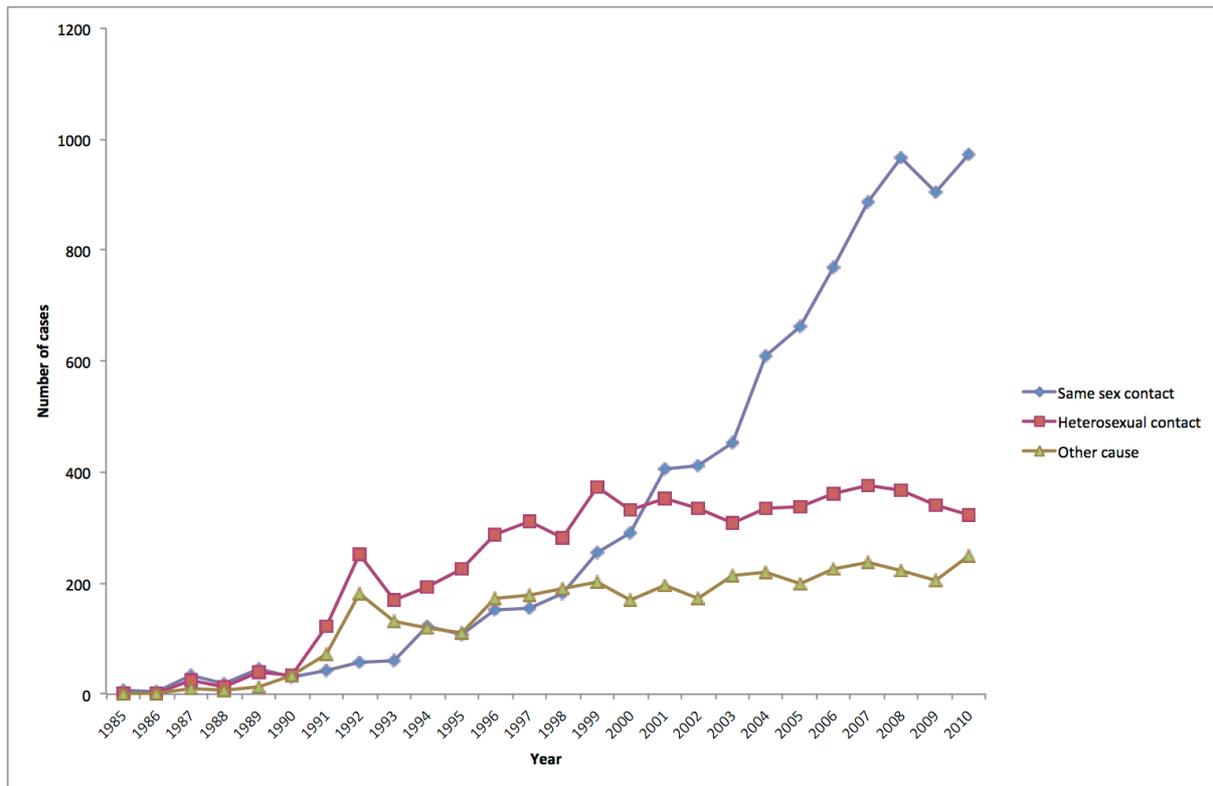


Figure 1: HIV and AIDS by transmission method, 1985-2010

Source: AIDS Prevention Information Network, 2011

This rapid increase is driven by low awareness of HIV, high-risk behavior amongst MSM, and limited focus on testing or awareness of serostatus. Newly-identified cases of HIV in Japan often have very low CD4 counts consistent with long-term infection[15], and in 2006 only 33% of newly-identified HIV cases arose from routine testing in public health centres or clinics; the remainder were identified through case-finding associated with clinical investigation of other STIs, or directly due to investigation of HIV-related symptoms[15].

Understanding of the status of the epidemic in Japan, and research into the risk behavior of MSM, is limited compared to countries at a similar level of economic development which experienced HIV first among MSM, such as Australia or the USA, and interventions amongst MSM are both less developed, less visible and heavily focused on behavioral interventions.

1.2. Biomedical and behavioral interventions to reduce HIV transmission in Japan

Recent research overseas has identified a promising role for biomedical interventions in preventing the transmission of HIV, and models in both developed[16] and developing[17] nation populations have shown the possibility that an intervention strategy based on universal access to voluntary counselling and testing (VCT) and antiretroviral treatment (ART) may contain or even eliminate the epidemic. These strategies require assumptions of high rates of testing and treatment against a backdrop of successful behavioral interventions that may not be realistic in many settings[18], but recent studies have shown that even with more realistic intervention assumptions, and allowing for high-risk sexual behavior in some sub-populations, elimination may be possible through test-and-treatment strategies, though over considerably longer time frames[19].

Most studies targeting elimination through test-and-treat strategies have been conducted in sub-Saharan Africa, however, in high-prevalence generalized epidemics, and less attention in the literature has been focused on elimination of epidemics in high-risk sub-populations.

Amongst MSM, epidemic control was achieved in some countries such as Australia and the USA before the availability of modern anti-retroviral treatment (ART), primarily through behavioral interventions, and behavioral interventions amongst other high-risk populations such as sex workers[20, 21] and injecting drug users[22] have also shown considerable success. Although guidelines for the testing and treatment of HIV/AIDS in MSM in countries with successful behavioral change campaigns now include early treatment as prevention[23], and some countries such as the USA are implementing a nationwide voluntary testing and

counseling strategy[24], it remains the received wisdom that behavioral interventions amongst MSM can be sufficient to contain the progress of HIV epidemics. Recent research, however, has confirmed that the early successes observed in some behavioral intervention strategies are not representative of the overall effectiveness of behavioral intervention programs, and that these programs alone cannot be expected to be successful either amongst MSM only[25] or in generalized epidemics[26].

In Japan, however, behavioral interventions remain the mainstay of the HIV prevention strategy[12]. In contrast to US HIV/AIDS treatment guidelines, the Japanese treatment guidelines do not yet recommend routine anti-retroviral treatment for prevention in asymptomatic newly-infected patients[27], and ART for preventive purposes is not supported by Japan's universal health coverage system. Testing is not widespread, and free anonymous HIV testing is only routinely available at a network of public health centres that are difficult to access and not widely advertised[28]. Testing is sometimes promoted during specific HIV testing events[29], and general HIV testing information is not directly linked to testing centres or activity. Instead, HIV prevention activities in Japan are focused around behavioral interventions promoted through community education, outreach and counseling[30]. There is no systematic research into the effectiveness of these intervention strategies or even the extent of their coverage.

Given the limited knowledge available about the sexual and risk behavior of MSM, it is unlikely that behavioral interventions operating in Japan will be effective. Without knowledge about the community being targeted, it is difficult to craft behavioral interventions

from a robust theoretical standpoint, or to target them at the correct people. Research has shown that information about homosexual transmission risks is not widely disseminated in school sex education classes[31], so young MSM are likely to enter this high-risk population with very little baseline knowledge about the risks they face and behavioral interventions developed overseas for use in populations with a higher level of safe sex knowledge are likely to be ineffective.

Assessing how such strategies might work in Japan requires both an understanding of the current level of awareness and utilization of HIV testing in the Japanese population, and projections of the future path of the epidemic. HIV prevention guidelines, decisions about testing and treatment strategies, and decisions about the size and distribution of HIV intervention funding, depend on understanding the scale of the problem and good projections of the future of the epidemic. Attempts have been made in the past to estimate the total size of the HIV epidemic in Japan[32], but past efforts at forecasting the future have been criticized for their inaccuracy and limited policy-development value[33]. In order to make decisions about the future of HIV prevention in Japan, better projections of the epidemic in the future are required, using more sophisticated models than those that have been used in the past.

1.3. Objectives

To date, there has been very little research focusing on the dynamics of the epidemic in Japan, and no attempts to project the possible future course of the epidemic. Given the increasing awareness of the high risk of HIV faced by MSM in Japan, such projections are

essential to help policy-makers understand the future health care burden that HIV may present in Japan, the importance of interventions, and the risk of the epidemic spreading beyond the MSM community.

This study presents projections of HIV transmission in Japan, employing a deterministic compartmental mathematical model to examine trends among MSM and non-MSM (male and female) over a 30 year period. Due to an absence of available research on sex work and injecting drug use in Japan, the non-MSM population did not include any assessment of these high-risk groups. Consistent with the risk patterns identified in surveillance data in Japan, for this study HIV risk was determined entirely in terms of homosexual sexual activity amongst men, and consistent with this all non-MSM were defined as low risk, and hereafter referred to as low-risk men and low-risk women.

The study aims to explore the development of the epidemic under reasonable starting assumptions, to identify the key weaknesses in current research among MSM, to understand the extent of risk of an uncontrolled HIV epidemic amongst MSM, and to determine what may need to be done to prevent the spread of this disease.

The deterministic compartmental model developed in this study will be used to conduct three key tasks:

1. Calculate projections of the future trend in prevalence of HIV amongst MSM, low-risk men and low-risk women under two scenarios, one representing the likely current state of knowledge and activity in Japan and one representing a realistic estimate of how

behavioral risks and testing and treatment activity could be changed through interventions

2. For the MSM population only, develop an analytical expression for the basic reproduction number, the key parameter describing evolution of the epidemic, explore its mathematical properties and the roles of key epidemic parameters that can be influenced through intervention strategies
3. Develop policy recommendations for the Japanese government, and recommend the most effective combination of intervention strategies that could be used to contain the HIV epidemic over the next 30 years

It is hoped that this research will provide crucial information to support efforts to combat HIV in a high-risk population that is clearly on the cusp of a major epidemic. Given the linear trend in new infections amongst MSM, it is clear that current intervention activities in Japan are not working. Through careful assessment of the future trends in HIV, and evaluation of a realistic intervention framework, it may be possible to develop recommendations for an improved HIV prevention strategy that can make a difference in the fight against HIV amongst Japanese MSM.

2. METHODS

2.1. A deterministic compartmental model of HIV

A mathematical model of the epidemiology of HIV was developed to describe the progress of HIV through 10 compartments across three risk groups, based on an existing published model[16]. The 10 compartments represent stages of progression of HIV infection from HIV-negative to AIDS, with HIV infection divided into symptomatic stages according to current treatment guidelines, and further divided into compartments according to knowledge of serostatus. The model was developed using population parameters for the 15-59 age group in 2005, enabling comparability with current estimates of the size of the MSM population[34]. Prevalence figures were obtained from the Ministry of Health, Labour and Welfare[35] for the population aged 15 – 59 years of age. Figures for those infected through contaminated blood represented less than 3% of all PLWH in 2011[35] and were difficult to divide by sex and other risk categories, so these cases were excluded from the model.

In this chapter I will describe the structure of this model, the mathematical methods used to explore its dynamic properties, and its implementation for projecting HIV prevalence in Japan.

2.1.1. Main model structure

In order to estimate HIV transmission and progression rates, I developed a deterministic compartmental model, capturing transmission through both heterosexual and homosexual contacts. I subdivided the target population into three groups: men who have sex with men (MSM), low-risk men and low-risk women. Once infected, individuals progress through asymptomatic, symptomatic, and AIDS stages. Although in Japan AIDS is a clinical condition defined in terms of a combination of clinical and virological criteria [ref], this model does not include stochastic properties of all possible opportunistic infections that might define an AIDS case, and the disease stages in the model are defined entirely in terms of CD4 counts, rather than a more nuanced clinical case definition. The model separates the basic compartments for these disease stages by serostatus (identified/unidentified) and treatment status (treated/untreated). Because voluntary testing and treatment strategies operate at a population level as well as amongst populations at higher risk, the model includes a compartment for HIV-negative individuals who have been tested and identified as negative, and who are assumed to remain aware of their HIV status for one year. This compartment in this model is an artifact of the testing process and is included for completeness; no differential risk behavior is assumed for this group. Figure 2 shows the compartmental structure of the model, with flows between compartments represented by arrows. This model structure expands on earlier models depicting test-and-treatment strategies[17] by allowing different rates of testing and treatment entry at each stage of the disease, and incorporates testing through passive case-finding and active VCT strategies. The compartmental structure

was developed based on a previous model used to describe HIV transmission dynamics in the USA[16] and China[36].

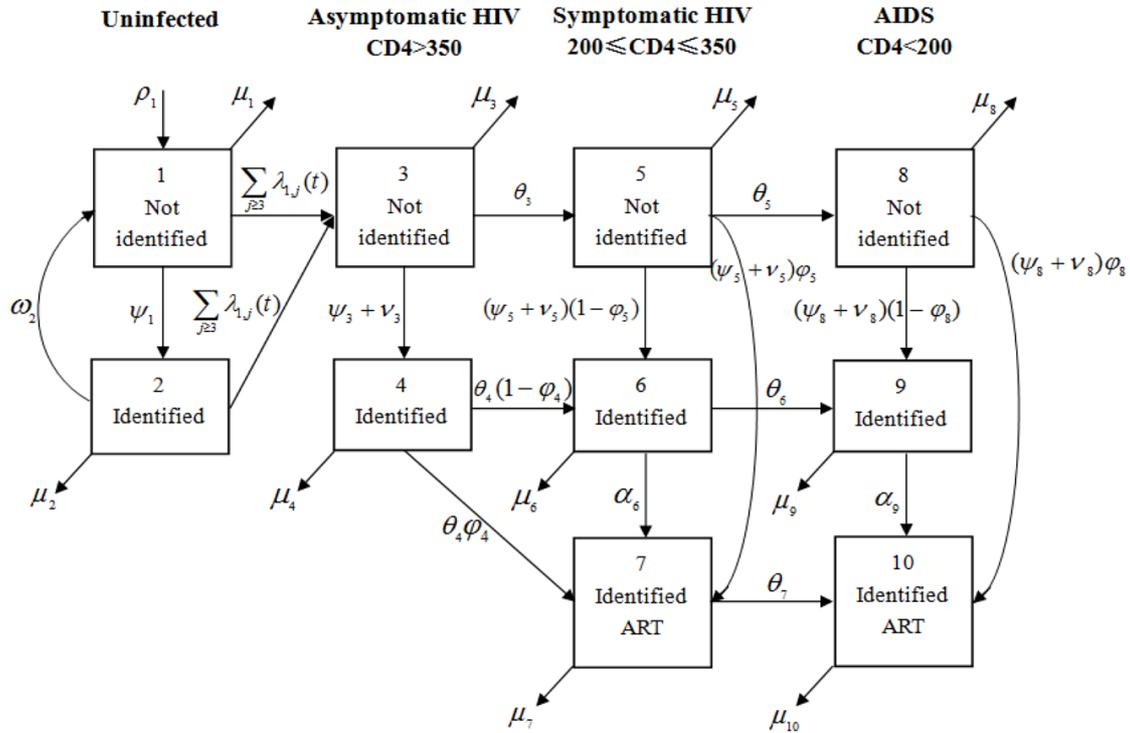


Figure 2: Compartmental structure of the mathematical model

All symbols shown in Figure 2 are defined in Table 1. Figure 2 shows the compartmental structure for a single risk group in the model, but the model divides the population into three risk groups: MSM, low-risk men and low-risk women. In Table 1 the risk groups are denoted by the subscript i , where $i \in [1, 2, 3]$ for MSM, low-risk men and low-risk women respectively. The compartments are denoted by the subscript j , with values of j corresponding with the numbers assigned to the compartments shown in Figure 2. The population of each compartment is then denoted by a capital X . Thus, for example, the population of low-risk men identified as HIV positive and currently receiving ART is denoted $X_{2,7}$. For any

mathematical expressions developed only for a single risk group model (such as in section 2.2), the subscript denoting risk group will be dropped, and all populations referred to only by their j subscript.

Forces of infection are represented through the symbol λ , testing rates by ψ and ν , and treatment entry rates by α . Mortality rates due to HIV are different in every compartment, and are denoted by μ ; in all HIV-positive cells background mortality rates for all other causes are denoted b . The model allows for HIV negative individuals to be identified as HIV negative (compartment 2) and contains a separate compartment for HIV positive individuals who have been identified through testing but are not yet in treatment in each of the three disease stages (compartments 4, 6 and 9). Consistent with current Japanese HIV treatment policy[27], asymptomatic individuals are not assumed to receive any form of highly-active antiretroviral treatment (HAART), but must enter the symptomatic stage before entering treatment. In the symptomatic and AIDS stages, individuals can enter treatment directly upon being identified as HIV positive, but some are assumed to spend a period of time untreated in these stages. The parameter ϕ determines the proportion of newly-identified cases that progress directly to treatment.

Table 1: Definition of variables and parameters in the compartmental model

Variables/Symbols	Definition
Demographic characteristics	
$X_{i,j}$	Number of people in risk group i with status j
b_j^i	Annual background mortality rate
μ_j^i	Annual mortality rate due to HIV/AIDS
μ_1^i, μ_2^i	Annual maturation rate
ρ_1^i	Annual entry rate
Sexual transmission	
$\sigma_{f,m}^z$	Annual transmission probability per partnership from female to male, where z = asymptomatic HIV, symptomatic HIV, and AIDS
$\sigma_{m,f}^z$	Annual transmission probability per partnership from male to female, where z = asymptomatic HIV, symptomatic HIV, and AIDS
$\sigma_{m,m}^z$	Annual transmission probability per partnership from male to male, where z = asymptomatic HIV, symptomatic HIV, and AIDS
n_1^s	Annual same-sex partners of MSM
u_1^s	Condom use with same-sex partners, percent

n_i^o Annual opposite-sex partners in risk group i

u_i^o Condom use with opposite-sex partners in risk group i

κ Condom effectiveness

HIV screening

ψ_j^i Fraction of population tested in past 12 months for risk group i
with status j , percent

$1/\omega_2^i$ Average duration (years) that uninfected individuals remain
identified after screening in risk group i

ν_j^i Annual probability of symptom-based case finding in risk group i
with status j , percent

r_1 Reduction in sexual behavior among persons identified as
HIV-positive, percent

r_1' Reduction in sexual behavior among patients with HIV-related
illness, percent

ART Treatment

ϕ_j^i Fraction starting ART at CD4 cell count of 350 in risk group i with
status j

α_j^i Annual ART entry rate if CD4 cell count <350 of risk group i with

	status j
r_2	Reduction in sexual infectivity due to ART, percent
Others	
θ_j^i	HIV disease progression rate for individuals in risk group i with status j
$\sum_{j \geq 3} \lambda_{i,j}(t)$	Transmission forces for each risk groups i

2.1.2. Model equations

Based on the model framework described in Section 2.1.1, the transition process described in Figure 2 can be expressed through a set of 10 differential equations describing the flow of individuals through all compartments in the model. Thus for three risk groups the complete model comprises 30 equations. The 10 equations for each risk group are shown in equation 1.

$$\frac{dX_{i,1}}{dt} = \rho_1^i \sum_{\forall j} X_{i,j} - \psi_1^i X_{i,1} + \omega_2^i X_{i,2} - \left(\sum_{j \geq 3} \lambda_{i,j}(t) \right) X_{i,1} - (\mu_1^i + b_1^i) X_{i,1}$$

$$\frac{dX_{i,2}}{dt} = \psi_1^i X_{i,1} - \omega_2^i X_{i,2} - \left(\sum_{j \geq 3} \lambda_{i,j}(t) \right) X_{i,2} - (\mu_2^i + b_2^i) X_{i,2}$$

$$\frac{dX_{i,3}}{dt} = \left(\sum_{j \geq 3} \lambda_{i,j}(t) \right) X_{i,1} + \left(\sum_{j \geq 3} \lambda_{i,j}(t) \right) X_{i,2} - (\psi_3^i + \nu_3^i) X_{i,3} - (\theta_3^i + \mu_3^i + b_3^i) X_{i,3}$$

$$\frac{dX_{i,4}}{dt} = (\psi_3^i + \nu_3^i) X_{i,3} - (\theta_4^i + \mu_4^i + b_4^i) X_{i,4}$$

$$\frac{dX_{i,5}}{dt} = \theta_3^i X_{i,3} - (\psi_5^i + \nu_5^i) X_{i,5} - (\theta_5^i + \mu_5^i + b_5^i) X_{i,5}$$

$$\frac{dX_{i,6}}{dt} = \theta_4^i (1 - \phi_4^i) X_{i,4} + (\psi_5^i + \nu_5^i) (1 - \phi_5^i) X_{i,5} - (\theta_6^i + \alpha_6^i + \mu_6^i + b_6^i) X_{i,6}$$

$$\frac{dX_{i,7}}{dt} = \theta_4^i \phi_4^i X_{i,4} + (\psi_5^i + \nu_5^i) \phi_5^i X_{i,5} + \alpha_6^i X_{i,6} - (\theta_7^i + \mu_7^i + b_7^i) X_{i,7}$$

$$\frac{dX_{i,8}}{dt} = \theta_5^i X_{i,5} - (\psi_8^i + \nu_8^i) X_{i,8} - (\mu_8^i + b_8^i) X_{i,8}$$

$$\frac{dX_{i,9}}{dt} = \theta_6^i X_{i,6} + (\psi_8^i + \nu_8^i) (1 - \phi_8^i) X_{i,8} - \alpha_9^i X_{i,9} - (\mu_9^i + b_9^i) X_{i,9}$$

$$\frac{dX_{i,10}}{dt} = \theta_7^i X_{i,7} + (\psi_8^i + \nu_8^i) \phi_8^i X_{i,8} + \alpha_9^i X_{i,9} - (\mu_{10}^i + b_{10}^i) X_{i,10}$$

Equation 1: Basic transition equations

where i denotes the risk group and the compartments are labeled 1 to 10 in this set of equations.

