

increased two-fold from 0.98 per 100,000 to 2.06 per 100,000. Given that heterosexual and injecting drug incident HIV infections have been stable this decade (as suggested by the number of diagnosed cases with these modes of transmission), it appears that the increase in blood donor prevalence mainly reflects the expanding epidemic among MSM.

- 4) The number of new HIV infections among MSM is estimated to be currently at about 850 HIV infections per year. It is estimated that there have been almost 9,000 HIV infections among MSM in Japan since the discovery of the epidemic in the early eighties.
- 5) Persistence, or increases, in current rate of diagnosis will likely lead to decline in the number of total new HIV infections per year, both diagnosed and undiagnosed, in the next three years after reaching the peak around 2007-2009. The number of new HIV diagnoses will peak within the next five years and start declining sometime between 2010 and 2015. The number of new HIV diagnoses may decline by as much as 10-15% from its peak by 2015. It appears that the average time between onset of infection and diagnosis *currently* is about 1.5 to 2 years. The vast majority (at least 90%) of incident HIV infections from 2008 to 2015 will be diagnosed before they develop AIDS. However this diagnosis rate is still considerably smaller than that in Western settings such as the U.S.A. where well over 50% of MSM test for HIV every year [1-3] and the inter-test interval is less than 10 months [4]. It has been recommended for MSM to be tested at least annually for HIV and for higher risk MSM [5], a testing once every three to six months is recommended [6].
- 6) It is estimated that persistence of the relatively high diagnostic rate currently will lead to a gradual decline in the number of newly diagnosed AIDS cases among MSM in the next few years after reaching the peak sometime within the next two to three years. It is expected that by 2012, the number of newly diagnosed AIDS cases could decline by about 20%.
- 7) We estimate that the substantial increases in uptake of HIV testing among MSM since the beginning of this decade have facilitated the diagnosis of large number of HIV infections. By the end of 2008, it is estimated that almost 70% of HIV infections among *living* MSM have already been diagnosed and that 55% of all HIV infections among MSM in Japan since the discovery of the epidemic were diagnosed prior to progression to AIDS. Given the assumed high diagnostic rate currently at 50% per

person-year, close to half of incident HIV infections are currently diagnosed every year.

- 8) HIV incident rate among MSM in Japan is estimated currently at about 1.1% per person-year. The incidence rate has been growing since the discovery of the epidemic and its fastest growth was between 1995 and 2005. The incidence slowed its growth in the last three years and given the relatively high diagnostic rates currently, the incidence rate is likely to stabilize at current rates for the next few years.
- 9) We estimate that there are 80 to 85 thousand sexually active MSM in Japan at risk of HIV infection. This estimate is substantially less than what is believed to be the number of sexually active MSM among key experts on MSM in Japan. The national sexual behavior survey of 1999 suggested that there are about 500,000 males who have ever experienced a homosexual contact. It appears that active sexual networks of MSM include only about 20% of those who ever experienced a homosexual contact.
- 10) The levels of reported sexual risk behavior appear to be substantially higher than what is implied by observed prevalence. This may suggest that condom use may be actually higher, particularly among the highest risk groups, than is currently reported at 60%. Alternatively, sexual partnership formation among MSM could be clustering within small social circles thereby limiting the avenues by which HIV propagates across the MSM population. Better surveillance of sexual networks among MSM may help settle this issue.
- 11) Japan has observed no decline in the number of newly diagnosed AIDS cases following the introduction of HAART unlike Western countries such as the U.S.A. Our model suggests that this occurred because the epidemic among MSM in Japan was delayed by roughly a decade compared to the MSM epidemics in Western countries. The lower diagnostic rates in the late nineties in Japan do not appear to explain the absence of decline among AIDS cases.
- 12) The overall picture that emerges is either that the HIV epidemic among MSM is a stabilizing epidemic given the assumed relatively high current diagnostic rates or either it is still an expanding epidemic if there is a substantial underreporting or misclassification of AIDS cases. One can think of two scenarios: high diagnosis or low diagnosis rates scenarios. The overall evidence used to parameterize the model, though not sufficient, suggests that the first scenario is more likely than the second one. The above predictions are the results of this scenario.

