HIV/AIDS elimination in Japanese MSM

日本の男性間性交渉者における HIV/AIDS の撲滅

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Abstract

Background: HIV has been a major global health challenge. Japan has a concentrated HIV epidemic, with the majority of transmission among men who have sex with men (MSM). In order to reduce the burden of HIV infection among the Japanese MSM population, it is helpful to assess the potential role of enhanced interventions. However, quantitative research in Japan is limited. Therefore, this study aimed to explore the effect of behavioral and biomedical interventions and their combination on the Japanese HIV epidemic among MSM and forecast the time required to eliminate HIV if policies are enhanced.

Methods: A deterministic compartmental model was built to reflect the mechanism of HIV progression, running on the Japanese MSM population aged 15-59 years old, which was applied to low risk and high risk MSM groups. I estimated and forecasted the HIV epidemic among Japanese MSM from 2010 to 2050 based on the framework of this model. The effective reproduction number was calculated for the whole MSM population to reflect the effect of interventions on the overall infectiousness of HIV. Interventions were designed to be implemented from 2022, taking an effective reproduction number in 2022 less than 1 as a necessary precondition for elimination, and incidence rate less than 1 case per 1000 person-years as the definition of elimination, the time required for HIV elimination under status quo, two behavioral interventions (partners reductions, increased condom use rate), two

biomedical interventions (enhanced testing and treatment, introducing PrEP) and three comprehensive behavioral and biomedical interventions (weak, moderate and strong) was calculated.

Results: Under the current policies, the HIV epidemic in Japanese MSM will not be eliminated by 2050, when the prevalence and incidence rate will reach 10.24% and 10.60 per 1000 person-years in 2050. Both behavioral interventions and both biomedical interventions can achieve HIV elimination by 2050 with annual number of sexual partners in HRMSM less than 9, or with condom use rate above 65%, or with testing rate and treatment rate above 65%, or with more than 10% PrEP coverage rate. Under the three comprehensive interventions, in all cases the time required for HIV elimination is much less than the time required in each single intervention, with HIV elimination achieved in 2033 (sensitivity range 2032 to 2034), 2026 (sensitivity range 2025 to 2027) and 2024 (sensitivity range 2024 to 2025) under weak, moderate and strong interventions, respectively.

Conclusion: HIV will not be eliminated by 2050 in the Japanese MSM population under current policies, and interventions will need to be enhanced in order to control the epidemic. Both behavioral interventions and biomedical interventions can achieve HIV elimination by 2050, but comprehensive interventions can accelerate the realization of HIV elimination with higher feasibility.

Keywords: HIV elimination, Japan, MSM, deterministic compartmental model, behavioral and biomedical interventions, comprehensive intervention

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List of abbreviations

HIV	Human immunodeficiency virus
AIDS	Acquired immunodeficiency syndrome
PLWH	People living with HIV
MSM	Men who have sex with men
PEPFAR	President's Emergency Plan for AIDS Relief
NSPs	Needle and syringe programmes
TasP	Treatment as Prevention
U=U	Undetectable = Untransmutable
WHO	World Health Organization
ART	Antiretroviral therapy
HAART	Highly active antiretroviral therapy
UNAIDS	Joint United Nations Programme on HIV/AIDS
PrEP	Pre-exposure prophylaxis
LASH	Love life and sexual health
JFAP	Japan Foundation for AIDS Prevention
NGOs	Non-government organizations
LRMSM	Low risk MSM
HRMSM	High risk MSM
ODE	Ordinary differential equation

MHLW	Ministry of Health, Labour and Welfare
DFE	Disease-free equilibrium
GPS	Global Positioning System

1 INTRODUCTION

1.1 Background Information

1.1.1 Global burden of HIV and prevention strategies

HIV/AIDS has been a major global health challenge since the first reported cases in 1981[1], with 32.7 million cumulative deaths from AIDS-related illnesses and 38.0 million people living with HIV (PLWH) at the end of 2019, and 1.7 million new HIV infections in 2019[2]. Sexual, parenteral and mother-to-child transmission are the three most common routes of HIV transmission.

The global pattern of HIV/AIDS epidemics can be divided into three categories: concentrated, generalized, and mixed. Transmission established in the general population is known as a generalized epidemic, while transmission mainly occurring in key populations[3], such as men who have sex with men (MSM), people who inject drugs, people in prisons and other closed settings, sex workers and their clients and transgender people, is called a concentrated epidemic. If transmission occurs in both general and key populations, the epidemic is mixed[4]. HIV in most of the world is predominantly found in concentrated epidemics, except for Sub-Saharan Africa where most epidemics are generalized and mixed[4] (Figure 1). Sub-Saharan Africa has the heaviest burden of HIV globally, with 71% of global cases and 74.6% of global HIV/AIDS deaths [5], especially in southern Africa (Figure 2).