2.1.3. Force of infection

The key driver of the dynamic process of infection in a deterministic compartmental model is the force of infection[37], denoted in this model by the symbol λ . The force of infection identifies the rate at which individuals from the susceptible population enter the infected population, and is composed of a combination of parameters reflecting the infectiousness of contacts and the probability of a potentially infectious contact occurring. In this

compartmental model the force of infection in risk group i is composed of the sum of forces of infection in that risk group due to all potentially infectious compartments,

$$\lambda_i = \sum_{j=3}^{10} \lambda_{i,j}$$

Susceptible individuals can become infected in two ways: heterosexual and homosexual contact. Table 2 shows the details of potential modes of infection between any two risk groups. Heterosexual transmission is considered to be possible for MSM in this model.

Table 2: Potential modes of HIV transmission by risk group

	MSM	Male	Female
MSM	Homosexual		Heterosexual
Male			Heterosexual
Female	Heterosexual	Heterosexual	

Transmission forces $\sum_{j \geq 3} \lambda_{i,j}(t)$ for the three risk groups can then be expressed in terms of the probability that an individual will *not* be infected by any sexual contact with an HIV-positive member of any risk group at time t . These probabilities for each of the three risk groups are written as:

N_MSM_j The probability of not being infected by any sexual contact with people from compartment j in the MSM risk group

N_M_j The probability of not being infected by any sexual contact with people from compartment

j in the male risk group

N_{-F_j} The probability of not being infected by any sexual contact with people from compartment

j in the female risk group

The total force of infection can then be calculated for each of these values based on the following assumptions:

1. The probability of infection from sexual contact is independent between individuals
2. The probability of infection from sexual contact is independent between risk groups
3. The probability of infection from sexual contact is independent between compartments

Under these assumptions the force of infection can be calculated as the complement of the probability of not being infected by any sexual contact with any risk group. Since the probability of not being infected by any sexual contact in a risk group is independent between risk groups and individuals, the total probability of not being infected by sexual contact in a given risk group is simply the product of the probability of not being infected in each sexual contact. The forces of infection are summarized in Equation 2.

$$\sum_{j \geq 3} \lambda_{1,j}(t) = \sum_{j \geq 3} \left\{ 1 - N_- M_j n_j^O (1 - u_1^O \kappa) \right\} + \sum_{j \geq 3} \left\{ 1 - N_- MSM_j n_j^S (1 - u_1^S \kappa) \right\}$$

$$\sum_{j \geq 3} \lambda_{2,j}(t) = \sum_{j \geq 3} \left\{ 1 - N_- M_j n_j^O (1 - u_2^O \kappa) \right\}$$

$$\sum_{j \geq 3} \lambda_{3,j}(t) = \sum_{i=1,2} \sum_{j \geq 3} \left\{ 1 - N_- F_{i,j} n_j^O (1 - u_3^O \kappa) \right\}$$

Equation 2: Forces of infection

2.1.4. Common transmission formulae

The probability that men are not infected by HIV-positive women in compartment j , through one heterosexual contact, $N_- M_j$ ($j=3 \sim 10$) is shown in Equation 3.

$$N_- M_3 = \left[1 - \left(\frac{X_{3,3} n_3^O (1 - u_3^O \kappa)}{CT_F} \sigma_{f,m}^a \right) \right]; N_- M_4 = \left[1 - \left(\frac{X_{3,4} n_3^O (1 - r_1) (1 - u_3^O \kappa)}{CT_F} \sigma_{f,m}^a \right) \right]$$

$$N_- M_5 = \left[1 - \left(\frac{X_{3,5} n_3^O (1 - u_3^O \kappa)}{CT_F} \sigma_{f,m}^s \right) \right]; N_- M_6 = \left[1 - \left(\frac{X_{3,6} n_3^O (1 - r_1) (1 - u_3^O \kappa)}{CT_F} \sigma_{f,m}^s \right) \right]$$

$$N_- M_7 = \left[1 - \left(\frac{X_{3,7} n_3^O (1 - r_1) (1 - u_3^O \kappa)}{CT_F} \sigma_{f,m}^s (1 - r_2) \right) \right]; N_- M_8 = \left[1 - \left(\frac{X_{3,8} n_3^O (1 - u_3^O \kappa)}{CT_F} \sigma_{f,m}^{AIDS} \right) \right]$$

$$N_- M_9 = \left[1 - \left(\frac{X_{3,9} n_3^O (1 - r_1') (1 - u_3^O \kappa)}{CT_F} \sigma_{f,m}^{AIDS} \right) \right]; N_- M_{10} = \left[1 - \left(\frac{X_{3,10} n_3^O (1 - r_1') (1 - u_3^O \kappa)}{CT_F} \sigma_{f,m}^{AIDS} (1 - r_2) \right) \right]$$

Equation 3: Common transmission probabilities (heterosexual men)

In equation 3 CT_F is the total number of heterosexual contacts among women. Parameters in these equations are described in Table 1, and include assumed condom effectiveness, number of partners, rates of condom use and effects of post-test counseling and AIDS diagnosis on numbers of partners.

In this model, the number of sexual contacts is assumed to be reduced amongst those who have received testing and treatment, due to the effect of post-test counseling and/or changes in sexual behavior after onset of AIDS. For this reason, the total number of sexual contacts in individual compartments are not equal, and the total number of sexual contacts needs to be calculated based on an assumed baseline number of sexual contacts in healthy women living with HIV who do not know their serostatus, modified by the effects of testing and treatment on sexual contacts in compartments 4 – 10. The formula for total heterosexual contacts among women is:

$$CT_F = \left(\sum_{j=1,2,3,5,8} X_{3,j} \right) n_3^o (1 - u_3^o \kappa) + \left(\sum_{j=4,6,7} X_{3,j} \right) n_3^o (1 - r_1) (1 - u_3^o \kappa) + \left(\sum_{j=9,10} X_{3,j} \right) n_3^o (1 - r_1') (1 - u_3^o \kappa)$$

The common probabilities that MSM are not infected by HIV-positive MSM in compartment j through one homosexual contact, N_MSM_j ($j=3\sim 10$) are shown in equation 4.

$$\begin{aligned}
N_MSM_3 &= \left[1 - \left(\frac{X_{1,3} n_1^S (1 - u_1^S \kappa)}{CT_{MSM}} \sigma_{m,m}^a \right) \right]; N_MSM_4 = \left[1 - \left(\frac{X_{1,4} n_1^S (1 - r_1) (1 - u_1^S \kappa)}{CT_{MSM}} \sigma_{m,m}^a \right) \right] \\
N_MSM_5 &= \left[1 - \left(\frac{X_{1,5} n_1^S (1 - u_1^S \kappa)}{CT_{MSM}} \sigma_{m,m}^s \right) \right]; N_MSM_6 = \left[1 - \left(\frac{X_{1,6} n_1^S (1 - r_1) (1 - u_1^S \kappa)}{CT_F} \sigma_{m,m}^s \right) \right] \\
N_MSM_7 &= \left[1 - \left(\frac{X_{1,7} n_1^S (1 - r_1) (1 - u_1^S \kappa)}{CT_{MSM}} \sigma_{m,m}^s (1 - r_2) \right) \right]; N_MSM_8 = \left[1 - \left(\frac{X_{1,8} n_1^S (1 - u_1^S \kappa)}{CT_{MSM}} \sigma_{m,m}^{AIDS} \right) \right] \\
N_MSM_9 &= \left[1 - \left(\frac{X_{1,9} n_1^S (1 - r_1) (1 - u_1^S \kappa)}{CT_{MSM}} \sigma_{m,m}^{AIDS} \right) \right]; N_MSM_{10} = \left[1 - \left(\frac{X_{1,10} n_1^S (1 - r_1) (1 - u_1^S \kappa)}{CT_{MSM}} \sigma_{m,m}^{AIDS} (1 - r_2) \right) \right]
\end{aligned}$$

Equation 4: Common transmission probabilities (Homosexual men)

where CT_{MSM} is the total number of homosexual contacts. As with women, this total number of contacts is derived as:

$$CT_{MSM} = \left(\sum_{j=1,2,3,5,8} X_{1,j} \right) n_1^S (1 - u_1^S \kappa) + \left(\sum_{j=4,6,7} X_{1,j} \right) n_1^S (1 - r_1) (1 - u_1^S \kappa) + \left(\sum_{j=9,10} X_{1,j} \right) n_1^S (1 - r_1) (1 - u_1^S \kappa)$$

$N_{F_{i,j}}$ ($i=1,2; j=3\sim 10$) is the probability that women are not infected through heterosexual contact with risk group i , and compartment j . The formulae for $N_{F_{i,j}}$ are shown in Equation 5. Here CT_M is the total number of heterosexual contacts with men. As in the other groups, this is calculated using different assumptions about the effect of testing and counseling:

$$CT_M = \sum_{i=1,2} \left[\left(\sum_{j=1,2,3,5,8} X_{i,j} \right) n_i^O (1 - u_i^O \kappa) + \left(\sum_{j=4,6,7} X_{i,j} \right) n_i^O (1 - r_i) (1 - u_i^O \kappa) + \left(\sum_{j=9,10} X_{i,j} \right) n_i^O (1 - r_i) (1 - u_i^O \kappa) \right]$$

Again i corresponds to 1: MSM, 2: Male, 3: Female; and j denotes the 10 compartments reflecting HIV progression (1: unidentified uninfected, 2: Identified uninfected, 3:unidentified asymptomatic, 4: Identified asymptomatic, 5: unidentified symptomatic, 6: Identified symptomatic, 7: Identified symptomatic with ART, 8: unidentified AIDS, 9: Identified AIDS, 10: Identified AIDS with ART).

$$\begin{aligned}
N_{F_{i,3}} &= \left[1 - \left(\frac{X_{i,3} n_i^o (1 - u_i^o \kappa)}{CT_M} \sigma_{m,f}^a \right) \right]; N_{F_{i,4}} = \left[1 - \left(\frac{X_{i,4} n_i^o (1 - r_1) (1 - u_i^o \kappa)}{CT_M} \sigma_{m,f}^a \right) \right] \\
N_{F_{i,5}} &= \left[1 - \left(\frac{X_{i,5} n_i^o (1 - u_i^o \kappa)}{CT_M} \sigma_{m,f}^s \right) \right]; N_{F_{i,6}} = \left[1 - \left(\frac{X_{i,6} n_i^o (1 - r_1) (1 - u_i^o \kappa)}{CT_M} \sigma_{m,f}^s \right) \right] \\
N_{F_{i,7}} &= \left[1 - \left(\frac{X_{i,7} n_i^o (1 - r_1) (1 - u_i^o \kappa)}{CT_M} \sigma_{m,f}^s (1 - r_2) \right) \right]; N_{F_{i,8}} = \left[1 - \left(\frac{X_{i,8} n_i^o (1 - u_i^o \kappa)}{CT_M} \sigma_{m,f}^{AIDS} \right) \right] \\
N_{F_{i,9}} &= \left[1 - \left(\frac{X_{i,9} n_i^o (1 - r_1) (1 - u_i^o \kappa)}{CT_M} \sigma_{m,f}^{AIDS} \right) \right]; N_{F_{i,10}} = \left[1 - \left(\frac{X_{i,10} n_i^o (1 - r_1) (1 - u_i^o \kappa)}{CT_M} \sigma_{m,f}^{AIDS} (1 - r_2) \right) \right]
\end{aligned}$$

Equation 5: Common transmission probabilities (Heterosexual women)

2.1.5. Model outputs

Prevalence, incidence, and cumulative incidence of HIV were calculated based on the compartments in Figure 2.

The number of susceptible individuals in risk-group i is given by

$$S_i = X_{i,1}(t) + X_{i,2}(t)$$

The number of PLWH in risk-group i is given by

$$I_i = \sum_{j=3}^{10} X_{i,j}(t);$$

HIV prevalence in risk-group i is given by

$$P_i = \frac{\sum_{j=3}^{10} X_{i,j}(t)}{\sum_{\forall j} X_{i,j}(t)}$$

New infections in risk-group i are calculated as

$$NI_i = \left(\sum_{j \geq 3} \lambda_{i,j}(t) \right) \times (X_{i,1}(t) + X_{i,2}(t))$$

Cumulative new infections in risk-group i are given by

$$CI_i = \int_0^t \left(\left(\sum_{j \geq 3} \lambda_{i,j}(t) \right) \times (X_{i,1}(t) + X_{i,2}(t)) \right) dt$$

2.2. Mathematical properties of the model

Mathematical models can be used to explore the properties of the epidemics they represent through simulation or through examination of the mathematical characteristics of the model itself. Section 2.3 describes how I examined the HIV epidemic in Japan, and the potential to contain it, through numerical implementation of the model under two separate scenarios. In this section, I describe how I explored the relationship between risk behavior, testing behavior and the future of the HIV epidemic through the examination of the mathematical properties of the dynamic system of equations itself. As is typical for a deterministic

compartmental model, this investigation proceeds through an analysis of the relationship between individual model parameters and the basic reproduction number of the model, R_0 .

2.2.1. The basic reproduction number of HIV

The basic reproduction number of a disease, R_0 , is a numerical value greater than 0 that indicates the propensity of the disease to spread through a community[38]. The value of R_0 indicates the number of new cases that will be generated by a single case of the disease in a completely susceptible population. Values of R_0 above unity indicate that the disease will propagate through the community, becoming an epidemic, while values below one indicate that the disease cannot replicate itself fast enough to spread, and will ultimately die out.

Identifying an expression for this value is crucial for the proper understanding of the risks that a disease poses to the community. Values of R_0 can range from about 1.5 in the case of influenza to as high as 20 for measles[37]. Typically, the basic reproduction number of a disease is context-specific but also biologically determined: basic virological properties combine with the social context of the disease and the risk behavior of its target population to determine R_0 . For example, seasonal influenza has a distinct virological profile, but children are more susceptible to this profile than adults and, due to schooling practices, children are more likely to socialize with other children than adults, making children more vulnerable to influenza epidemics; case isolation through such mechanisms as mandatory home care or school closures can therefore reduce the value of R_0 for the entire population, because of the differential risk behavior and susceptibility of this group[39]. In such a case,

understanding the effect of case isolation vs. treatment on the value of R_0 helps policy-makers to judge the most effective intervention to contain or prevent an influenza epidemic.

Unlike influenza, HIV has several transmission mechanisms and in mature epidemics is usually seen as spreading through three different transmission mechanisms: injecting drug use, homosexual activity between men, and heterosexual activity. The basic reproduction number of HIV varies depending upon the degree of each type of risk behavior in the community and the extent to which these groups interact, but simple likelihood-based estimates using data from Western Europe suggest that HIV can have a basic reproduction number between 3 and 4 during the early growth phase of an epidemic[40].

Calculation of the basic reproduction number of HIV is complicated by the existence of high-risk groups with non-heterogeneous mixing[38], and the possibility of changes in infectiousness over time[41]. However, for populations still undergoing rapid early growth and with relatively heterogeneous mixing, a method for calculating R_0 based on the next-generation method exists^[42]. Although the accuracy of this method depends on the degree of heterogeneous mixing in the population being studied, the resulting expressions for R_0 can offer useful insights into the dynamics of the HIV epidemic. In particular, the relationship between the basic reproduction number and some key parameters subject to intervention can be explored.

2.2.2. Calculating the basic reproduction number using the next generation method

To calculate the basic reproduction number of HIV in this model, I use the next generation method[43]. I apply the next generation method to a simplified version of the model described in section 2.1. This simplified version of the model has the same compartmental structure but only one risk group, MSM. This simplification makes calculation of the next generation matrix mathematically feasible, and defensible provided the heterosexual transmission component of HIV within the MSM risk group is negligible compared to the homosexual component. We will see in section 2.3 and the results of chapter 4 that this assumption is reasonable, so for the analysis of dynamic properties of the model I will proceed to calculate R_0 for a model with a single risk group of MSM.

The next generation method decomposes the system of ordinary differential equations (ODEs) that describe the transitions in all *infectious* cells of the compartmental model (equation 1) into two processes: the generation of new infections in particular compartments, and the transition of previously-generated infections between compartments due to processes such as symptom transitions, disease identification and treatment.

For the mathematical model described in equation 1 with only one risk group, MSM, these two processes are expressed as two vectors. Both of these vectors have eight entries, one for each infectious compartment in the model. The infection generation vector, \mathbf{f} , consists of all elements of the ODEs in equation 1 that correspond with the generation of new infections.

The transition vector, \mathbf{v} , consists of all components of the ODEs in equation 1 that

correspond with transitions between the compartments for all other reasons. Both \mathbf{f} and \mathbf{v} are 8x1 vectors.

For a model with only one risk group, MSM, the i subscript in equation 1 can be dropped, and all variable subscripts can then be assumed to refer to their corresponding compartment.

For the remainder of this section, we will use the i subscript to denote elements of a vector or rows of a matrix; the j subscript will denote columns of a matrix, or will be used in partial derivatives to represent differentiation over a dimension orthogonal to that of the differand.

Using the notation $\left|_I\right.$ to denote a component of a differential equation that corresponds with infection generation, and $\left|_T\right.$ to denote a component corresponding with transition, we can express the i -th entry of \mathbf{f} as

$$\mathbf{f}_i = \left. \frac{dX_i}{dt} \right|_I$$

and the i -th entry of \mathbf{v} as

$$\mathbf{v}_i = \left. \frac{dX_i}{dt} \right|_T$$

Between them, these two vectors contain all components of the right hand side of equation 1.

From both vectors we then calculate Jacobian matrices, whose $(i, j)^{th}$ element contains the partial derivative of the i -th element of the vector with respect to the j -th variable. That is, we can generate a new infection Jacobian matrix \mathbf{F} with $(i, j)^{th}$ element

$$\mathbf{F}_{ij} = \frac{\partial f_i}{\partial X_j}$$

and a transition Jacobian matrix \mathbf{V} with $(i,j)^{th}$ element

$$\mathbf{V}_{ij} = \frac{\partial \mathbf{v}_i}{\partial X_j}$$

The value of the basic reproduction number, R_0 , is then obtained as the maximum eigenvalue of the product of \mathbf{F} and the inverse of \mathbf{V} , that is

$$R_0 = \max(\rho_j) \quad j = 1, \dots, 10$$

where ρ_j represent the eigenvalues of the matrix product \mathbf{FV}^{-1} , that is they represent the eight possible solutions to the polynomial expression obtained from the standard matrix expression,

$$|\rho \mathbf{I} - \mathbf{FV}^{-1}| = 0$$

where here \mathbf{I} is the identity matrix.