Recommendations for further biological and behavioral surveillance data

- 1) Better quantification of the levels of HIV diagnosis (fraction of those who test for HIV within the previous 12 months) historically, currently and the likely future trends.
- 2) Better qualification and quantification of behavioral data such as number of partners over last year and whether they are casual or regular, new or old, and levels of condom use. Furthermore, more information about the social and sexual networks of MSMs would be useful. In particular, more data are needed to examine whether or not sexual partnerships tend to cluster among small social networks with limited mixing between clusters.
- 3) A second generation bio-behavioral surveillance survey among MSM, that includes also STI surveillance with HSV-2 in particular, may substantially enhance our understanding of the epidemic, provide an estimate of actual HIV prevalence among MSM, and provide more accurate estimate of some of the model parameters.

Key model assumptions

- 1) We assume that the diagnostic rate per person-year is approximately provided by the fraction of the MSM population that reported being tested for HIV in the previous year. We assume that the diagnostic rate was 20% per person-year from the beginning of the epidemic up to the year 2000 (Justification as per Professor Hashimoto's work). Starting from 2000, the testing rate increased linearly at a specified rate up to 2004 and after 2004 it continued to increase linearly up to 2008, but at a faster rate. We assume that the diagnostic rate has reached 50% per person-year by 2008.
- 2) We assume that all AIDS cases among MSM in Japan are currently diagnosed following progression to AIDS and that there is no under-diagnosis or misclassification of AIDS cases in Japan.
- 3) We assume that there were about 80 HIV/AIDS infections among MSM in Japan in the mid eighties when the first case of AIDS was diagnosed. Changing this assumed initial pool of infected persons may affect our estimate for the size of the active MSM population in Japan.
- 4) We assume that the fraction of the population in each risk group of the 10 risk groups is provided by a classification of risk based on the number of reported sexual partners in the last 6 months per Table 1.
- 5) We use the reported number of partners in the last six months as our basis for choosing the effective rate of partner change (that is level of risk to HIV acquisition

per each risk group). We adjust the reported number of partners by the multiplier $\left(\frac{i-1}{10}\right)$ to correct for the fact that not all sexual partners are new partners. We further multiply the reported number of partners by a behavioral fitting parameter $b(i)$ to correct for the fact that the reported number of partners alone is not sufficient to describe the levels of risk per each risk group due to sexual network effects [7-9], informational limitations of ego-centric sexual behavior data, and non-random biases in sexual behavior reporting [10].

- 6) We assume that 60% of coital acts are protected by condoms and that condoms have a 100% efficacy in preventing HIV transmission.
- 7) We assume that 10% of those already diagnosed with HIV infection continue to be part of the MSM population being tested for HIV despite knowing their HIV sero-status.
- 8) We assume that diagnosed HIV/AIDS cases reduce their risk behavior by 80% following diagnosis.

Fitted epidemiologic measures

We fit our model to three kinds of measured data:

- 1) HIV prevalence as measured in point-prevalence surveys at testing locations or during testing events.
- 2) Number of newly diagnosed HIV cases every year.
- 3) Number of newly diagnosed AIDS cases every year.

Fitting parameters

We use the following parameters as our fitting parameters:

- 1) The size of the active MSM population.
- 2) The behavioral fitting parameter $b(i)$ that corrects for sexual network effects [7-9], informational limitations of ego-centric sexual behavior data, and non-random biases in sexual behavior reporting [10]. Since the model is mainly sensitive to the risk behavior in the higher risk groups as HIV prevalence is still a low level, We fix the $b(i)$ for $i=1,2,3,4,5$ at 0.30, and use $b(i)$ for $i=6,7,8,9,10$ as the fitting parameters yielding fitted values in the range of 0.23 to 0.70 for these parameters.
- 3) The degree of assortativeness (e) in the mixing between the different risk groups.