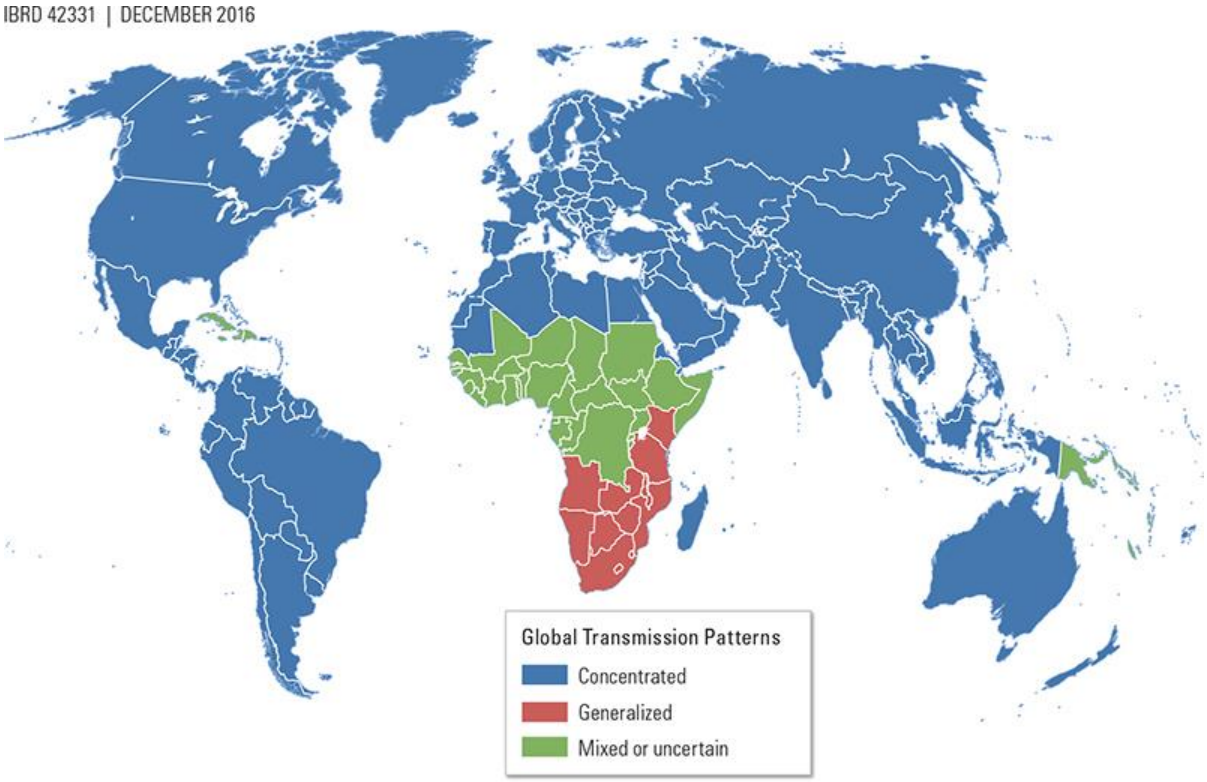

Figure 1 Global patterns of HIV/AIDS transmission. (Source: Tailoring the local HIV/AIDs response to local HIV/AIDs epidemics, 2017[4])