The same method can be applied to equation 1 derived for the full three risk groups, but requires a more complex expression for \mathbf{f} and \mathbf{v} (as 24x1 vectors) and is more difficult to solve analytically, since calculating R_0 in this case would require calculation of the inverse of a 24x24 matrix. For such a situation the basic reproduction number can be derived numerically for specific cases, using a matrix mathematics package to perform numerical calculations with parameter values inserted directly into \mathbf{F} and \mathbf{V} . In this section, however, with only one risk group, the maximum eigenvalue can be calculated by hand, and an analytical expression for the basic reproduction number derived directly. However, the process of long-hand calculation of this eigenvalue, though not difficult, involves calculation

of the inverse of a 8x8 matrix, or at least the derivation of the form of a series of cofactors[44], and is prone to error. For this reason, the final calculation of the maximum eigenvalue was performed using Mathematica 8.0, which is capable of symbolic mathematics with matrices of this size. The detailed derivation of \mathbf{F} and \mathbf{V} and calculation of the basic reproduction number is given in section 3.1.

2.2.3. Analysis of the basic reproduction number

Once an analytical expression for the basic reproduction number has been obtained, values of R_0 will be plotted for different key parameters. Specifically, values of R_0 will be plotted against the following parameters:

- Testing rates
- Condom use proportions
- Treatment entry rates
- Number of partners

In each case, the plots will be generated for a range of fixed values of the remaining parameters, and also in every case with the remaining parameters fixed at those used in the base case model implementation. The purpose here is to explore the complex relationships between the key parameters that can be influenced by specific interventions, under different assumptions about the range of values that other parameters may take.

From these plots, we will infer information about the best possible range of values for different parameters under different assumptions. Once the model has been implemented under two different scenarios, model implementation results will be compared with the findings from the analysis of the basic reproduction number. Numerical analysis of the formula for the basic reproduction number and a variety of parameter values is shown in section 3.2.

2.3. Model implementation

The model was solved for specific starting parameters and variables using a difference-equation method. For each of the differential equations shown in section 2.1.2 a difference-equation form was identified. These difference equations were coded using MATLAB R2011. I then ran the program forward for 30 years, based on the starting parameters. Sensitivity analysis was conducted using a Monte Carlo simulation-based approach to generate 1000 replicates of the original model from randomly-varying starting parameters. Model outputs were plotted for the 30-year forward projection. Finally, outputs after 30 years were regressed against initial values of key parameters and starting populations to identify the influence of these parameters on long-term trends in HIV prevalence in Japan.

2.3.1. Key parameters of the base case model

Starting values of the key parameters for the model are shown in Table 3.

Table 3: Baseline parameters used in the compartmental model

Variable	Value	References
Demographic characteristics		
Annual mortality rate (background)		
Men	0.0092	[45]
Women	0.0045	[45]
Annual mortality rate (due to HIV/AIDS)		
Asymptomatic ($CD4 > 350$)	0.02	[46]
Symptomatic ($200 \leq CD4 \leq 350$)	0.063	[46]
AIDS ($CD4 < 200$)	0.22	[47, 48]
Annual mortality rate (due to HIV/AIDS)		
Symptomatic with ART	0.05	[46]
AIDS with ART	0.075	[46]
Annual maturation rate		
Men	0.0271	Calculated, Census Data
Women	0.0232	Calculated, Census Data

Annual entry rate

Men 0.0167 Calculated, Census Data

Women 0.0162 Calculated, Census Data

Initial population (aged 15-59)

MSM 680,000 [34]

Low-risk population

Men 38,056,434 Calculated, Census Data

Women 37,491,351 Calculated, Census Data

Initial prevalence (aged 15-59), %

MSM 2.1% (1.2-4.7%) Calculated: [35],[34]

Low-risk population

Men 0.03% Calculated: [35], Census

Women 0.02% Calculated: [35], Census

Sexual transmission

Transmission probability per partnership

Heterosexual (female to male)

Asymptomatic HIV 0.01 [49]

Symptomatic HIV 0.02 [49]

AIDS 0.03 [49]

Heterosexual (male to female)

Asymptomatic HIV 0.03 [49]

Symptomatic HIV 0.04 [49]

AIDS 0.08 [49]

Homosexual (male to male)

Asymptomatic HIV 0.04 [50]

Symptomatic HIV 0.05 [50]

AIDS 0.12 [50]

Annual same-sex partners

MSM 5.5 [31]

Annual opposite-sex partners

MSM 0.1 Assumed

Low-risk population

Men 1.1 Calculated: [51]

Women 1.12 Calculated^a

Condom use with same-sex partners, %

MSM 37% [28, 30, 31]

Condom use with opposite-sex partners, %

MSM 20% [52]

General population

Men 20% [51, 52]

Women 20% [51, 52]

Condom effectiveness 0.9 [53]

HIV screening

Proportion of population tested in past 12 months, %

MSM 13% [30]

Low-risk groups 5% Calculated:[54, 55]

Average period that uninfected individuals remain identified after screening, years	1	
Annual probability of symptom-based case finding, %		
HIV	10%	Assumed
AIDS	100%	Assumed
Reduction in sexual partners among identified HIV-positive, %	20%	[56]
Reduction in sexual behavior among patients with HIV-related illness, %	90%	Assumed
ART		
Proportion starting ART at CD4 cell count of 350	75%	Assumed
Annual ART entry rate if CD4 cell count >350	0.05	Assumed
Reduction in sexual infectivity due to ART, %	90%	[57]
Progression Rates		
From asymptomatic to symptomatic	0.152	[17]
From symptomatic to AIDS		

Untreated 0.303 [17]

Treated 0.165 [17]

^aThis number was calculated to balance total contacts amongst women with total sexual contacts amongst all men.

2.3.2. Population entry and maturation

The target population is adults aged 15-59 years old. The rate at which people enter the target group is composed from the background population growth rate and the rate of maturation into adulthood. In the same way, the maturation rate is the sum of the background mortality rate and the rate of aging.

HIV prevalence in risk group i:

$$p_i = \frac{\text{Number of People living with HIV in risk group i}}{\text{Population of risk group i}}$$

Entry Rates:

$$\rho = -\ln\left(1 - \frac{\text{15 years old population}}{\text{15-59 years old population}}\right) + \text{growth rate}$$

Maturation Rates:

$$\mu = -\ln\left(1 - \frac{\text{59 years old population}}{\text{15-59 years old population}}\right) + \text{mortality rate}$$

2.3.3. Estimates of the MSM population

The number of MSM in Japan has been estimated at about 2% of the male population based on probability samples[34]. Although these probability surveys have low response rates and may not be representative, this proportion is consistent with estimates from other Asian countries. This population prevalence was assumed for this study, but because of the difficulty of identifying this population precisely and the likely sensitivity of the model to the size of this high-risk population, the population of MSM was included in sensitivity analysis.

2.3.4. Prevalence estimates

Counts of reported cases of HIV/AIDS by year until 2010 were obtained[35] and the combined count of men living with HIV/AIDS whose HIV was reported as due to “homosexual activity” or “unknown origin” was used to estimate the number of HIV cases among MSM. All other cases were considered to have occurred amongst the low-risk population. All observed values of the number of HIV cases were inflated by a factor of 2.7 to reflect the assumption that only 37% of non-AIDS HIV cases have been identified[28], and to reflect criticisms of a previously-assumed ratio of 5.1[33]. However, the number of unidentified AIDS cases was assumed to be zero at baseline.

Initial values for the population of each risk group and compartment are shown in Table 3, calculated from population size and prevalence information in existing studies.

Table 4: Starting populations by risk group and compartment

Risk Group	Compartment									
	1	2	3	4	5	6	7	8	9	10
MSM	422,466	248,115	4035	2370	1281	188	564	0	0	981
Male	23,541,451	13,825,931	3281	1927	1042	153	459	0	0	2190
Female	23,616,306	13,869,894	2237	1314	710	104	313	0	0	473

2.3.5. Estimating sexual risk behavior

Information on number of partners and condom usage was obtained wherever possible from Japan-specific surveys of sexual behavior. These may not be representative population surveys, having been carried out through postal survey or through interview surveys in only a limited area[51]. All risk behavior variables were included in the sensitivity analysis in order to reflect this. No clear information was available on rates of partnership between MSM and women, so a nominal, small rate was assumed and given a wide possible range in sensitivity analysis. In modeling HIV/AIDS transmission in Asia it is important to model this risk behavior, since different sexual identities and attitudes towards homosexuality, family and public identity mean that many homosexual men are likely to adopt publicly heterosexual identities[58], a phenomenon that has been described specifically in Japan[13]. Little is understood about this behavior or the extent to which it may affect the progress of the HIV epidemic in Japan, and little has been done to model the possible effects of this phenomenon

in Asian populations. Given the very low prevalence of HIV in the heterosexual population in Japan, heterosexual interaction between MSM and wives or occasional female partners may form an important mechanism by which the epidemic can break out from a focused to a generalized epidemic. Given low rates of migration and low incidence of HIV/AIDS among foreigners living in Japan, it is possible that this interaction between high-risk MSM and otherwise low-risk heterosexual women may be the only mechanism by which such an epidemic transition could occur.

2.3.6. Treatment and screening parameters

Treatment guidelines for Japan indicate that people with asymptomatic HIV and a CD4 cell count below 350 cells /mL should be advised to take up HAART in consultation with a doctor [27]. Because no research is available on treatment uptake rates amongst patients with asymptomatic HIV, treatment uptake was assumed to be 75% for patients in this stage, representing effective implementation of the guidelines. Rates of HIV testing are difficult to estimate in Japan, but some reports suggest that 13% of MSM in some community surveys received an HIV test in the past year [30]. Using data on total HIV tests conducted per year [54, 55], and assuming near-complete testing amongst pregnant women, it is possible to estimate the rate of testing amongst non-MSM. The population of people living with HIV was assigned to symptomatic or asymptomatic condition states in proportion to the inverse of the death rate for each condition (Table 4), which put about 75% of all people with HIV in the asymptomatic state. Passive case-finding was assumed to occur at twice the rate of the

testing rate among non-MSM, since no research was available on the nature of case-finding procedures in Japan.

Given that Japan has universal health coverage, it was assumed that 100% of symptomatic AIDS cases would be identified every year. At baseline, all AIDS cases were assumed to be identified and in treatment. This assumption, though likely incorrect, guarantees that the model results give conservative projections for the future.

2.3.7. Multivariate sensitivity analysis

The range of possible values that could be used in the model and their effect on the overall outcomes was estimated using multivariate sensitivity analysis. This sensitivity analysis was implemented using Latin Hypercube Sampling (LHS), in which values were simultaneously sampled from specified distributions for several of the parameters considered most significant in the model. Under this method, the range of possible values for every parameter is divided into sections of equal width, and these sections are sampled without replacement. From within each section a value is sampled randomly, based on the assumed probability distribution, and the resulting set of values is then entered into the model. This enables the full range of possible values for each parameter to be sampled efficiently. The model results were compared to observed numbers of new HIV infections amongst males for a run-in period between 2006 to 2010, using the modeling efficiency parameter EF[59] to assess goodness of fit. One thousand Latin hypercube samples were taken, and the 200 models with

the best EF statistic were retained for comparison with the baseline model. All models were then run for 30 years from 2010.

Table 5 summarizes values used in the multivariate sensitivity analysis. The triangular distribution was used to eliminate any risk of selecting negative values, while retaining the assumption that the value used for the point estimate was the most likely value.

Table 5: Parameters used in sensitivity analysis and their ranges

Variable	Value	Possible Range
Number of MSM	682,800	450,648 – 908,125
Testing rate	10%	2% - 20%
Rate of ART Treatment for CD4 count= 350 mg/mL	75%	50-100%
Number of sexual partners per year		
MSM	5.5	3 – 7
Low-risk men	1.1	0.8 – 2
Female partners of MSM	0.1	0.01 – 0.3
Low-risk women	1.12*	Calculated ^a

Condom use

MSM 0.37 0.2 – 0.5

Low-risk population 0.2 0.1 – 0.3

^aThis value is calculated to balance with the total number of male sexual contacts with women.

2.3.8. Forecast scenarios

Two scenarios were modeled. The base case, modeled to represent the situation in Japan now, is referred to as the *High HIV Risk* scenario. A second counter-factual scenario, based on the assumption of successful but limited behavioral intervention, was also modeled. This is referred to as the *Lower HIV Risk* scenario, and assumes higher rates of condom use amongst MSM, higher rates of HIV testing, and more effective passive case finding in people living with HIV/AIDS.

These scenarios were defined in terms of three key variables: condom use, testing rates and passive case finding rates. These variables were chosen because experience in other countries has shown that these three variables are the easiest to control through behavioral intervention and awareness raising, and the analysis of the basic reproduction number showed that these variables have more influence on the progress of HIV than variables such as treatment entry rates. Interventions that control influential variables should be favoured over those that influence variables that have less influence on the progress of the disease, or those that

attempt to influence variables that are more difficult to change. These three variables can be seen as constructing a three-dimensional subspace of the total (very high) dimensional space of all parameters affecting the model. Within this subspace there is a region of values of these three variables within which the basic reproduction number will be below unity; the edge of this region, which is likely to be an obloid sphere in shape, is a surface in this subspace that defines the combined values of the three variables below which the basic reproduction number will be less than unity. The goal of any public health intervention is then to change the combination of all three variables such that they lie inside this surface, within the region of the subspace corresponding with a basic reproduction number with low enough value to halt the growth of the disease.

The specific parameter values were:

- *High HIV Risk Scenario*: condom use amongst MSM and the low-risk population was 37% and 20% respectively, MSM were screened at a rate of 13% per year, and the passive case-finding rate was 10% per year
- *Lower HIV Risk Scenario*: condom use amongst MSM and the low-risk population was 55% and 30% respectively, MSM were screened at a rate of 35% per year, and the passive case-finding rate was 40% per year

The values for the *Lower HIV Risk* scenario represent a compromise between the current low values observed in Japan and the extremely high awareness of HIV in developed countries such as Australia, which has achieved testing rates of 50-70% and high condom use rates of about 60-80% [60].

2.3.9. Statistical analysis of long-range forecasts

Linear regression analysis was conducted on the 30-year model results to identify the parameters most strongly associated with long-term increases in prevalence. The key model output was prevalence presented as a percentage, but for some risk groups the long-range forecasts produced very low prevalence estimates. To reduce the risk of confidence intervals for predicted values that overlapped zero, the rate ratio (RR) at 30 years was modeled. RR is simply the ratio of the prevalence at 30 years and the baseline prevalence (measured in 2010). These models were conducted separately for the lower and higher awareness scenarios. The models were run separately for the low-risk women and MSM risk groups, since different predictors were expected to be important in each risk group. Low-risk men showed a long-term reduction in HIV prevalence in both scenarios, so models were not constructed for this risk group.

3. RESULTS

3.1. Dynamics of HIV among MSM

In this section I will develop a theoretical explanation of the dynamics of HIV among a single risk group – MSM – based on the use of the next generation method described in section 2.2.

In section 3.1 I derive the form of the new infection generation vector and the transition vector, and their corresponding Jacobian matrices. In section 3.2 I present the formula for the basic reproduction number derived from these objects. In section 3.3 I analyse this quantity numerically, for a general range of conditions and for the parameters assumed in the two projection scenarios described in section 2.3.8. Section 3.4 offers a brief summary of the key dynamic properties of this HIV model.

All the material developed in this section assumes a population with only one risk group (MSM). This is equivalent to the assumption that the sexual activity between MSM and low-risk women is of such low risk as to be essentially ignorable, and that the MSM risk group can be described entirely in terms of interactions within this group. Given the value of the sexual activity numbers assumed in section 2.3.1 this assumption appears defensible, and we will see in chapter 4 that there is very little effect of sexual interaction between MSM and low-risk women; furthermore, in the few models where there is any effective coupling between the risk groups it serves to increase HIV prevalence in low-risk women but shows very little influence on dynamics amongst MSM, suggesting that the reduction of the model to a single risk group for dynamic analysis purposes is defensible.

3.2. Transition vectors and Jacobian matrices

The new infection generation vector \mathbf{f} has eight elements representing the number of new infections generated in each infectious compartment per unit time. Note that this vector does not include elements for the first two compartments of Figure 2, because these are the uninfected cells and never contain any infectious cases due to either the generation of new infections or transition of old infections. In fact all elements of \mathbf{f} except the first are zero, because new infections are only generated in compartment 3 of the model, which corresponds to the first element of \mathbf{f} . Thus \mathbf{f} can be expressed as

$$\mathbf{f} = \left[\sum_{j \geq 3} \lambda_j(t)(X_1 + X_2), 0, 0, 0, 0, 0, 0, 0 \right]$$

For calculation of R_0 we require that the system be at disease-free equilibrium (DFE)[43], which requires that there be no infections in the system, i.e. that $X_i = 0$ for $i \geq 3$, which implies that $X_1 + X_2 = N$, so we can rewrite the expression for \mathbf{f} as

$$\mathbf{f} = \left[\sum_{j \geq 3} \lambda_j N, 0, 0, 0, 0, 0, 0, 0 \right]$$

The transition vector is more complex, because it contains all other transition processes derived from equation 1. Equation 6 shows the eight elements of \mathbf{v} .

$$\mathbf{v}_1 = (\psi_3 + \nu_3 + \theta_3 + \mu_3 + b_3)X_3$$

$$\mathbf{v}_2 = (\theta_4 + \mu_4 + b_4)X_4 - (\psi_3 + \nu_3)X_3$$

$$\mathbf{v}_3 = (\psi_5 + \nu_5 + \theta_5 + \mu_5 + b_5)X_5 - \theta_3X_3$$

$$\mathbf{v}_4 = (\theta_6 + \alpha_6 + \mu_6 + b_6)X_6 - \theta_4(1 - \phi_4)X_4 - (\psi_5 + \nu_5)(1 - \phi_5)X_5$$

$$\mathbf{v}_5 = (\theta_7 + \mu_7 + b_7)X_7 - \alpha_6X_6 - (\psi_5 + \nu_5)\phi_5X_5 - \theta_4\phi_4X_4$$

$$\mathbf{v}_6 = (\mu_8 + b_8 + \nu_8 + \psi_8)X_8 - \theta_5X_5$$

$$\mathbf{v}_7 = (\mu_9 + b_9 + \alpha_9)X_9 - \theta_6X_6 - (\psi_8 + \nu_8)(1 - \phi_8)X_8$$

$$\mathbf{v}_8 = (\mu_{10} + b_{10})X_{10} - \alpha_9X_9 - (\psi_8 + \nu_8)\phi_8X_8 - \theta_7X_7$$

Equation 6: Elements of the transition vector

Note that \mathbf{v} does not need to be calculated at DFE.