Model structure

We used a population-based compartmental model to study the HIV epidemic among MSM in Japan. The model is based on an adaptation of earlier HIV transmission models [11, 12] and was solved both deterministically and stochastically. The deterministic version of the model consists of a system of six differential equations for each risk group of ten MSM risk groups in the population:

$$\begin{aligned}
 \frac{dS(i)}{dt} &= \mu N_0(i) - \mu S(i) - \Lambda_{HIV}^{S(i)} S(i) \\
 \frac{dY_1(i)}{dt} &= \Lambda_{HIV}^{S(i)} S(i) - \mu Y_1(i) - \omega_{Y_1} Y_1(i) - \eta_1(i) Y_1(i) \\
 \frac{dY_2(i)}{dt} &= \omega_{Y_1} Y_1(i) - \mu Y_2(i) - \omega_{Y_2} Y_2(i) - \eta_2(i) Y_2(i) \\
 \frac{dD_1(i)}{dt} &= \eta_1(i) Y_1(i) - \mu D_1(i) - \omega_{D_1} D_1(i) \\
 \frac{dD_2(i)}{dt} &= \eta_2(i) Y_2(i) + \omega_{D_1} D_1(i) - \mu D_2(i) - \omega_{D_2} D_2(i) \\
 \frac{dD_3(i)}{dt} &= \omega_{Y_2} Y_2(i) + \omega_{D_2} D_2(i) - \mu D_3(i) - \omega_{D_3} D_3(i)
 \end{aligned} \tag{1}$$

For the stochastic version, we used the same transition rates in this deterministic system of equations to generate the stochastic process.

The index i in the above equations stands for an i -sexual risk population where $i = 1, 2, \dots, 10$ represents the ten different risk groups in the MSM population. The level of risk increases with the index i so that the tenth risk group is at the highest risk of exposure. Here, $S(i)$ is the HIV susceptible population, $Y_\alpha(i)$ are the HIV infected but undiagnosed populations, and $D_\alpha(i)$ are the HIV infected and diagnosed populations. The index α marks the stage of HIV pathogenesis; $\alpha = 1, 2, 3$ stand for acute, latent, and late stages respectively. The $N(i)$ is the population size, and $N_0(i)$ is the initial population size, of each i -risk group. N^{Total} is the total population size of all risk groups.

The progression of HIV is described by the rate of progression from acute to latent stage for undiagnosed ($\omega_{Y_{\alpha+1}}$) and diagnosed ($\omega_{D_{\alpha+1}}$), the rate from latent to AIDS stage for undiagnosed ($\omega_{Y_{\alpha+2}}$) and diagnosed ($\omega_{D_{\alpha+2}}$), and the rate of HIV/AIDS disease mortality for diagnosed AIDS cases ($\omega_{D_{\alpha+3}}$). Implicitly, all AIDS cases are assumed to be diagnosed in

Japan. The rates $\Lambda_{HIV}^{S(i)}$ are the HIV forces of infection (hazard rates of infection) experienced by each susceptible population $S(i)$. The $\Lambda_{HIV}^{S(i)}$ is given by

$$\Lambda_{HIV}^{S(i)} = \rho_{S(i)} \sum_{j=1, K, 10} \sum_{\alpha'=1, 2, 3} t_{Y_{\alpha'}(j) \rightarrow S(i)} G(i, j) \frac{\rho_{Y_{\alpha'}(j)} Y_{\alpha'}(j)}{\rho_{S(j)} S(j) + \sum_{\alpha'=1, 2} \rho_{Y_{\alpha'}(j)} Y_{\alpha'}(j) + \sum_{\alpha'=1, 2, 3} \rho_{D_{\alpha'}(j)} D_{\alpha'}(j)} +$$

$$\rho_{S(i)} \sum_{j=1, K, 10} \sum_{\alpha'=1, 2, 3} t_{D_{\alpha'}(j) \rightarrow S(i)} G(i, j) \frac{\rho_{D_{\alpha'}(j)} D_{\alpha'}(j)}{\rho_{S(j)} S(j) + \sum_{\alpha'=1, 2} \rho_{Y_{\alpha'}(j)} Y_{\alpha'}(j) + \sum_{\alpha'=1, 2, 3} \rho_{D_{\alpha'}(j)} D_{\alpha'}(j)}$$

(2)

In these expressions, $\rho_{X(i)}$ describes the *effective* new sexual partner acquisition rate for each population variable $X(i)$. Note that we use the term effective rate of partner change, as opposed to rate of partner change, since this parameter does not merely reflect the actual rate at which individuals change their partners, but also represents other behavioral mechanisms that effectively modify this quantity such as concurrency and topology of sexual networks [7-9], and variability in risk behavior [13]. In essence this is merely a parameter describing the level of exposure risk for each risk group in the population.

The mixing between the ten risk groups in the population is dictated by the sexual-mixing matrix $G(i, j)$ that provides the probability that an individual in risk group i would choose a partner in risk group j [11]. It is given by the expression

$$G(i, j) = e\delta_{i,j} + (1-e) \frac{\rho_{S(j)} S(j) + \sum_{\alpha=1, 2} \rho_{Y_{\alpha}(j)} Y_{\alpha}(j) + \sum_{\alpha=1, 2, 3} \rho_{D_{\alpha}(j)} D_{\alpha}(j)}{\sum_{k=1, K, 10} \left(\rho_{S(k)} S(k) + \sum_{\alpha=1, 2} \rho_{Y_{\alpha}(k)} Y_{\alpha}(k) + \sum_{\alpha=1, 2, 3} \rho_{D_{\alpha}(k)} D_{\alpha}(k) \right)}$$

(3)

Here, $\delta_{i,j}$ is the identity matrix and the parameter $e \in [0, 1]$ measures the degree of assortativeness in the mixing. At the extreme $e = 0$, the mixing is fully proportional while at the other extreme $e = 1$, the mixing is fully assortative as individuals choose partners only from within their risk group.

The parameters $t_{Y_{\alpha}(i) \rightarrow S(j)}$ ($t_{D_{\alpha}(i) \rightarrow S(j)}$) stand for HIV transmission probability per partnership in a partnership between a member of the susceptible population $S(j)$ and a member of the HIV infected population $Y_{\alpha}(i)$ ($D_{\alpha}(i)$), and are expressed in terms of HIV transmission probability per coital act per HIV stage in this partnership $p_{Y_{\alpha}(i) \rightarrow S(j)}^{HIV}$ ($p_{D_{\alpha}(i) \rightarrow S(j)}^{HIV}$), the frequency of unprotected coital acts per HIV stage in this partnership

$n_{Y_a(i) \leftrightarrow S(j)}$ ($n_{D_a(i) \leftrightarrow S(j)}$), the frequency of condom protected coital acts per HIV stage in this partnership $n_{Y_a(i) \leftrightarrow S(j)}^C$ ($n_{D_a(i) \leftrightarrow S(j)}^C$), and the duration $\tau_{Y_a(i) \leftrightarrow S(j)}$ ($\tau_{D_a(i) \leftrightarrow S(j)}$) of this partnership, using the binomial model

$$\begin{aligned}
 t_{Y_a(i) \rightarrow S(j)} &= 1 - \left(1 - P_{Y_a(i) \rightarrow S(j)}^{HIV}\right)^{n_{Y_a(i) \leftrightarrow S(j)} \tau_{Y_a(i) \leftrightarrow S(j)}} \left(1 - (1 - CE) P_{Y_a(i) \rightarrow S(j)}^{HIV}\right)^{n_{Y_a(i) \leftrightarrow S(j)}^C \tau_{Y_a(i) \leftrightarrow S(j)}^C} \\
 t_{D_a(i) \rightarrow S(j)} &= 1 - \left(1 - P_{D_a(i) \rightarrow S(j)}^{HIV}\right)^{n_{D_a(i) \leftrightarrow S(j)} \tau_{D_a(i) \leftrightarrow S(j)}} \left(1 - (1 - CE) P_{D_a(i) \rightarrow S(j)}^{HIV}\right)^{n_{D_a(i) \leftrightarrow S(j)}^C \tau_{D_a(i) \leftrightarrow S(j)}^C}
 \end{aligned}
 \tag{4}$$

In these expressions, CE is the condom efficacy in reducing HIV transmission probability per coital act. Finally, we assume a constant birth rate in the model and we do not stratify the population according to age.