In order to calculate the Jacobian matrices \mathbf{F} and \mathbf{V} we need to calculate partial derivatives of every element of the corresponding transition vector with respect to every variable. We consider the partial derivatives of elements of \mathbf{f} first, but before we do so it is necessary to consider the elements of the force of infection, λ , which themselves contain the variables X_i . From equation 2, the force of infection for MSM is (ignoring the contribution of heterosexual women)

$$\sum_{j \geq 3} \lambda_j(t) = \sum_{j \geq 3} \left\{ 1 - N_MSM_j^{n_1^s(1-u_1^s\kappa)} \right\}$$

N_MSM_j given in equation 3 we note that we can rewrite each of the infection probabilities in the form

$$N_MSM_j = 1 - \frac{g(X_j)}{h(X_3, \dots, X_{10})}$$

Then, by application of the quotient rule to the partial derivatives of N_MSM_j , we obtain equation 7 for the k-th partial derivative of the total force of infection.

$$\begin{aligned} & \frac{\partial}{\partial X_k} \lambda \\ &= \frac{\partial}{\partial X_k} \sum_{j \geq 3} \left\{ 1 - \left(1 - \frac{g(X_j)}{h(X_3, \dots, X_{10})} \right)^{n_1^s (1 - u_1^s \kappa)} \right\} \\ &= - \sum_{j \geq 3} \frac{\partial}{\partial X_k} \left(1 - \frac{g(X_j)}{h(X_3, \dots, X_{10})} \right)^{n_1^s (1 - u_1^s \kappa)} \\ &= - \sum_{j \geq 3} \left[n_1^s (1 - u_1^s \kappa) \left(1 - \frac{g(X_j)}{h(X_3, \dots, X_{10})} \right)^{n_1^s (1 - u_1^s \kappa) - 1} \left[- \left(\frac{\frac{\partial g(X_j)}{\partial X_k} h(X_3, \dots, X_{10}) - g(X_j) \frac{\partial h(X_3, \dots, X_{10})}{\partial X_k}}{h(X_3, \dots, X_{10})^2} \right) \right] \right] \end{aligned}$$

Equation 7: Partial derivatives of the total force of infection

This all needs to be calculated at DFE, where we have

$$h(X_3, \dots, X_{10}) = (X_1 + X_2) n_1^s (1 - u_1^s \kappa) = N n_1^s (1 - u_1^s \kappa)$$

and, at DFE,

$$g(X_j) = X_j n_1^s (1 - u_1^s \kappa) \sigma_j = 0 \quad \forall j \geq 3$$

where here σ_j can be taken to mean $\sigma_{m,m}^a$, $\sigma_{m,m}^S$ or $\sigma_{m,m}^{AIDS}$ depending on the value of j

(see Equation 4). We further note that

$$\frac{\partial g(X_j)}{\partial X_k} = 0 \quad \forall j \neq k$$

Inserting these simplified expressions into the equation for $\frac{\partial \lambda}{\partial X_k}$, we obtain

$$\frac{\partial}{\partial X_k} \lambda = \frac{n_1^s (1 - u_1 \kappa) \frac{\partial g(X_k)}{\partial X_k}}{N n_1^s (1 - u_1 \kappa)} = \frac{1}{N} \frac{\partial g(X_k)}{\partial X_k}$$

Furthermore, $\frac{\partial g(X_k)}{\partial X_k}$ can be easily shown to take the following values depending on the

value of k:

$$\frac{\partial g(X_3)}{\partial X_3} = n_1^s (1 - u_1 \kappa) \sigma_{m,m}^a$$

$$\frac{\partial g(X_4)}{\partial X_4} = n_1^s (1 - u_1 \kappa) (1 - r_1) \sigma_{m,m}^a$$

$$\frac{\partial g(X_5)}{\partial X_5} = n_1^s (1 - u_1 \kappa) \sigma_{m,m}^s$$

$$\frac{\partial g(X_6)}{\partial X_6} = n_1^s (1 - u_1 \kappa) (1 - r_1) \sigma_{m,m}^s$$

$$\frac{\partial g(X_7)}{\partial X_7} = n_1^s (1 - u_1 \kappa) (1 - r_1) (1 - r_2) \sigma_{m,m}^s$$

$$\frac{\partial g(X_8)}{\partial X_8} = n_1^s (1 - u_1 \kappa) \sigma_{m,m}^{AIDS}$$

$$\frac{\partial g(X_9)}{\partial X_9} = n_1^s (1 - u_1 \kappa) (1 - r_1') \sigma_{m,m}^{AIDS}$$

$$\frac{\partial g(X_{10})}{\partial X_{10}} = n_1^s (1 - u_1 \kappa) (1 - r_1') (1 - r_2) \sigma_{m,m}^{AIDS}$$

Inserting these simplified versions of $g(X_j)$ and $h(X_3, \dots, X_{10})$ into the expression for $\frac{\partial \lambda}{\partial X_k}$

, we obtain expressions for the force-of-infection components of the Jacobian shown in

Equation 8.

$$\frac{\partial}{\partial X_3} \lambda = \frac{n_1^s(1-u_1\kappa)\sigma_{m,m}^a}{N}$$

$$\frac{\partial}{\partial X_4} \lambda = \frac{n_1^s(1-u_1\kappa)(1-r_1)\sigma_{m,m}^a}{N}$$

$$\frac{\partial}{\partial X_5} \lambda = \frac{n_1^s(1-u_1\kappa)\sigma_{m,m}^S}{N}$$

$$\frac{\partial}{\partial X_6} \lambda = \frac{n_1^s(1-u_1\kappa)(1-r_1)\sigma_{m,m}^S}{N}$$

$$\frac{\partial}{\partial X_7} \lambda = \frac{n_1^s(1-u_1\kappa)(1-r_1)(1-r_2)\sigma_{m,m}^S}{N}$$

$$\frac{\partial}{\partial X_8} \lambda = \frac{n_1^s(1-u_1\kappa)\sigma_{m,m}^{AIDS}}{N}$$

$$\frac{\partial}{\partial X_9} \lambda = \frac{n_1^s(1-u_1\kappa)(1-r_1')\sigma_{m,m}^{AIDS}}{N}$$

$$\frac{\partial}{\partial X_{10}} \lambda = \frac{n_1^s(1-u_1\kappa)(1-r_1')(1-r_2)\sigma_{m,m}^{AIDS}}{N}$$

Equation 8: Force of infection components of the infection Jacobian matrix

We will denote these components of the force-of-infection elements of the Jacobian by β_k ,

where $k = 3, \dots, 10$. Then we can write

$$\frac{\partial}{\partial X_k} \lambda = \frac{\beta_k}{N}$$

at DFE.

From these terms, we can generate the Jacobian matrix associated with \mathbf{f} as

$$\mathbf{F}_{ij} = \left[\frac{\partial f_i}{\partial X_j} \right] = \begin{cases} \beta_i & \text{if } j = 1 \\ 0 & \text{if } j > 1 \end{cases}$$

i.e. \mathbf{F} is a matrix with the first row non-zero and composed of the set of β_k , and all other rows zero. Written explicitly, we have

$$\mathbf{F} = \begin{bmatrix} \beta_1 & \beta_2 & \beta_3 & \beta_4 & \beta_5 & \beta_6 & \beta_7 & \beta_8 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}$$

with β_k written as above.

We can now turn our attention to the calculation of \mathbf{v} , which is simpler because the vector does not contain the force of infection terms, and thus we do not need to apply the quotient rule in partial differentiation. By partial differentiation of each element of \mathbf{v} with respect to the variables X_j we obtain the matrix shown in equation 9.

$$\mathbf{V} = \begin{bmatrix} \psi_3 + \nu_3 + \theta_3 + \mu_3 + b_3 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ -(\psi_3 + \mu_3) & \theta_4 + \mu_4 + b_4 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ -\theta_3 & 0 & \psi_5 + \nu_5 + \theta_5 + \mu_5 + b_5 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & -\theta_4(1 - \phi_4) & -(\psi_5 + \nu_5)(1 - \phi_5) & \theta_6 + \alpha_6 + \mu_6 + b_6 & 0 & 0 & 0 & 0 & 0 \\ 0 & -\theta_4\phi_4 & -(\psi_5 + \nu_5)\phi_5 & -\alpha_6 & \theta_7 + \mu_7 + b_7 & 0 & 0 & 0 & 0 \\ 0 & 0 & -\theta_5 & 0 & 0 & \psi_8 + \mu_8 + b_8 + \nu_8 & 0 & 0 & 0 \\ 0 & 0 & 0 & -\theta_6 & 0 & -(\psi_8 + \nu_8)(1 - \phi_8) & \mu_9 + b_9 + \alpha_9 & 0 & 0 \\ 0 & 0 & 0 & 0 & -\theta_7 & -(\psi_8 + \nu_8)\phi_8 & -\alpha_9 & \mu_{10} + b_{10} & 0 \end{bmatrix}$$

Equation 9: Transition Jacobian matrix

We can then combine \mathbf{F} and \mathbf{V}^{-1} and calculate R_0 as their maximum eigenvalue.

Conducting this calculation in Mathematica, we obtain the value of R_0 shown in equation 10.

Equation 10 shows that, as expected, the basic reproduction number is linear in the number of partners and condom use rates (the various β_j values established in equation 8), and shows a non-linear relationship with other parameters, which measure testing, disease transition, treatment entry and mortality rates.

$$\begin{aligned}
R_0 = & \frac{\beta_1}{b_3 + \theta_3 + \mu_3 + \nu_3 + \psi_3} + \frac{\beta_2 (v_3 + \psi_3)}{(b_4 + \theta_4 + \mu_4) (b_3 + \theta_3 + \mu_3 + \nu_3 + \psi_3)} + \\
& \frac{\beta_3 \theta_3}{(b_3 + \theta_3 + \mu_3 + \nu_3 + \psi_3) (b_5 + \theta_5 + \mu_5 + \nu_5 + \psi_5)} + \\
& \frac{\beta_4 \theta_3 (1 - \phi_5) (v_5 + \psi_5)}{(b_6 + \alpha_6 + \theta_6 + \mu_6) (b_3 + \theta_3 + \mu_3 + \nu_3 + \psi_3) (b_5 + \theta_5 + \mu_5 + \nu_5 + \psi_5)} + \\
& \frac{\beta_4 \theta_4 (1 - \phi_4) (v_3 + \psi_3)}{(b_4 + \theta_4 + \mu_4) (b_6 + \alpha_6 + \theta_6 + \mu_6) (b_3 + \theta_3 + \mu_3 + \nu_3 + \psi_3)} + \\
& \frac{\beta_5 \alpha_6 \theta_3 (1 - \phi_5) (v_5 + \psi_5)}{(b_6 + \alpha_6 + \theta_6 + \mu_6) (b_7 + \theta_7 + \mu_7) (b_3 + \theta_3 + \mu_3 + \nu_3 + \psi_3) (b_5 + \theta_5 + \mu_5 + \nu_5 + \psi_5)} + \\
& \frac{\beta_5 \alpha_6 \theta_4 (1 - \phi_4) (v_3 + \psi_3)}{(b_4 + \theta_4 + \mu_4) (b_6 + \alpha_6 + \theta_6 + \mu_6) (b_7 + \theta_7 + \mu_7) (b_3 + \theta_3 + \mu_3 + \nu_3 + \psi_3)} + \\
& \frac{\beta_5 \theta_3 \phi_5 (v_5 + \psi_5)}{(b_7 + \theta_7 + \mu_7) (b_3 + \theta_3 + \mu_3 + \nu_3 + \psi_3) (b_5 + \theta_5 + \mu_5 + \nu_5 + \psi_5)} + \\
& \frac{\beta_5 \theta_4 \phi_4 (v_3 + \psi_3)}{(b_4 + \theta_4 + \mu_4) (b_7 + \theta_7 + \mu_7) (b_3 + \theta_3 + \mu_3 + \nu_3 + \psi_3)} + \\
& \frac{\beta_6 \theta_5 \theta_3}{(b_3 + \theta_3 + \mu_3 + \nu_3 + \psi_3) (b_5 + \theta_5 + \mu_5 + \nu_5 + \psi_5) (b_8 + \mu_8 + v_8 + \psi_8)} + \\
& \frac{\beta_7 \theta_5 \theta_3 (1 - \phi_8) (v_8 + \psi_8)}{(b_9 + \alpha_9 + \mu_9) (b_3 + \theta_3 + \mu_3 + \nu_3 + \psi_3) (b_5 + \theta_5 + \mu_5 + \nu_5 + \psi_5) (b_8 + \mu_8 + v_8 + \psi_8)} - \\
& \frac{\beta_7 \theta_6 \theta_3 (1 - \phi_5) (v_5 + \psi_5)}{(b_6 + \alpha_6 + \theta_6 + \mu_6) (b_9 + \alpha_9 + \mu_9) (b_3 + \theta_3 + \mu_3 + \nu_3 + \psi_3) (b_5 + \theta_5 + \mu_5 + \nu_5 + \psi_5)} - \\
& \frac{\beta_7 \theta_6 \theta_4 (1 - \phi_4) (v_3 + \psi_3)}{(b_4 + \theta_4 + \mu_4) (b_6 + \alpha_6 + \theta_6 + \mu_6) (b_9 + \alpha_9 + \mu_9) (b_3 + \theta_3 + \mu_3 + \nu_3 + \psi_3)} - \\
& \frac{\beta_8 \alpha_9 \theta_5 \theta_3 (1 - \phi_8)}{(b_9 + \alpha_9 + \mu_9) (b_{10} + \mu_{10}) (b_3 + \theta_3 + \mu_3 + \nu_3 + \psi_3) (b_5 + \theta_5 + \mu_5 + \nu_5 + \psi_5) (b_8 + \mu_8 + v_8 + \psi_8)} - \\
& \frac{\beta_8 \theta_6 \alpha_9 \theta_3 (1 - \phi_5) (v_5 + \psi_5)}{(b_6 + \alpha_6 + \theta_6 + \mu_6) (b_9 + \alpha_9 + \mu_9) (b_{10} + \mu_{10}) (b_3 + \theta_3 + \mu_3 + \nu_3 + \psi_3) (b_5 + \theta_5 + \mu_5 + \nu_5 + \psi_5)} - \\
& \frac{\beta_8 \theta_6 \alpha_9 \theta_4 (1 - \phi_4) (v_3 + \psi_3)}{(b_4 + \theta_4 + \mu_4) (b_6 + \alpha_6 + \theta_6 + \mu_6) (b_9 + \alpha_9 + \mu_9) (b_{10} + \mu_{10}) (b_3 + \theta_3 + \mu_3 + \nu_3 + \psi_3)} + \\
& \frac{\beta_8 \theta_5 \theta_3 \phi_8 (v_8 + \psi_8)}{(b_{10} + \mu_{10}) (b_3 + \theta_3 + \mu_3 + \nu_3 + \psi_3) (b_5 + \theta_5 + \mu_5 + \nu_5 + \psi_5) (b_8 + \mu_8 + v_8 + \psi_8)} + \\
& \frac{\beta_8 \theta_7 \alpha_6 \theta_3 (1 - \phi_5) (v_5 + \psi_5)}{(b_6 + \alpha_6 + \theta_6 + \mu_6) (b_7 + \theta_7 + \mu_7) (b_{10} + \mu_{10}) (b_3 + \theta_3 + \mu_3 + \nu_3 + \psi_3) (b_5 + \theta_5 + \mu_5 + \nu_5 + \psi_5)} + \\
& \frac{\beta_8 \theta_7 \alpha_6 \theta_4 (1 - \phi_4) (v_3 + \psi_3)}{(b_4 + \theta_4 + \mu_4) (b_6 + \alpha_6 + \theta_6 + \mu_6) (b_7 + \theta_7 + \mu_7) (b_{10} + \mu_{10}) (b_3 + \theta_3 + \mu_3 + \nu_3 + \psi_3)} + \\
& \frac{\beta_8 \theta_7 \theta_3 \phi_5 (v_5 + \psi_5)}{(b_7 + \theta_7 + \mu_7) (b_{10} + \mu_{10}) (b_3 + \theta_3 + \mu_3 + \nu_3 + \psi_3) (b_5 + \theta_5 + \mu_5 + \nu_5 + \psi_5)} + \\
& \frac{\beta_8 \theta_7 \theta_4 \phi_4 (v_3 + \psi_3)}{(b_4 + \theta_4 + \mu_4) (b_7 + \theta_7 + \mu_7) (b_{10} + \mu_{10}) (b_3 + \theta_3 + \mu_3 + \nu_3 + \psi_3)}
\end{aligned}$$

Equation 10: The basic reproduction number

3.3. Dynamic properties of the basic reproduction number

The dynamic properties of the mathematical model can be explored through examination of the effect of different parameters on the basic reproduction number as described by equation 10. First, I will plot the relationship between R_0 and key testing and treatment variables across a range of behavioral factors. Specifically, I will plot separate charts of the relationship between R_0 and the testing and treatment entry rates at condom use rates of 20%, 40%, 60% and 80%; I will then plot these charts again for annual average number of partners of 1.2, 2.5, 5.5, 7.5 and 10. Subsequently, I will explore the effect of testing, treatment entry and condom use rates in the setting of the two specific scenarios described in section 2.3.9 (the *High HIV Risk* and *Lower HIV Risk* scenarios).

3.3.1. Effect of testing rates on epidemic progress

In order to explore the effect of testing rates on epidemic progress, I calculated values of R_0 using assumed parameter values from the *High HIV Risk* scenario, across a range of levels of behavioral risk. These ranges of behavioral risk were expressed in terms of condom use rates and partner numbers, and the basic reproduction number was plotted varying these values separately. Where the condom use rates were varied, partner numbers were set at the base case assumption in the *High HIV Risk* scenario (5.5 partners per year); where the partner numbers were varied, condom use rates were also set at the base case assumption in the *High HIV Risk* scenario (condoms used in 37% of all sexual encounters).

Figure 3 shows the relationship between R_0 and testing rates across the full range of testing rates and at different levels of risk behavior. It shows a non-linear relationship between testing rates and R_0 , with the largest effect of increases in testing rates being observed in the lower half of the range. Although not explored quantitatively, it appears from Figure 3 that the inflexion point – beyond which the benefits of increased testing rates begin to diminish – shifts to the right as the level of risk behavior (measured as lower condom rates or higher partner numbers) increases, suggesting that in high-risk populations scale up of testing has benefits across a wider range of testing rates than is the case in low-risk groups

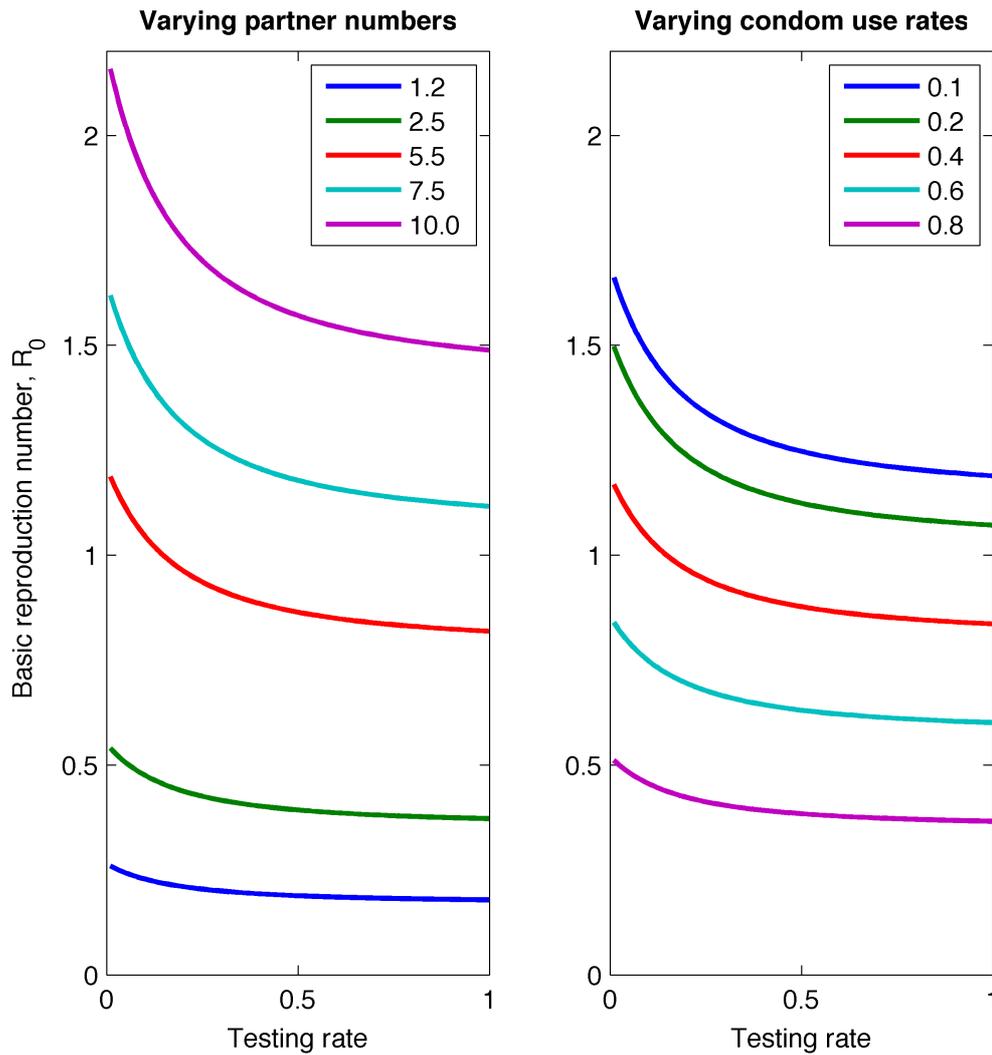


Figure 3: Relationship between basic reproduction number and testing rate

The presence of inflexion points in the curves in Figure 3 also suggests that scaling up of testing rates has diminishing returns beyond a certain point. For example, for the scenario with 37% condom use and 5.5 partners (Figure 3, left panel, red line) the relationship between R_0 and the testing rate becomes approximately linear beyond a testing rate of about 0.4, while before this point R_0 is decreasing rapidly.