Model parameters and basic assumptions

HIV pathogenesis is described by the three stages of acute, latent, and AIDS. The relative risks of transmission per coital act per HIV stage are extracted from the measurements of Wawer *et al.* [14] by collapsing the sub-strata in their classification of incident, prevalent, and late stages into the three stages of acute, latent, and late [15]. The transmission probability per anal sex act per HIV stage is assumed to be five fold higher than that of heterosexual sex consistent with measurements of this probability [16].

HIV pathogenesis for undiagnosed HIV sero-positives is described by the three stages of acute, latent, and AIDS whose durations are assumed to be 2.5 months (acute), 10 years (latent), and 1 year (AIDS), respectively. These values are based on the transmission probability classification in Wawer *et al.* [14] and recent reassessment of HIV natural history by the UNAIDS Reference Group on Estimates, Modeling and Projections [17]. For the diagnosed population, HIV pathogenesis is described by the three stages of acute, latent, and AIDS whose durations are assumed to be 2.5 months (acute), 30 years (latent), and 1 year (AIDS), respectively. The duration of the latent stage is based on the distribution from infection to AIDS in presence of antiretroviral therapy when patients are eligible for such therapy [18].

In terms of the number of coital acts per partnership, we assume that the average number of acts per partnership for the first risk group is 0.1 per partnership since this group has not been sexually active in the last six months. For the second and third risk groups we assume that the number of acts to be as measured in the national sexual behavior survey at 23 coital acts per partnership. For the rest of the groups, we assume that the number of acts decreases

linearly the higher is the risk behavior with the highest risk group experiencing 7 acts per partnership. In mixed partnerships between a member of risk group i and risk group j , we assume that the number of acts per partnership is given by $n_{i \leftrightarrow j} = \sqrt{n_{acts}(i)n_{acts}(j)}$, where $n_{acts}(k)$ is the number of acts per partnership among the k -risk group.

The duration of the sexual lifespan is set at 35 years to conform with the 15-49 years age groups that is typically used to define the sexually active population by the WHO as well as many HIV studies [19].

Epidemiologic measures of special interest

We define true prevalence based on standard convention as the fraction of the MSM population that is infected with HIV:

$$\text{Prevalence} = \frac{\sum_{j=1,K,10} \left(\sum_{\alpha=1,2} Y_{\alpha}(j) + \sum_{\alpha=1,2,3} D_{\alpha}(j) \right)}{\sum_{j=1,K,10} N(j)} \quad (5)$$

Since HIV prevalence among MSM in Japan has been measured only at testing sites or in testing events and has not yet been determined using standard methodologies for measuring infection prevalence such as second generation surveillance [20], we define the “measured point-prevalence” as the fraction of the population that are sero-positive for HIV in a sampling that is biased to those who have never been tested for HIV:

$$\text{Measured Point-Prevalence} = \frac{\sum_{j=1,K,10} \left(\sum_{\alpha=1,2} Y_{\alpha}(j) + f_{\text{Repeat Testers}} \sum_{\alpha=1,2,3} D_{\alpha}(j) \right)}{\sum_{j=1,K,10} \left(N(j) - \sum_{\alpha=1,2,3} D_{\alpha}(j) + f_{\text{Repeat Testers}} \sum_{\alpha=1,2,3} D_{\alpha}(j) \right)} \quad (6)$$

This expression corrects for the fact that diagnosed HIV sero-positive persons are less likely to participate at such point-prevalence testing locations or events since they already know their HIV status. In this expression, $f_{\text{Repeat Testers}}$ describes the fraction of already diagnosed HIV/AIDS cases who would continue to be part of the MSM population being tested for HIV despite knowing their HIV sero-status.