Figure 3 also shows that very high testing rates do not necessarily guarantee elimination of HIV where risk behavior is high – that is, the basic reproduction number does not drop below unity at any testing rate. For example, for the scenario with 20% condom use and 5.5 partners per year (Figure 3, right panel, green line) the value of R_0 is above 1 across the entire range of testing rates. This suggests that the interaction between testing and treatment entry and risk behavior includes a threshold effect: at very high levels of risk behavior, testing and treatment strategies alone will be insufficient to control the epidemic, and some level of successful behavioral intervention will be essential.

Finally, Figure 3 shows that for partner numbers of about 5.5 per year, and condom use rates of 37% (Figure 3, left panel, red line), epidemic elimination may be possible even with relatively low rates of testing of about 0.1 – 0.2. The High HIV Risk scenario functions in this range of risk behavior (5.5 partners per year and 37% condom usage), so it is possible that containment of the epidemic can be achieved with modest scale up of testing.

3.3.2. Effect of treatment entry rates on epidemic progress

The effect of testing on the HIV epidemic is dependent on the rate at which tested subjects enter into treatment. Current Japanese HIV treatment guidelines do not recommend automatic entry into treatment for people with CD4 cell count greater than 350 cells/ μ L, and the official health insurance policy does not allow reimbursement for treatment of asymptomatic HIV; however, HIV is defined as a disability in Japan and people living with HIV can obtain a

special disability support card that entitles them to free treatment, and consistent with the guidelines many HIV specialists recommend ART treatment. For these reasons the baseline assumption in the mathematical model is that 75% of newly-identified HIV cases with CD4 cell counts of 350 cells/ μ L or below proceed immediately to treatment. The remaining 25% are assumed to enter treatment at a rate of 0.05 per year. It is important to understand the relationship between treatment entry and epidemic dynamics amongst those newly-identified HIV cases who do not proceed directly to treatment, since low treatment entry rates will reduce the effectiveness of testing strategies.

Figure 4 shows the relationship between treatment entry rates among identified HIV-positive individuals who did not proceed directly to treatment, and R_0 at different levels of risk behavior for the parameters fixed in the base case model of the *High HIV Risk* scenario. The left hand panel shows the effect of treatment entry rates across a range of partner numbers and the right hand panel shows the effect across different levels of condom use. The relationship between treatment entry rates and R_0 is essentially flat, with very little effect of treatment entry rates on the dimensions of the epidemic. This reflects the dynamics of rapid direct entry into treatment amongst newly-identified symptomatic individuals, and low rates of HIV testing in the community. With very few people being tested annually and the majority of newly-identified symptomatic cases entering treatment immediately the primary driver of new infections is unidentified asymptomatic HIV positive individuals. Increasing treatment entry rates amongst newly-identified individuals who do not immediately enter treatment will have little effect, since such an approach will only affect a very small number

of high-risk individuals. It is much more important to raise testing rates amongst the entire community at risk than to improve treatment entry rates in a small number of identified asymptomatic individuals.

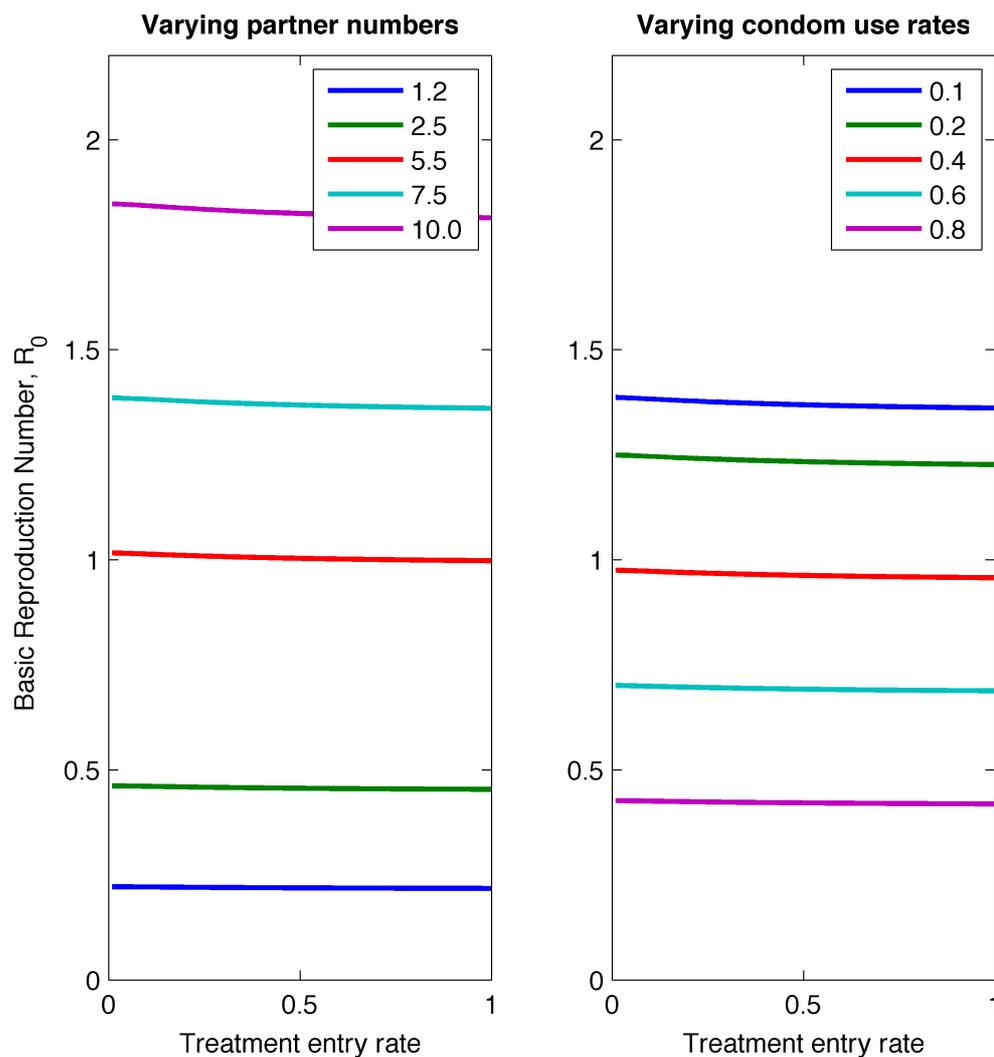


Figure 4: Relationship between treatment entry rates and basic reproduction number

In the context of the current Japanese HIV epidemic, reform of treatment guidelines will make little difference until testing rates can be improved.

3.3.3. Comparison of testing rates in two scenarios

In this study I modeled two different HIV awareness scenarios representing different levels of HIV awareness. One of these scenarios was developed based on available data for the current situation in Japan; the other represents a modest improvement in awareness amongst Japanese MSM towards a level similar to – but not intended to be equivalent to – the level of awareness in MSM communities in Australia and the USA that have effectively contained HIV. These scenarios primarily differ on rates of screening, passive case-finding and condom use, and assume no difference in treatment entry rates or partner numbers. The two scenarios are described below.

Figure 5 shows the effect of testing rates on the basic reproduction number in each of these scenarios.

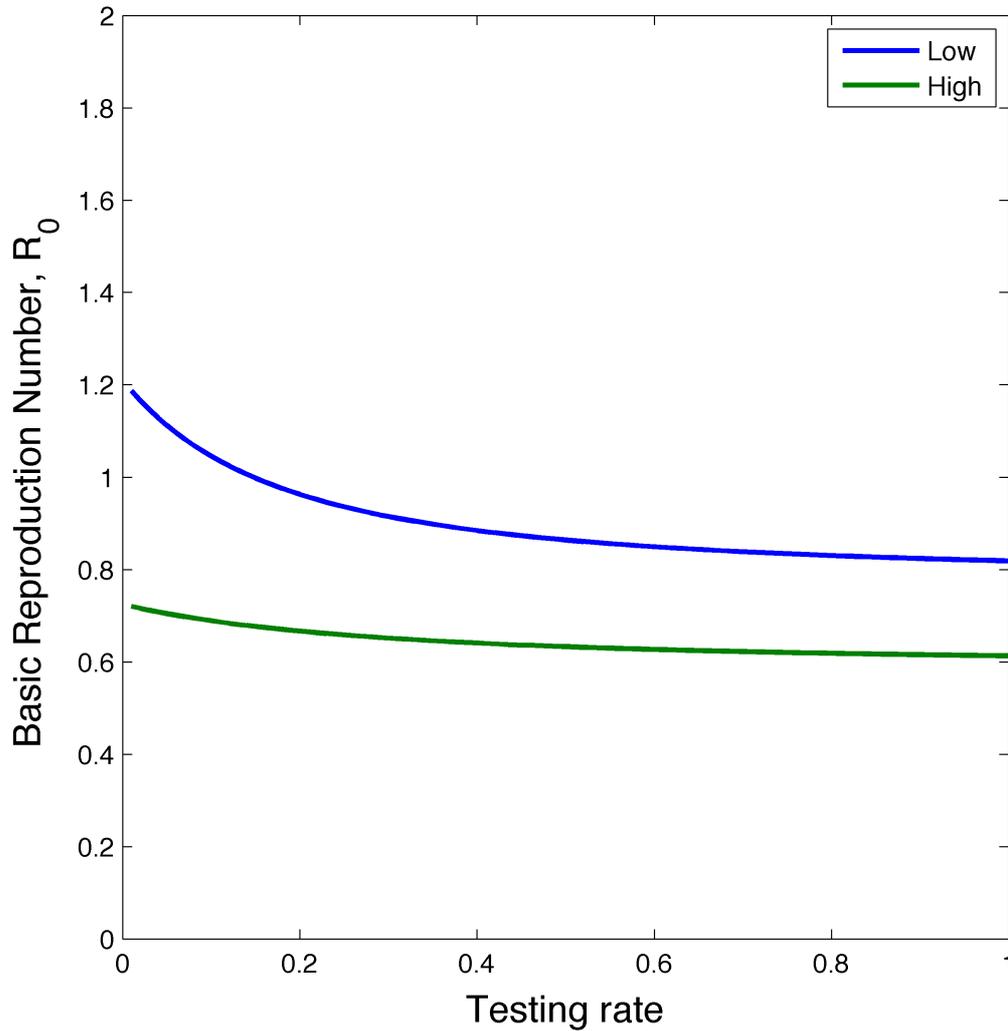


Figure 5: Effect of testing rates in two scenarios

In the low awareness scenario increases in testing rates have a large effect on the basic reproduction number, and increasing these rates beyond 0.2 (20% of all MSM receiving testing every year) will likely force the value of R_0 below unity, ensuring the epidemic can be contained or eliminated. Thus, without any significant reductions in personal risk behavior, the HIV epidemic amongst MSM may be contained by an approximate doubling of current testing rates.

3.4. Summary: HIV dynamics and testing policy in Japan

In this section I have developed an analytical expression for the basic reproduction number of HIV based on the mathematical model developed in section 2. Closed form expressions of R_0 are rare in the literature due to the complexity of the mathematical models required to describe the epidemic in the era of test-and-treat strategies, and to the best of my knowledge this is the first attempt to explore R_0 analytically using the next generation method for a model of this size and complexity.

Analysis of the dynamics of the mathematical model based on the relationship between key parameters and R_0 suggests that the HIV epidemic amongst MSM is fragile and close to the edge of the parameter space required to maintain epidemic expansion. Small increases in testing rates, or small reductions in risk behavior, may be sufficient to drive R_0 below 1, suggesting containment and eventual elimination of the epidemic.

While evidence from overseas suggests that achieving behavioral change is difficult and may not be sufficient to control the HIV epidemic even amongst MSM[25], improving testing rates is a feasible intervention in most MSM communities[61]. This is likely to be particularly successful in Japan, where a large proportion of newly-identified cases have already progressed to low CD4 cell counts and are likely to be immediately referred to treatment under current guidelines, although such an intervention would be even more successful if the guidelines were to be updated to ensure that all people living with HIV/AIDS receive immediate treatment for prevention regardless of CD4 cell count.

Analysis of epidemic dynamics based on the basic reproduction number have their limitations, however. The expression for R_0 developed here depends on strong assumptions about disease free equilibrium that obviously do not apply in a rapidly expanding epidemic such as Japan is currently experiencing. HIV is also known to be spread through high-risk behavior in small sub-populations, and estimates of the basic reproduction number from models that assume homogeneous mixing (as this model does) are by necessity limited[62]. Analysis of this model in a setting with heterogeneous mixing might lead to a different range of values of the basic reproduction number[63]. These constraints do not change the fundamental relationship between parameters driving the model, however, and only affect specific estimates of the values of parameters required to achieve the threshold value of the basic reproduction number (i.e. $R_0 = 1$) required for disease elimination[64]. Thus the broad conclusions about relationships between key disease parameters drawn in this chapter should hold even where the constraints on analysis of R_0 prevent precise analytical estimates of the threshold values required for epidemic containment in Japan. To reflect these limitations on analysis of R_0 using the methods described here, I have avoided giving precise estimates of threshold values of key parameters necessary to eliminate HIV, and have given only heuristic descriptions of the effects of the variables and their inter-relationships.

3.5. HIV Projections: The High HIV Risk Scenario

The model was run for 30 years under the baseline assumptions given for the *High HIV Risk* scenario, starting in 2010. The range of prevalence values for each of the three risk groups, and the histogram of HIV prevalence among MSM at year 30, is plotted in Figure 6. The values for the base case model are shown in red.

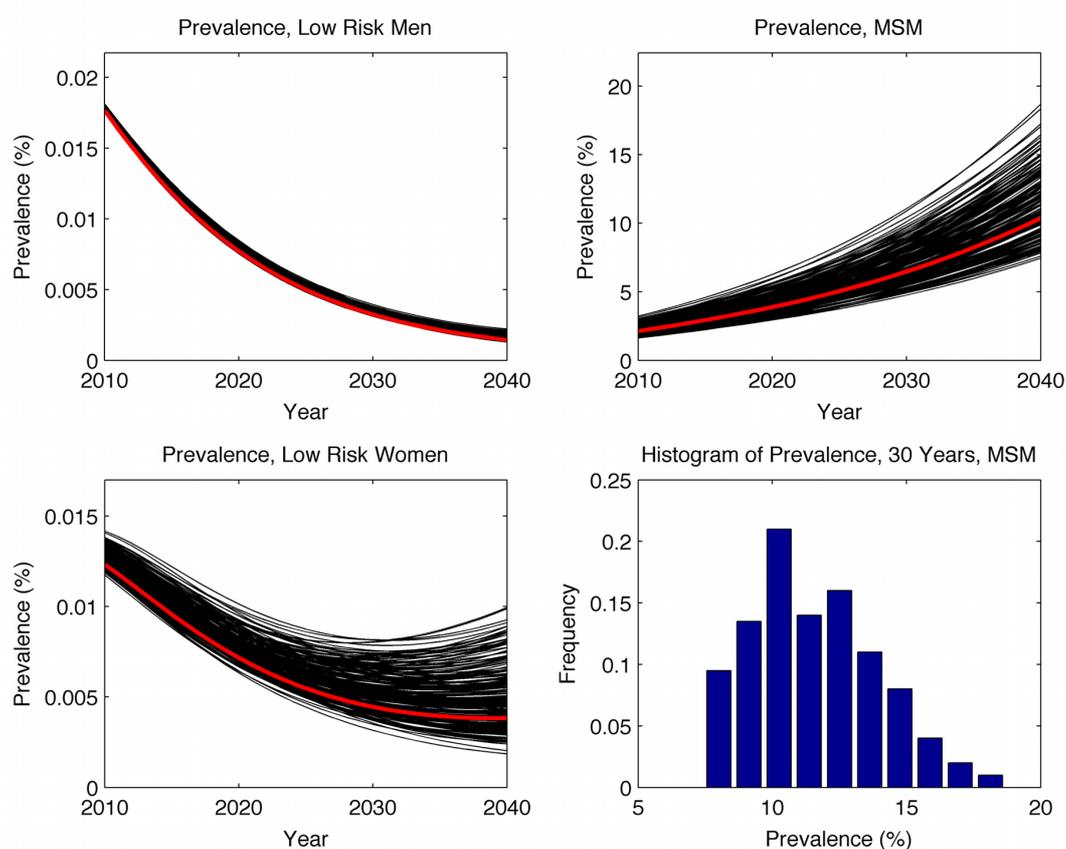


Figure 6: 30 year projections of HIV/AIDS prevalence among three risk groups and histogram of prevalence among MSM at 30 year endpoint, Low Awareness Scenario

From a baseline value of 2.1%, prevalence among MSM increases over 30 years to 10.4% (sensitivity range: 7.4—18.7%). Prevalence decreases amongst low-risk men from 0.018% to

0.0014% (sensitivity range: 0.0013—0.0022%) and amongst women from 0.012% to 0.0038% (sensitivity range: 0.0019—0.0099%). The number of MSM was varied in sensitivity analysis to allow for uncertainty in the definition of this risk group, while counts of HIV cases remained fixed, with the consequence that initial prevalence rates entered into the model also varied, and it is clear from Figure 6 that the final prevalence over 30 years among MSM is highly dependent on the initial prevalence. This suggests that long-term prevalence amongst MSM in Japan is highly dependent on trends in prevalence over the next few years, and also implies that accurate knowledge of HIV prevalence in Japan is essential for predicting long-term trends of the epidemic.

For low-risk women the model bifurcates, and two model outcomes are possible. The lower range of values in Figure 6 corresponds with epidemic extinction, and shows HIV prevalence among low-risk women declining in a similar way to low-risk men. However, the higher range of values corresponds to epidemic growth, though still at a very low absolute level. Inspection of the relationship between parameter values and end-state prevalence in low-risk women suggests that the main driver of this bifurcation appears to be the rate of heterosexual contact with MSM. This relationship is illustrated in Figure 7, which shows the rate ratio of HIV prevalence at 30 years for each model run compared to the HIV prevalence for the model with the lowest heterosexual/MSM contact rate, plotted against the rate of annual sexual contacts between low-risk women and MSM for each model. There is a clear linear relationship between this contact rate and the rate ratio, which indicates that the primary driver of HIV prevalence in low-risk women at 30 years is the heterosexual/MSM contact

rate. This effect is particularly striking because it appears to occur independently of the HIV prevalence in low-risk men. This bifurcation also occurs in only some of the model runs, and is delayed until 15 or 20 years into the simulations, indicating that it only occurs after HIV prevalence amongst MSM reaches higher values. This suggests that in the absence of significant in-migration of HIV-positive cases to Japan, the only risk of HIV transmission spreading beyond MSM lies in contact between MSM and heterosexual women.

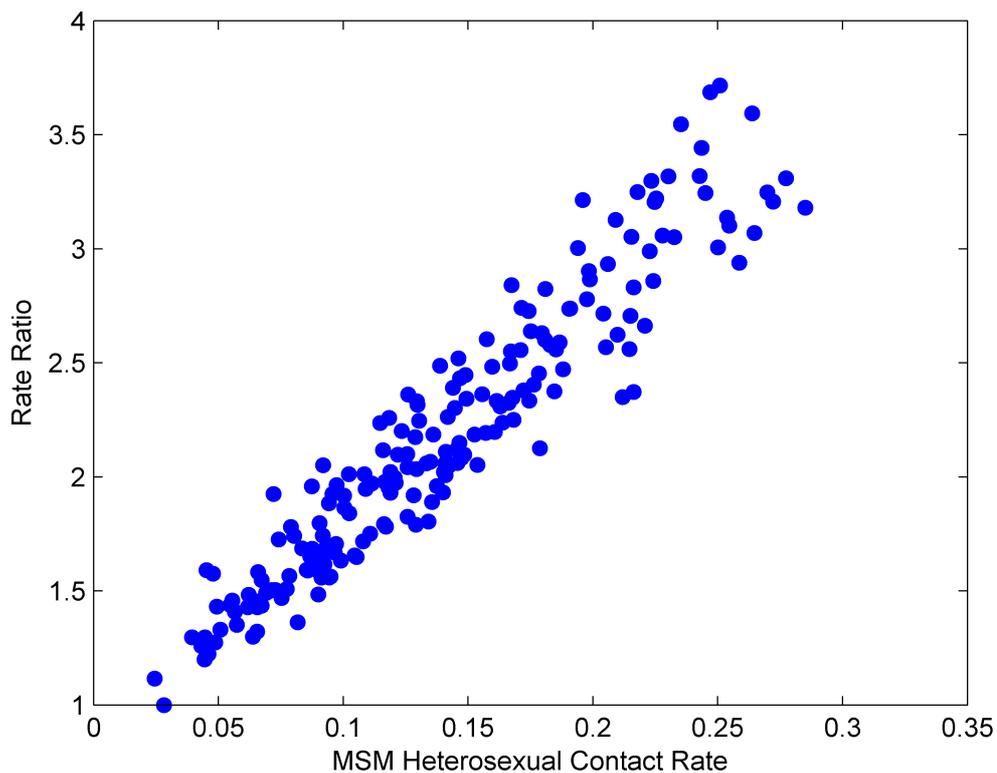


Figure 7: Ratio of HIV prevalence at 30 years in all model runs against the model with the lowest MSM heterosexual contact rate, plotted against MSM heterosexual contact rate

3.5.1. Statistical analysis of predictors of long-range prevalence

Figure 8 shows the relationship between HIV prevalence at 30 years and HIV prevalence at baseline amongst MSM and low-risk women. The prevalence of HIV amongst MSM at 30 years is highly dependent on the prevalence at baseline (year 2010), showing a strong linear relationship, while amongst low-risk women this relationship is weaker. This reflects the strong dependence of the HIV epidemic among low-risk women on sexual interaction with MSM.

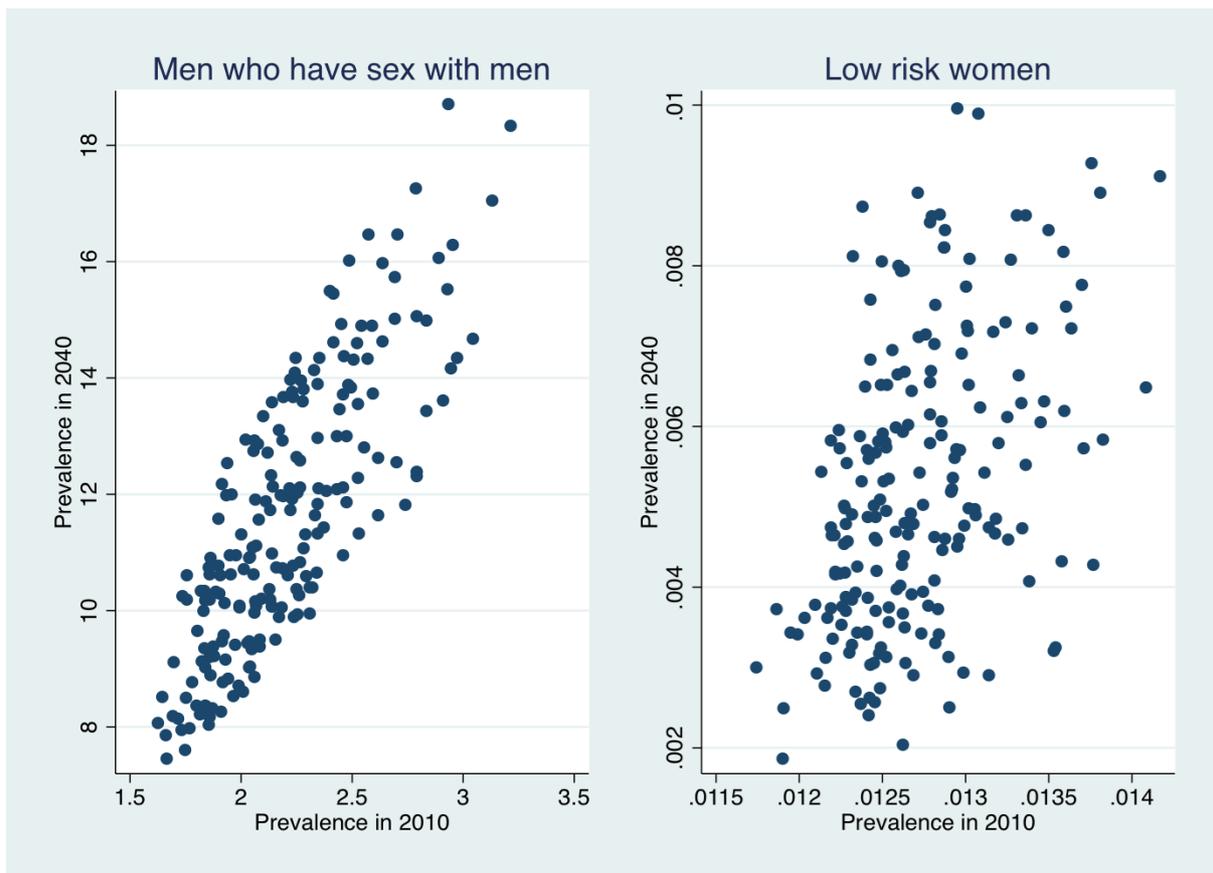


Figure 8: Relationship between prevalence in 2040 and prevalence in year 2010, low HIV-awareness scenario

Figure 9 shows the relationship between HIV prevalence at 30 years and the testing rate for MSM and low-risk women. This figure shows that there is no clear relationship between prevalence at 30 years and the proportion of people receiving tests from in each year. This is likely due to the confounding effect of condom use, number of partners and initial prevalence. In order to explore the relationship between the model parameters and long-term prevalence it is necessary to construct a linear regression model.

A linear regression model of prevalence at 30 years with baseline prevalence as a predictor showed very poor residuals, indicating that additional non-linear terms would be necessary to properly estimate the relationship between all parameters and final prevalence using such a model. However, a linear regression of the rate ratio (prevalence at 2040 divided by prevalence at 2010) showed good residuals, that were both normally distributed and showed no pattern over the range of predicted values. For this reason, regression models in this chapter are based on the model of rate ratios rather than raw prevalences.

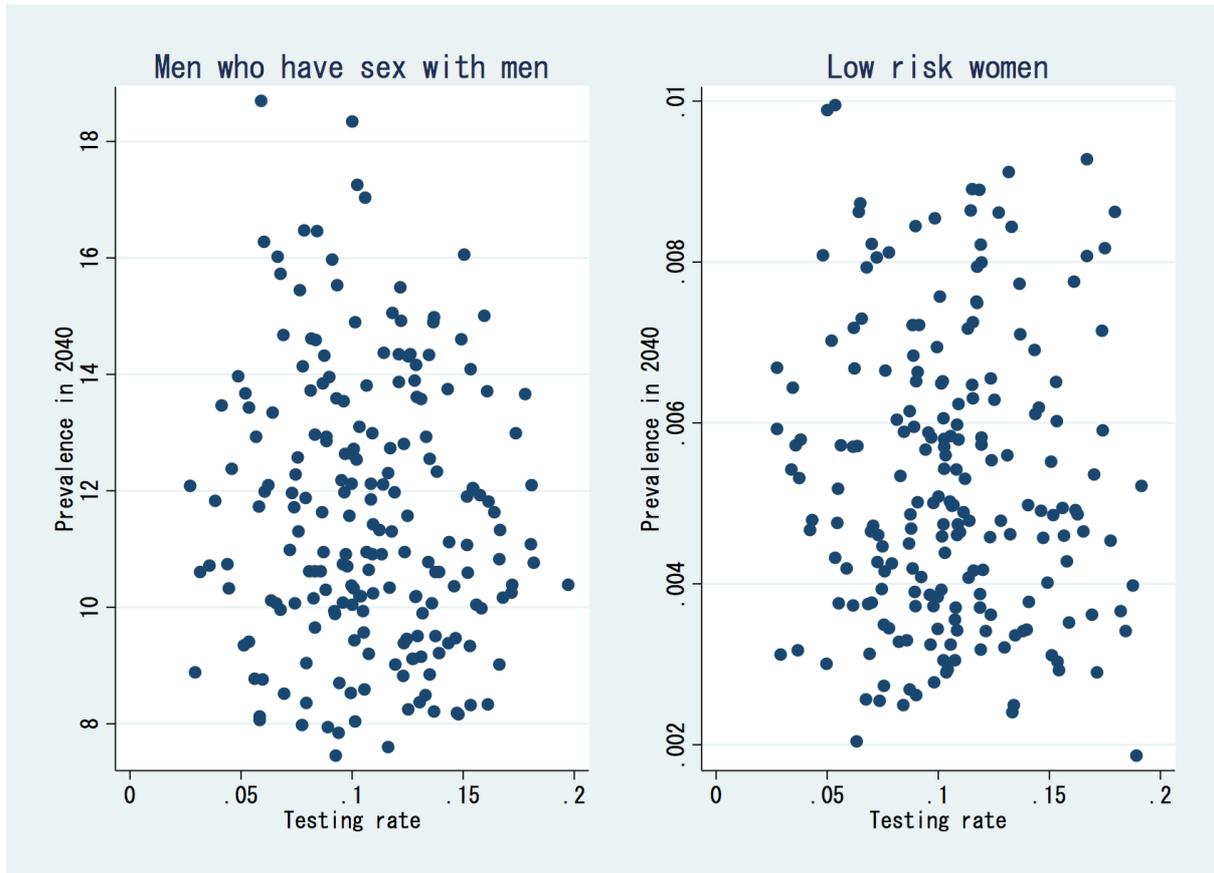


Figure 9: Relationship between prevalence at 30 years and testing rates, low HIV-awareness scenario

Table 6 shows the results of linear regression of the rate ratio of prevalence at 30 years against baseline parameters, for MSM and low-risk women. The model for MSM had an R-squared statistic of 0.89, indicating that the model explained 89% of the variance in the rate ratio. The model for low-risk women had a similar R-squared statistic of 0.90, explaining 90% of the variance in the rate ratio.

This regression model shows that in the absence of significant test-and-treatment interventions, the long-term prevalence of HIV in MSM is highly dependent on behavioral variables, most especially the number of partners. In the lower-awareness scenario, every

percentage point increase in the proportion of MSM who receive testing annually reduces the long-term rate ratio of HIV by 0.05, but even very small increases in the number of partners, or decreases in condom usage, will swamp the effect of case-finding. This indicates that when testing-based interventions are limited, the epidemic is essentially uncontained and its growth determined only by contact behavior.

Table 6: Regression model of rate ratio against baseline parameters, low-awareness scenario

Parameter	Effect on RR	95% confidence interval	P value
Men who have sex with men			
Testing rate	-0.054	-0.062 to -0.046	<0.001
Number of partners	4.321	4.108 to 4.541	<0.001
Condom use proportion	-0.316	-0.330 to -0.297	<0.001
Low-risk women			
Testing rate	-0.002	-0.003 to -0.000	0.03
Number of partners	-0.030	-0.055 to -0.005	0.02
Condom use proportion	-0.003	-0.004 to -0.001	<0.001
Number of MSM contacts	2.089	1.992 to 2.187	<0.001

This effect is not observed to the same extent among low-risk women, where condom use has a limited effect on the progress of the disease. The main driver of the long-term rate ratio in this risk group is the number of sexual contacts with MSM. The contradictory effect of increasing the number of partners reflects the fact that the total number of heterosexual partner numbers for women is balanced against that for low-risk men, and so a higher number of heterosexual partners necessarily constrains the number of MSM sexual contacts. Note that although heterosexual behavior has limited effect on the RR in this risk group, the number of sexual contacts varies amongst a much smaller range, and testing can still serve a role in reducing the long-term prevalence regardless of initial prevalence. Compared to MSM, amongst low-risk women the benefit of increasing testing is greater relative to behavioral interventions, because their risk behavior is generally assumed to be low and so interventions reducing risk behavior will have limited benefits.

3.6. HIV Projections: The Lower HIV Risk scenario

3.6.1. HIV prevalence projections

Prevalence estimates from the *Lower HIV Risk* scenario, with sensitivity analysis ranges and a histogram of prevalence among MSM at year 30, are shown in Figure 10. The main model for this scenario is plotted in red. The prevalence at 30 years among MSM is 1.1%, with a sensitivity range between 0.2% and 4.1%. Among low risk men prevalence declines to

0.0013% (sensitivity range: 0.0012%—0.0016%) and among low risk women prevalence declines to 0.0015% (sensitivity range: 0.0012%—0.0033%). In the *Lower HIV Risk* scenario the epidemic tends to extinction in both low-risk women and low-risk men, and appears to be slowly declining amongst MSM for the majority of cases. A small number of models show epidemic growth amongst MSM but this result does not appear common in this sensitivity analysis. There is no evidence that heterosexual contacts between MSM and women are sufficiently infective as to produce epidemic growth amongst women.

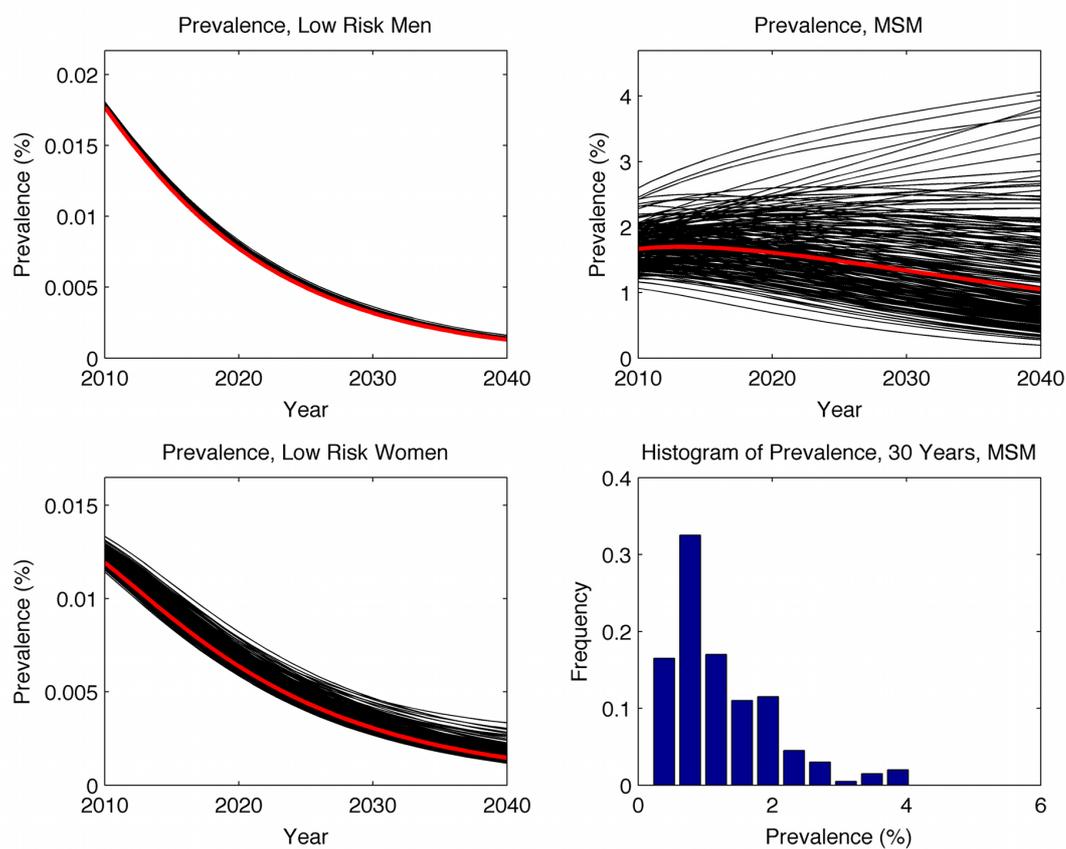


Figure 10: 30 year projections of HIV/AIDS prevalence among three risk groups and histogram of prevalence among MSM at 30 year endpoint, Higher Awareness Scenario

The *Lower HIV Risk* scenario differs from the *High HIV Risk* scenario only in that it models a small increase in condom use rates amongst MSM and a significant improvement in passive case-finding and voluntary testing rates amongst MSM. These changes would be sufficient to reduce the prevalence of HIV among MSM to approximately 1% over 30 years. Epidemic growth is rare in the *Lower HIV Risk* scenario.

3.6.2. Statistical analysis of predictors of long-term prevalence

Figure 11 shows the relationship between prevalence at 30 years and baseline prevalence for MSM and low-risk women. The relationship between baseline prevalence and long-term prevalence in MSM is less pronounced than in the lower awareness scenario, while it is more obvious amongst low risk women. There are also some outliers amongst MSM, in which the final prevalence is much higher than might be expected given the initial prevalence; this is possibly consistent with a non-linear relationship between final and initial prevalence, and reflects the small number of break-away epidemics in the high HIV-awareness scenario (Figure 6). For all initial prevalence values, however, there are some final prevalence values that are lower than the starting value, indicating that in the high HIV-awareness scenario it is always possible to control long-term prevalence through control of health-system and behavioral factors; this is not the case for any of the model runs in the low HIV-awareness scenario.

The relationship between initial and final prevalence is also more pronounced among low-risk women in the high HIV-awareness scenario. This reflects the reduced effect of sexual contact with MSM in this scenario. In the absence of contact with this high-risk group,

low risk women's risk of HIV is primarily determined by the prevalence of HIV in the heterosexual community.