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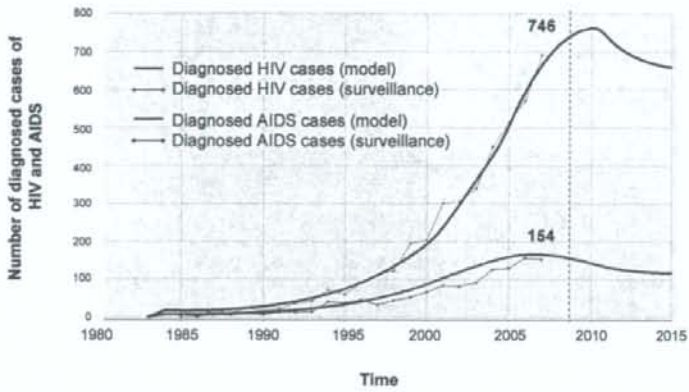
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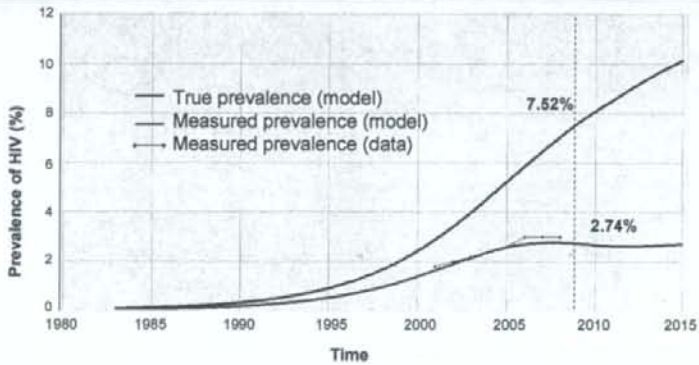
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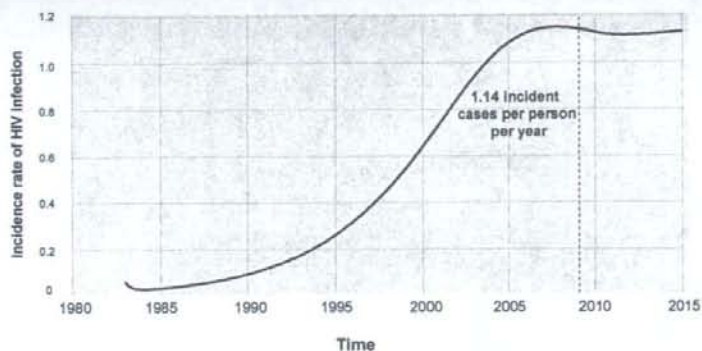
The model was fitted to the available data on the number of diagnosed HIV and AIDS cases among MSM people in Japan



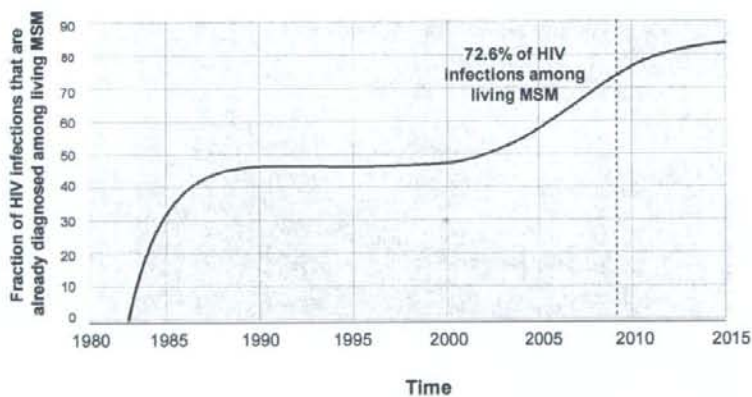
True Prevalence compared to Measured Prevalence of HIV among MSM population in Japan



Incident rate of HIV infection per person per year among MSM population in Japan



Fraction of HIV infections that are diagnosed among living MSM population in Japan



研究成果の刊行に関する一覧表

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代表者 木 原 正 博

連絡先 京都大学大学院医学研究科
社会健康医学系専攻社会疫学分野
〒606-8501 京都市左京区吉田近衛町
TEL 075-753-4350 FAX 075-753-4359

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