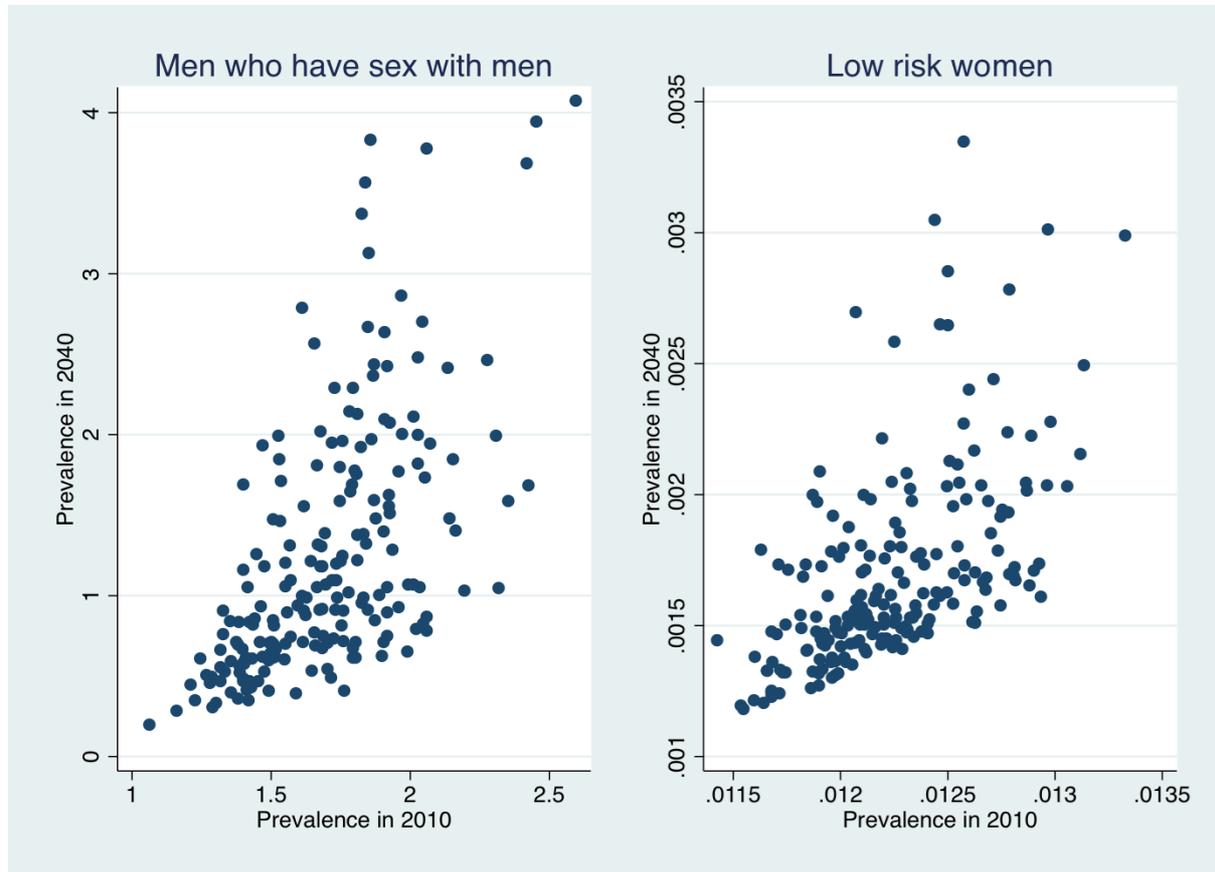


Figure 11: Relationship between prevalence in 2040 and prevalence in year 2010, high HIV-awareness scenario

Figure 12 shows the relationship between prevalence at 30 years and testing rates for MSM and low-risk women. Despite the higher levels of testing seen in this scenario, the relationship between testing and final year prevalence remains unclear and confounded by other variables in these charts.

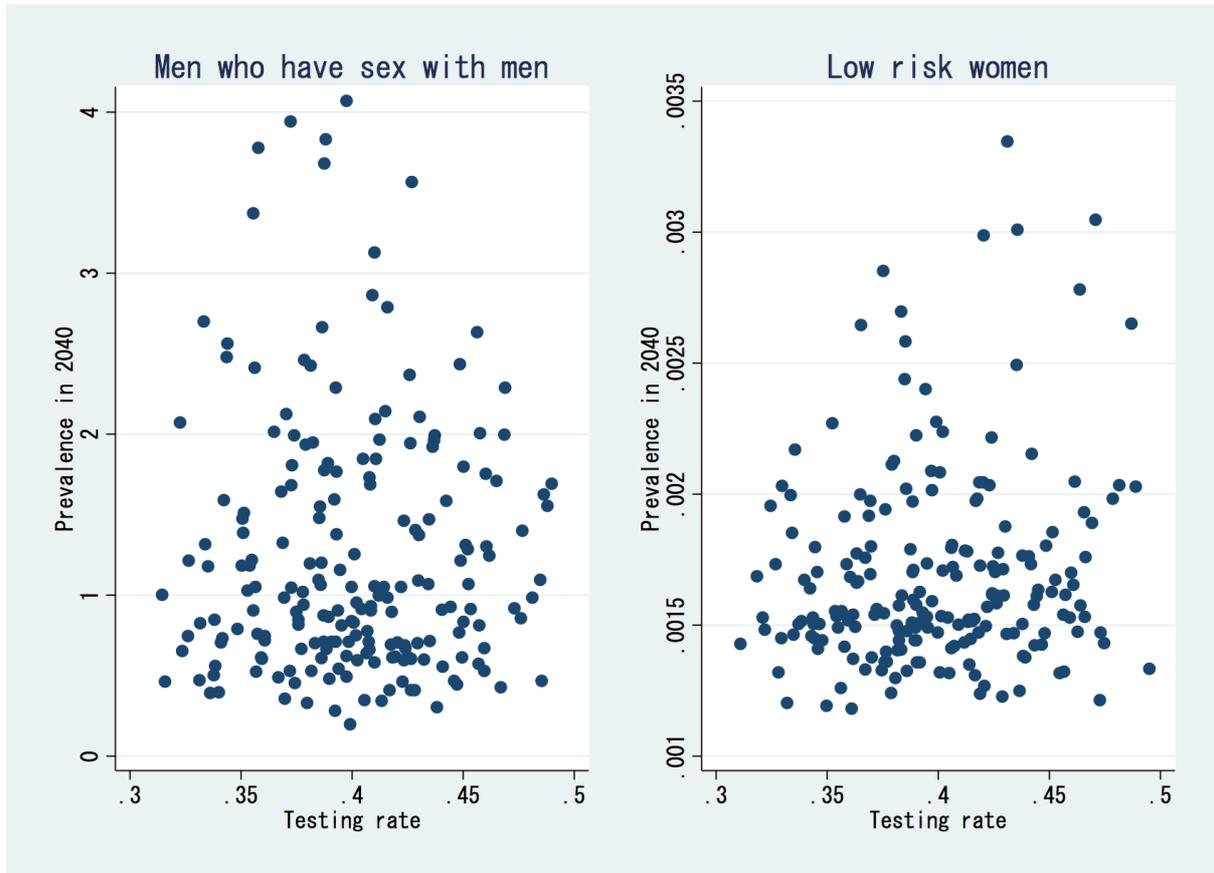


Figure 12: Relationship between prevalence at 30 years and testing rates, high HIV-awareness scenario

Table 7 shows the results of linear regression analyzing the relationship between baseline parameters and the rate ratio of prevalences at 30 years, in MSM and low-risk women. The R-squared statistic for the model among MSM is 0.87, similar to that of the low HIV-awareness model. The R-squared statistic in the model among low risk women is 0.49, indicating just under half of the variance in rate ratios is explained by this model. This lower R-squared value reflects the downward trend in prevalence amongst all model runs for low risk women in the high awareness scenario, and suggests that there are threshold levels of one or more of the model parameters above which all models behave similarly. In this scenario a

much larger proportion of all variance arises from random variation in starting values rather than from the particular effects of model parameters.

This effect can also be seen from the regression coefficients presented in Table 7. Although testing is no longer significantly associated with a reduction in rate ratio at 30 years, the effect of number of partners and condom use is significantly reduced. This is most noticeable in MSM, with the effect on the rate ratio of the number of partners reduced by a factor of 10. The effect of increasing condom use is also reduced by a factor of 10 compared to the low-awareness scenario. A similar relative reduction in the importance of MSM contacts and condom use is observed among low-risk women.

Table 7: Regression model of rate ratio against baseline parameters, high-awareness scenario

Parameter	Effect on RR	95% confidence interval	P value
Men who have sex with men			
Testing rate	-0.002	-0.007 to 0.002	0.3
Number of partners	0.423	0.393 to 0.453	<0.001
Condom use proportion	-0.041	-0.045 to -0.038	<0.001
Low-risk women			
Testing rate	-0.001	-0.001 to 0.001	0.1
Number of partners	0.020	0.009 to 0.031	<0.001
Condom use proportion	-0.001	-0.002 to -0.001	<0.001
Number of MSM contacts	0.285	0.239 to 0.330	<0.001

In the context of higher rates of testing and condom use, a very different relative balance of effectiveness exists in the model outputs. This indicates a non-linear effect of test-and-treat policies on the progress of the epidemic. Where attention to knowing HIV serostatus is

limited, the epidemic is free to spread rapidly amongst those taking higher risks. However, when test-and-treat policies are scaled up, the effect of risky behavior is significantly limited. This ten-fold reduction in the effect of increases in behavioral risk has been achieved by an average three-fold increase in screening behavior and a four-fold increase in passive-case finding rates. The resulting testing and case-finding rates are modest compared to the goals of new screening policies in, for example, the USA. Even small increases in biomedical responses to the epidemic can significantly reduce the dangers of risky behavior. This has significant implications for the control of HIV, since behavioral change is difficult to achieve in many contexts, and suggests that the epidemic can be controlled with smaller reductions in high-risk behavior when case-finding rates – and subsequent treatment entry rates – are higher. This relationship is also supported by the findings in chapter 3, that the largest gains in control of the epidemic arise with increases in testing rates in the range of testing rates (0.1 – 0.2) below those assumed in the *Lower HIV Risk* scenario.

3.7. Summary: The future of HIV in Japan

Long-term projections of HIV prevalence in Japan show that under current conditions the epidemic is likely to continue to grow rapidly, showing approximately quadratic growth over the next 30 years. Final prevalence at 30 years in this scenario is heavily dependent on initial prevalence, suggesting that better understanding of the prevalence of HIV in the present is crucial for long-term predictions of its spread. This finding also suggests that delays in

implementing changes to risk and testing behavior will have long-term ramifications for total prevalence, and that expansion of interventions is urgently needed.

Long-term projections were also run under an assumed *Lower HIV Risk* scenario in which voluntary testing and passive case finding rates, and condom use proportions are increased modestly. This model shows almost no risk of epidemic growth over the next 30 years in any of the three risk groups, and a large proportion of model runs are driven towards elimination over this period. This suggests that even moderate improvements in awareness and reductions in risk behavior will have a huge long-term benefit.

Both of these models support the findings of chapter 3, that the HIV epidemic in Japan is near the edge of the parameter space required to maintain growth and that modest but urgent changes in risk behavior – that could be implemented through an expansion of testing and treatment strategies – would be sufficient to control the epidemic in the near future.

4. DISCUSSION

In this study I developed a deterministic, compartmental model of the HIV epidemic in Japan which incorporates testing, treatment, and differential treatment entry rates suitable for replicating the current Japanese treatment context. I derived a closed-form expression for the basic reproduction number, and explored the influence of different behavioral and intervention parameters on the progress of the epidemic by numerical analysis of this expression for the basic reproduction number. I then ran a pair of numerical simulations, with uncertainty estimates, to reflect the situation in Japan as it is best understood at present, and the effect of a moderate improvement in HIV awareness, expressed through testing and treatment.

This is the first model to project the prevalence of HIV in Japan in the era of testing and treatment, and the first time that an analytical expression for the basic reproduction number has been derived for a model of this kind. It is also the first attempt to model the effect of a comprehensive behavioral- and treatment-based intervention on the progress of HIV over the next 30 years. The findings of this model are important for policy-makers and planners concerned with the future progress of the HIV epidemic in Japan, and should act as a warning about the risks facing MSM in Japan over the near future.

4.1.1. Findings of the Models

Under the baseline assumptions given in Table 3, HIV prevalence amongst MSM will increase over the next 30 years from the current low level of about 2% to over 10%, while prevalence amongst the low-risk population will decline slowly over the same period. The epidemic will become increasingly entrenched among the MSM community, though there is evidence that the progress of the epidemic amongst low risk women depends strongly on the degree of overlap between the heterosexual and homosexual communities. This finding of rapidly growing HIV prevalence is consistent with the findings of earlier mathematical models of HIV in Japan [33, 65], though earlier models presented a more rapid and earlier rise than shown in this model[66], probably because they were implemented before the HIV transmission prevention properties of HAART were well understood. The difference in model design and different assumptions about the proportion of HIV cases that are identified make comparison of the final numbers in the different models impossible, but the general findings of all the models are similar. Projections from this model show a slower epidemic growth path than predicted in some earlier models, but the same general trend, and the results of this model offer no basis for complacency. They show that after 10 years of interventions the basic dynamics of the HIV epidemic in Japan is largely unchanged from that predicted in earlier models.

Understanding the sexual risk patterns of bisexual and homosexual men in Japan and rates of sexual contact with women is thus essential to predicting the long-term patterns of HIV in women. The results of the *Lower HIV Risk* scenario suggest that with consistent and realistic

increases in rates of safe sex, limited intervention to improve voluntary testing rates amongst MSM, supported by better training and engagement of physicians who provide health services to MSM, the epidemic could remain stable and HIV prevalence could even decline over the long term.

I also analysed the relationship between key disease parameters and the basic reproduction number, using the next generation method to generate the basic reproduction number. This method was applied to a simplified single risk group population in order to ensure mathematical tractability, but the results from this analysis supported the findings of the models run empirically using estimated prevalence and population data from Japan. The findings of this analysis suggest that small increases in testing rates alone would be sufficient to contain the HIV epidemic in the short term, and probably to eliminate the disease over the long term. This analysis also found that the rate of entry into treatment among those testing positive had little effect on the pattern of HIV infection, with increases in testing coverage much more important than improvements in rates of entry into treatment. This finding is similar to recent modeling work conducted in Australia[67], which used simulations from a very similar model to estimate the effect of these two parameters on future numbers of cases. These simulations showed that increasing the proportion of MSM entering testing had a significant effect on numbers of new cases, but that this effect was non-linear and the biggest gains in reducing new infections were achieved in early scale-up – a finding that I have replicated with my analysis of the basic reproduction number. This Australian model also showed through simulation that increasing the number of people entering treatment after

diagnosis had a limited effect on transmission, and that increasing the coverage rate was the key to reducing new infections. My analysis also expanded on these simulation findings, by showing that in settings with very high levels of risk behavior it is impossible to contain the epidemic through changing testing alone, but the parameters obtained from literature review for the Japanese setting are well below the thresholds for an uncontrollable epidemic identified in this analysis. Thus, it appears that through moderate increases in testing alone the HIV epidemic can be contained, and this finding is supported through both the mathematical analysis of chapter 3 and the empirical analysis of chapter 4.

4.2. Limitations

Although the simulation outcomes of a deterministic compartmental model and a stochastic model might be expected to be the same, I chose to use a deterministic compartmental model for this analysis for two main reasons. Deterministic compartmental models offer an analytically tractable method for estimating the basic reproduction number as a function of the key parameters in the model[43], while a stochastic model only allows numerical estimation of this property based on fitting the outcomes of the model to a dataset through maximum likelihood[68]. For the purposes of this analysis a closed-form solution to the basic reproduction number was important, and more open to analysis than a solution based on numerical estimation.

Although a deterministic model enables analysis of the basic reproduction number, it does have limitations. Given the limited research available on MSM and HIV in Japan, in particular due to the lack of population-representative prevalence data[69], this model is clearly highly dependent on assumptions about key variables. The possible effect of these assumptions was tested using sensitivity analysis, and showed a wide range of possible outcomes. However, qualitatively, the majority of all possible outcomes from sensitivity analysis on this data indicate that the epidemic will continue to grow amongst MSM without rapid and sustained intervention. Furthermore, the goals of this intervention, in terms of improvements in condom use and voluntary testing rates, though high relative to current Japanese practice[30], are not unreasonable when compared to the behavior of MSM in other countries with mature but contained epidemics among MSM, such as Australia[60]. Sensitivity analysis of the Lower HIV Risk scenario suggests that the epidemic can be contained in Japan if safer sex and testing behavior can be increased to lie within a range of achievable values, suggesting that although the specific parameters defining the future of the epidemic in Japan are not clearly understood, the broad findings of this study about the results of improved HIV awareness in MSM are robust.

Another limitation of this study is the simplicity of the model, which especially affects the conclusions of the mathematical analysis in chapter 3. This model did not allow for heterogeneity between high-risk and low-risk MSM, even though such heterogeneity has been shown to be an important driver of epidemic structure for HIV[63]. This lack of heterogeneity prevented the calculation of specific values or ranges of values of testing,

condom use or partner numbers that would be required to eliminate or contain HIV in this population, but does not restrict the general findings about the structure of the epidemic's response to testing rates, the relative importance of different parameters in driving the epidemic, or the existence of likely ranges of risk behavior in which testing alone cannot effectively contain the epidemic. This simple model structure was chosen primarily because sufficient information is simply not available in the Japanese context to support a more complex model of heterogeneity. Even were such data available, the inclusion of testing and treatment compartments in this model made it complex and vulnerable to inaccuracies through assumptions about parameter values, and to further extend this complexity into heterogeneity and differential risk structures would likely further complicate the modeling process and introduce significant risk of mis-estimation and loss of precision. Given the limited data available in the Japanese context, simplicity was deemed essential to produce interpretable model results.

4.3. Recommendations

4.3.1. Implications for Intervention Planning

This study finds that HIV prevalence will continue to increase unless sustained changes in MSM risk behavior can be achieved. Current behavioral interventions amongst MSM in Japan are clearly insufficient, and more intensive, sustained and widespread interventions are necessary. Interventions should move from occasional community-specific events to an

ongoing, organized campaign of awareness-raising and behavioral intervention. These programs should be consistent with international best practice interventions, which act simultaneously to improve MSM awareness of the risks of HIV infection, increase rates of testing, and establish a community context in which safer sex is considered the norm[70]. Such campaigns in other countries have required coordinated actions, including the establishment of specialist health centres, promotion of access to testing and treatment, legal changes, public health activism by gay rights organizations, intervention in sex venues and bars, and the widespread availability and promotion of condoms. Experience in these countries has shown that interventions of this kind can be implemented quickly and effectively at a community level where the political will exists[71]. Given the high rates of testing and treatment these campaigns require [17, 18], it is unlikely that biomedical interventions based on testing and treatment will be effective based on current low rates of testing in Japan. HIV testing needs to be easily available, free and anonymous and all MSM should be encouraged to obtain testing regularly. Given that even extensive community, political and public health activism in places like Sydney and San Francisco has failed to see the elimination of this disease in MSM[72, 73], the continued fragmentary, low-level and unsustainable activities being conducted in Japan will be unlikely to have any significant impact on the spread of the disease. Japan's public health community and MSM activists need to work together for a more open, forthright, active and sustained campaign to prevent HIV amongst MSM. Furthermore, Japan's public health infrastructure readily supports a program to rapidly scale up testing in this community, by leveraging existing community organizations in areas with large numbers of MSM, and utilizing the existing network of

public health centres (*hokensho*). Historical experience in developed nations indicates that such an expansion of testing and treatment is as much a question of political will and community awareness as availability of resources[74].

Unfortunately, however, the Japanese context is very different from the early 1980s, when countries like Australia and the USA were forced to confront a rapid increase in HIV. The spread of HIV in Japan occurs against a backdrop of effective treatment for HIV, which has seen HIV transformed from a fatal infectious disease to a chronic illness, with very different management strategies and cultural attitudes. In countries that successfully contained HIV amongst MSM in the 1980s, young MSM have become complacent about the risks of HIV[75], and this complacency is greatest amongst those most at risk[76].

Risk-compensation has been identified as a possible risk to the effectiveness of test-and-treat strategies[77], and optimism about the benefits of treatment may encourage risk behavior[78].

Countries such as Australia, with mature epidemics and well-established campaigns of behavioral intervention and testing, have recently seen a plateau in the number of new infections[79], indicating that even well-established and internationally recognized campaigns are having increasing difficulty making further gains. These countries saw rapid changes in the early 1980s, when HIV was easily characterized as a direct and immediate health threat, but in the era of HAART it may be very difficult for a country like Japan to implement effective interventions in a population with widespread treatment optimism and very different attitudes towards sexual risk than the cohort of MSM who first experienced HIV in the 1980s.

4.3.2. Implications for Surveillance and Research

Available data on new cases of HIV suggests that the prevalence of HIV is increasing rapidly in men, especially MSM, and that the epidemic is effectively uncontrolled in MSM[1, 35].

However, very little information is available about the key parameters that drive the progress of HIV/AIDS in the Japanese population. Although efforts have been made to estimate the number of MSM, there appears to be very little information that can be used to identify key risk behavior.

Information about rates of testing and treatment in existing populations is essential not only for predicting the future progress of the HIV epidemic, but also for judging the potential effectiveness and cost-effectiveness of more refined interventions, such as pre- or post-exposure prophylaxis, the relative effectiveness of which depends heavily on the number of infections occurring during the primary infection period, and the rate at which new infections can be identified relative to existing infections[67]. Furthermore, guidelines for the effective implementation of pre-exposure prophylaxis depend on a detailed understanding of risk and testing behavior in the population[80] – information that is not readily available in Japan. Proper planning of Japan's HIV prevention strategy thus depends heavily on better understanding of these factors.

With no evidence that HIV can be controlled under the assumptions given about the current knowledge and behavior of the MSM community, the future research agenda for HIV

researchers in Japan needs to focus on well-designed, regular and widespread assessments of the sexual behavior of MSM, which requires:

1. Sentinel surveillance, similar to that conducted in Australia[81] that extends on the current notification system[82] to enable identification of the sexual identity of those receiving HIV testing and the reasons for this testing, including attempts to estimate the proportion of new infections detected every year. Incidence databases established amongst doctors providing services to MSM, and/or at health clinics providing anonymous testing, would enable a better understanding of incidence rates and levels of detection of new infection, as well as monitoring disease progression, reducing overlap of case notifications, and enable more accurate assessment of the duration of unidentified asymptomatic infection in cohorts of PLWH
2. Rapid assessment surveys amongst at-risk groups – particularly MSM – including prevalence testing by finger-prick sampling, and basic risk behavior, similar to those implemented at Needle/Syringe Programs in Australia[83]
3. Research amongst doctors who work with MSM, for sentinel surveillance and understanding MSM's voluntary testing and ART treatment behavior
4. Establishment of a clinical cohort of PLWH, in order to better understand disease progression and survival rates in the Japanese context

4.4. Conclusion

The HIV epidemic at its current stage in Japan is vulnerable to even small changes in sexual behavior, and could potentially be brought under control – even amongst MSM – within a generation if these small behavioral changes, and improvements in active and passive case-finding, were to occur soon. However, there is a significant risk that the epidemic will grow out of control in the near future. HIV researchers need to focus on identifying the key behavioral factors driving the epidemic, to facilitate change in these behaviors. Health workers and HIV activists need to develop new, innovative methods to significantly improve HIV testing rates, make them more accessible to the highest risk MSM, and significantly raise the awareness of the importance of HIV testing in the MSM community. By enacting such a coherent, concerted and sustained campaign, it is possible to ensure that the disease does not get a solid foothold in Japan.

5. References

1. UNGASS. *Japan - 2010 Country Progress Report*. Geneva: UNAIDS; 2010.
2. Koerner J, Ichikawa S. The Epidemiology of HIV/AIDS and Gay Men's Community-Based Responses in Japan. *Intersections: Gender and Sexuality in Asia and the Pacific* 2011,**26**:5.
3. National Centre in HIV Epidemiology and Clinical Research. *HIV/AIDS and related diseases in Australia 1997*. Sydney: National Centre in HIV Epidemiology and Clinical Research; 1997.
4. Wand H, Wilson D, Yan P, Gonnermann A, McDonald A, Kaldor J, *et al*. Characterizing trends in HIV infection among men who have sex with men in Australia by birth cohorts: results from a modified back-projection method. *Journal of the International AIDS Society* 2009,**12**:19.
5. Centres for Disease Control. Advancing HIV Prevention: New Strategies for a Changing Epidemic - United States, 2003. *Morbidity and Mortality Weekly Report* 2003,**52**:329-332.
6. Miyazaki M, Naemura M. Epidemiological characteristics on human immunodeficiency virus infection and acquired immunodeficiency syndrome in Japan. *International Journal of STD & AIDS* 1994,**5**:273-278.
7. Yamamoto T, Itoh S, Nihon Kokusai Kōryū Sentā, Sekai Kikin Shien Nihon Iinkai. *Fighting a rising tide: The response to AIDS in East Asia*. Tokyo: Japan Center for International Exchange; 2006.
8. Miyazaki M, Naemura M. HIV/AIDS surveillance system and reported cases of human immunodeficiency virus infection and acquired immunodeficiency syndrome in Japan (1983-1993). *Asia Pacific Journal of Public Health* 1995,**8**:162-166.
9. Cullinane J. Tainted blood and vengeful spirits: The legacy of Japan's yakugai eizu (AIDS) trial. *Culture Medicine and Psychiatry* 2005,**29**:5-31.

10. Cullinane J. The domestication of AIDS: Stigma, gender, and the body politic in Japan. *Medical Anthropology* 2007,**26**:255-292.
11. Sawazaki Y. HIV/AIDS Epidemic and Overview of MSM Programs in Japan. *The Asian Administrators Meeting on HIV/AIDS*. Tokyo, Japan; 2010.
12. Ichikawa S. [The HIV/AIDS epidemic among MSM and gay NGO activities in Japan]. *Nihon Rinsho* 2010,**68**:546-550.
13. Sawazaki Y. Gay Men and HIV in Japan. *Journal of Acquired Immune Deficiency Syndromes* 1997,**14**:S47-S50.
14. Japanese Committee on Trends in AIDS. Classification of Reported HIV/AIDS Infections in 2012. Tokyo: AIDS Prevention and Information Network; 2013.
15. Takano M, Okada M, Oka S, Wagatsuma Y. The relationship between HIV testing and CD4 counts at HIV diagnosis among newly diagnosed HIV-1 patients in Japan. *International Journal of STD & AIDS* 2012,**23**:262-266.
16. Long EF, Brandeau ML, Owens DK. The cost-effectiveness and population outcomes of expanded HIV screening and antiretroviral treatment in the United States. *Annals of Internal Medicine* 2010,**153**:778-789.
17. Granich RM, Gilks CF, Dye C, De Cock KM, Williams BG. Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model. *Lancet* 2009,**373**:48-57.
18. Kretzschmar MEE, van der Loeff MFS, Coutinho RA. Elimination of HIV by test and treat: a phantom of wishful thinking? *AIDS* 2012,**26**:247-248.
19. Hontelez JA, Lurie MN, Barnighausen T, Bakker R, Baltussen R, Tanser F, *et al.* Elimination of HIV in South Africa through expanded access to antiretroviral therapy: a model comparison study. *PLoS Medicine* 2013,**10**:e1001534.
20. Ford N, Koetsawang S. A pragmatic intervention to promote condom use by female sex workers in Thailand. *Bulletin of the World Health Organization* 1999,**77**:888-894.
21. Rojanapithayakorn W, Hanenberg R. The 100% condom program in Thailand. *AIDS* 1996,**10**:1-7.
22. National Centre in HIV Epidemiology and Clinical Research. Return on Investment 2: Evaluating the Cost Effectiveness of Needle Syringe Programs in Australia. Canberra, Australia: Department of Health and Ageing; 2009.

23. Labarga P. New DHHS guidelines recommend antiretroviral therapy to all HIV-infected persons. *AIDS Reviews* 2012,**14**:154.
24. Bayer R, Oppenheimer GM. Routine HIV testing, public health, and the USPSTF--an end to the debate. *The New England Journal of Medicine* 2013,**368**:881-884.
25. Sullivan PS, Carballo-Diequez A, Coates T, Goodreau SM, McGowan I, Sanders EJ, *et al.* Successes and challenges of HIV prevention in men who have sex with men. *Lancet* 2012,**380**:388-399.
26. Coates TJ, Richter L, Caceres C. Behavioural strategies to reduce HIV transmission: how to make them work better. *Lancet* 2008,**372**:669-684.
27. Koibuchi T, Odawara T, Shirasaka T. Anti-HIV Treatment Guidelines. Osaka: Osaka National Hospital; 2011.
28. Kaneko N, Utsumi M, Ichikawa S. HIV Testing Behavior and HIV Preventive Behavior among Gay and Bisexual Men in Tokai Area. *Journal of the Japan Society of Nursing Research* 2007,**30**:37-43.
29. Ichikawa S. The HIV/AIDS epidemic among MSM in Japan: Background and gay NGO response. *Asian Administrators Meeting on HIV/AIDS*. Tokyo; 2010.
30. Ichikawa S. Research Into HIV Prevention Methods and Interventions Amongst MSM in Japan. In: *Combined Research Reports of the MSM Research Group, 2008-2010*. Edited by Ichikawa S. Nagoya: Nagoya City University; 2010.
31. Hidaka Y, Ichikawa S, Koyano J, Urao M, Yasuo T, Kimura H, *et al.* Substance use and sexual behaviours of Japanese men who have sex with men: A nationwide internet survey conducted in Japan. *BMC Public Health* 2006,**6**:239.
32. Nishiura H, Yanai H, Yoshiyama T, Kakehashi M. Simple approximate backcalculation method applied to estimate HIV prevalence in Japan. *Japanese Journal of Infectious Diseases* 2004,**57**:133-135.
33. Nishiura H. Lessons from previous predictions of HIV/AIDS in the United States and Japan: epidemiologic models and policy formulation. *Epidemiologic Perspectives and Innovations* 2007,**4**:3.
34. Koerner J, Shiono S, Kaneko N, Shingae A, Ichikawa S. Survey investigating homosexual behavior and attraction among adult males used to estimate HIV/AIDS prevalence and incidence among MSM in Japan. *Japan-German AIDS Symposium*. Tokyo; 2010.

35. Japanese Committee on Trends in AIDS. Classification of Reported HIV/AIDS Infections in 2010. Tokyo: AIDS Prevention and Information Network; 2011.
36. Li J, Gilmour S, Zhang H, Koyanagi A, Shibuya K. The epidemiological impact and cost-effectiveness of HIV testing, antiretroviral treatment and harm reduction programs. *AIDS* 2012,**26**:2069-2078.
37. Vynnycky E, White RG. *An introduction to infectious disease modelling*. New York: Oxford University Press; 2010.
38. Grassly NC, Fraser C. Mathematical models of infectious disease transmission. *Nature Reviews Microbiology* 2008,**6**:477-487.
39. Nishiura H, Cook AR, Cowling BJ. Assortativity and the Probability of Epidemic Extinction: A Case Study of Pandemic Influenza A (H1N1-2009). *Interdisciplinary Perspectives on Infectious Diseases* 2011:194507.
40. Nishiura H. Correcting the actual reproduction number: a simple method to estimate $R(0)$ from early epidemic growth data. *International Journal of Environmental Research and Public Health* 2010,**7**:291-302.
41. Chowell G. *Mathematical and statistical estimation approaches in epidemiology*. Dordrecht: Springer; 2009.
42. Nishiura H, Chowell G, Safan M, Castillo-Chavez C. Pros and cons of estimating the reproduction number from early epidemic growth rate of influenza A (H1N1) 2009. *Theoretical Biology and Medical Modelling* 2010,**7**:1.
43. Heffernan JM, Smith RJ, Wahl LM. Perspectives on the basic reproductive ratio. *Journal of The Royal Society Interface* 2005,**2**:281-293.
44. Anton H, Rorres C. *Elementary Linear Algebra: Applications Version*. 9th ed. New York: Wiley; 2005.
45. The World Health Organization. Mortality Country Fact Sheet 2006 - Japan. Geneva: WHO; 2006.
46. Palella FJ, Deloria-Knoll M, Chmiel JS, Moorman AC, Wood KC, Greenberg AE, *et al*. Survival Benefit of Initiating Antiretroviral Therapy in HIV-Infected Persons in Different CD4+ Cell Strata. *Annals of Internal Medicine* 2003,**138**:620-626.
47. Ickovics JR, Hamburger ME, Vlahov D, Schoenbaum EE, Schuman P, Boland RJ, *et al*. Mortality, CD4 Cell Count Decline, and Depressive Symptoms Among

- HIV-Seropositive Women. *JAMA: The Journal of the American Medical Association* 2001,**285**:1466-1474.
48. Dunn D, Woodburn P, Duong T, Peto J, Phillips A, Gibb D, *et al.* Current CD4 cell count and the short-term risk of AIDS and death before the availability of effective antiretroviral therapy in HIV-infected children and adults. *Journal of Infectious Diseases* 2008,**197**:398-404.
 49. Quinn TC, Wawer MJ, Sewankambo N, Serwadda D, Li C, Wabwire-Mangen F, *et al.* Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai Project Study Group. *The New England Journal of Medicine* 2000,**342**:921-929.
 50. Mastro TD, de Vincenzi I. Probabilities of sexual HIV-1 transmission. *AIDS* 1996,**10 Suppl A**:S75-82.
 51. Munakata T, Tajima K. Japanese risk behaviors and their HIV/AIDS-preventive behaviors. *AIDS Education and Prevention: Official Publication of the International Society for AIDS Education* 1996,**8**:115-133.
 52. Ono-Kihara M, Sato T, Kato H, Sugumimoto-Watanabe S, Zamani S, Kihara M. Demographic and behavioral characteristics of non-sex worker females attending sexually transmitted disease clinics in Japan: a nationwide case-control study. *BMC Public Health* 2010,**10**:106.
 53. Davis KR, Weller SC. The effectiveness of condoms in reducing heterosexual transmission of HIV. *Family Planning Perspectives* 1999,**31**:272-279.
 54. Pharmaceutical and Food Safety Bureau. HIV Antibody Testing Amongst Blood Donors in Japan. Tokyo, Japan: Ministry of Health Labour And Welfare; 2011.
 55. Pharmaceutical and Food Safety Bureau. Antibody Testing at Public Health Centres in Japan. Tokyo, Japan: Ministry of Health Labour And Welfare; 2011.
 56. McCusker J, Stoddard AM, Mayer KH, Zapka J, Morrison C, Saltzman SP. Effects of HIV antibody test knowledge on subsequent sexual behaviors in a cohort of homosexually active men. *American Journal of Public Health* 1988,**78**:462-467.
 57. Donnell D, Baeten JM, Kiarie J, Thomas KK, Stevens W, Cohen CR, *et al.* Heterosexual HIV-1 transmission after initiation of antiretroviral therapy: a prospective cohort analysis. *Lancet* 2010,**375**:2092-2098.

58. Wells W, Bartlett N, Bezbaruah S, Causey P. MSM and HIV/AIDS Risk in Asia: What is Fueling the Epidemic Among MSM and How Can It Be Stopped? New York: TREAT Asia; 2006.
59. Waller LA, Smith D, Childs JE, Real LA. Monte Carlo assessments of goodness-of-fit for ecological simulation models. *Ecological Modelling* 2003,**164**:49-63.
60. National Centre in HIV Epidemiology and Clinical Research. HIV, viral hepatitis and sexually transmissible infections in Australia Annual Surveillance Report 2010. Sydney: National Centre in HIV Epidemiology and Clinical Research; 2010.
61. Martin EG, Schackman BR. Updating the HIV-testing guidelines--a modest change with major consequences. *New England Journal of Medicine* 2013,**368**:884-886.
62. Colgate SA, Stanley EA, Hyman JM, Layne SP, Qualls C. Risk behavior-based model of the cubic growth of acquired immunodeficiency syndrome in the United States. *Proceedings of the National Academy of Sciences* 1989,**86**:4793-4797.
63. Anderson RM, Medley GF, May RM, Johnson AM. A preliminary study of the transmission dynamics of the human immunodeficiency virus (HIV), the causative agent of AIDS. *IMA Journal of Mathematics Applied in Medicine & Biology* 1986,**3**:229-263.
64. Inaba H, Nishiura H. The state-reproduction number for a multistate class age structured epidemic system and its application to the asymptomatic transmission model. *Mathematical Biosciences* 2008,**216**:77-89.
65. Hashimoto S, Kawado M. Attempt at short-term prediction of the numbers of HIV/AIDS cases reported and not reported to surveillance in Japan. *Journal of AIDS Research* 2009,**11**:152-157.
66. Hashimoto S, Fukutomi K, Ishikawa S, Matsuyama H, Nakamura K, Kihara M. Future prediction of the number of HIV-infected persons and AIDS cases. *Journal of AIDS Research* 2000,**2**:35-42.
67. Wilson DP, Hoare A, Regan DG, Law MG. Importance of promoting HIV testing for preventing secondary transmissions: modelling the Australian HIV epidemic among men who have sex with men. *Sexual Health* 2009,**6**:19-33.

68. Andersson Hk, Britton T. *Stochastic epidemic models and their statistical analysis*. New York: Springer; 2000.
69. Ichikawa S, Kaneko N, Koerner J, Shiono S, Shingae A, Ito T. Survey investigating homosexual behaviour among adult males used to estimate the prevalence of HIV and AIDS among men who have sex with men in Japan. *Sexual Health* 2011,**8**:123-124.
70. UNAIDS. Intensifying HIV prevention: UNAIDS policy position paper. Geneva: UNAIDS; 2005.
71. Merson MH, O'Malley J, Serwadda D, Apisuk C. The history and challenge of HIV prevention. *Lancet* 2008,**372**:475-488.
72. Guy R, McDonald A, Bartlett M, Murray J, Giele C, Davey T, *et al*. HIV diagnoses in Australia: diverging epidemics within a low-prevalence country. *Medical Journal of Australia* 2007,**187**:437-440.
73. Kaiser Family Foundation. The National HIV Prevention Inventory: The State of HIV Prevention Across the U.S. California: Kaiser Family Foundation; 2009.
74. Curran JW, Jaffe HW. AIDS: the early years and CDC's response. *MMWR Surveillance Summaries* 2011,**60 Suppl 4**:64-69.
75. Mackellar DA, Hou SI, Whalen CC, Samuelsen K, Valleroy LA, Secura GM, *et al*. A plausible causal model of HAART-efficacy beliefs, HIV/AIDS complacency, and HIV-acquisition risk behavior among young men who have sex with men. *AIDS and Behavior* 2011,**15**:788-804.
76. MacKellar DA, Hou SI, Whalen CC, Samuelsen K, Valleroy LA, Secura GM, *et al*. HIV/AIDS complacency and HIV infection among young men who have sex with men, and the race-specific influence of underlying HAART beliefs. *Sexually Transmitted Diseases* 2011,**38**:755-763.
77. Crepaz N, Hart TA, Marks G. Highly active antiretroviral therapy and sexual risk behavior - A meta-analytic review. *JAMA: The Journal of the American Medical Association* 2004,**292**:224-236.
78. Begley K, Chan DJ, Jeganathan S, Batterham M, Smith DE. Correlates of unprotected anal intercourse in HIV positive men attending an HIV/AIDS clinic in Sydney. *Current HIV Research* 2008,**6**:579-584.

79. McDonald A ZL, Tapia M, Wilson D. HIV, viral hepatitis and sexually transmissible infections in Australia: Annual surveillance report, 2014. Sydney, Australia: The Kirby Institute; 2014.
80. Centres for Disease Control. Interim guidance: preexposure prophylaxis for the prevention of HIV infection in men who have sex with men. *MMWR. Morbidity and Mortality Weekly Reports* 2011,**60**:65-68.
81. McDonald AM, Gertig DM, Crofts N, Kaldor JM. A national surveillance system for newly acquired HIV infection in Australia. National HIV Surveillance Committee. *American Journal of Public Health* 1994,**84**:1923-1928.
82. Kihara M, Ono-Kihara M, Feldman MD, Ichikawa S, Hashimoto S, Eboshida A, *et al.* HIV/AIDS Surveillance in Japan, 1984-2000. *Journal of Acquired Immune Deficiency Syndromes* 2003,**32**:S55-S62.
83. Iversen J, Topp L, Shying K, Maher L. *Australian NSP Survey National Data Report 2005-2009*. Sydney: National Centre in HIV Epidemiology and Clinical Research; 2010.