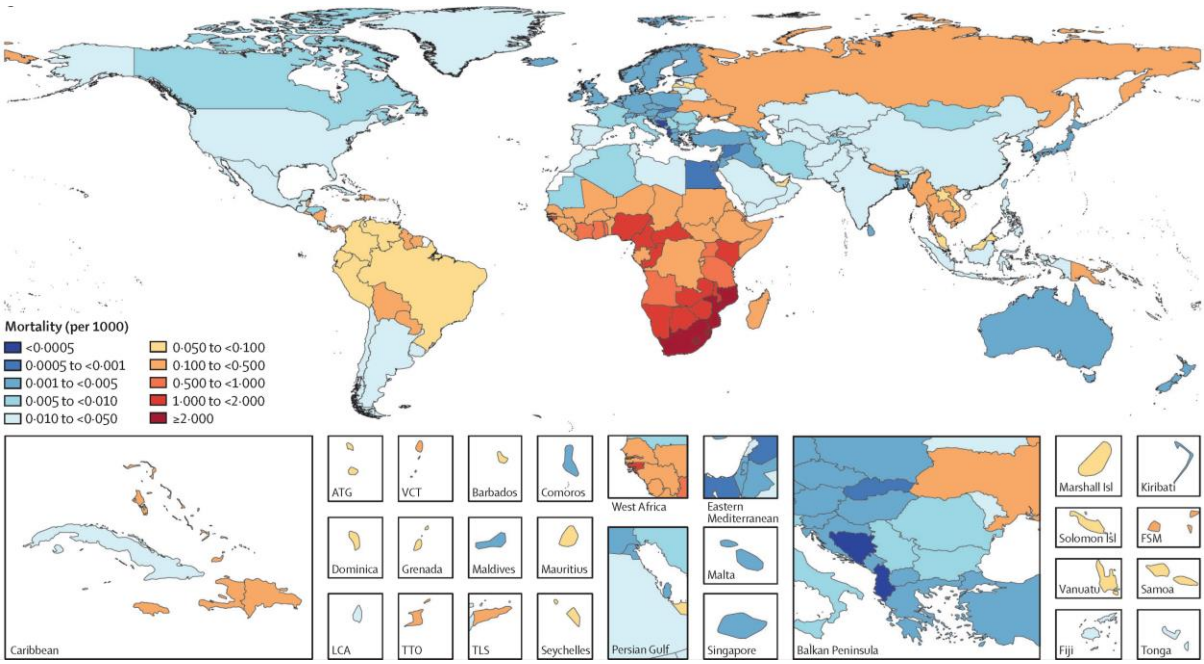

Figure 2 Age-standardized HIV mortality, 2017. (Source: Lancet HIV, 2019[5])

Great efforts have been made to prevent HIV transmission and contain the HIV pandemic. Prevention programmes can be divided into behavioural interventions, which control the HIV epidemic by reducing individual risk behaviours, and biomedical interventions which reduce HIV transmission risk using medical approaches.

In the early years of the pandemic (1980s to 2000s), behaviour change strategies were the only available methods of prevention. The aims of behavioural interventions include reducing high-risk sexual or injecting drug use behaviour, which cause most HIV infections. Condom promotion is an essential part of preventing sexual transmission of HIV, with condoms reducing HIV transmission risk by 90%-95% when used consistently[6]. Major early programs in sub-Saharan Africa to prevent HIV transmission, such as the President's Emergency Plan for AIDS Relief (PEPFAR), supported an ***ABC*** strategy of sexual behaviour change based on Uganda's model[7], in which ***A*** means abstinence, ***B*** means be faithful or partner reduction and ***C*** means condom use. However this strategy had limited effect because PEPFAR mandated almost one third of funding of prevention funds on the abstinence component of ABC, which made it difficult to implement other interventions[8]. Harm reduction programmes such as needle and syringe programmes (NSPs) and opiate substitution treatment are preventions aimed to prevent HIV spread associated with drug use, and have successfully reduced new infections caused by injecting drugs in countries that started the programmes such as Switzerland, the United Kingdom and Australia to almost zero[9], but still have been poorly implemented in many countries[10]. Despite the proven benefits and effectiveness of these behavioural change strategies, behavioural interventions are still not

sufficient for HIV prevention and control due to the limited efficacy when behavioural interventions are used by themselves[8] and lack of sustainability in countries with limited resources[11, 12].

Since HIV treatment became available, treatment as prevention has become a major component of HIV prevention. Treatment as Prevention (TasP), the foundation of the "Undetectable = Untransmittable" (U=U) campaign[13], first introduced in 2006[14] and officially publicized by World Health Organization (WHO) in 2012, uses antiretroviral therapy (ART) in PLWH to reduce the their chance of HIV transmission as a new HIV prevention strategy. HIV testing is a crucial component of the TasP strategy, as the first step of the HIV treatment and care path. The US Centers for Disease Control and Prevention recommends at least one HIV test for everyone between the ages of 13 and 64, and at least annual testing for people at high risk[15], while the WHO has provided guidelines on HIV testing services that are followed in many countries[16]. The TasP strategy relies on the effectiveness of modern highly active antiretroviral therapy (HAART) in reducing the infectiousness of PLWH taking the treatment[17, 18], and has formed the cornerstone of modern prevention strategies such as PEPFAR[19]. When HAART was first introduced, decisions about when to start treatment were based on the clinical stages of patients[20]. In 2009, mathematical modelling by Granich et al suggested HIV could be eliminated using annual universal HIV testing with immediate treatment in generalized epidemics[21], and the HPTN052 study demonstrated the benefit of early initiation of ART, with 96% reduction of HIV transmission in the early ART group compared with delayed ART group[22]. This

evidence led to a testing and treatment strategy, officially included in WHO guidelines since 2016, which recommends HAART should be initiated in PLWH after diagnosis, regardless of WHO clinical stage or at any CD4 cell count[23]. This strategy aims to involve PLWH into treatment as soon as possible, thereby reducing the rate of transmission to other people. Countries like Australia and the UK have incorporated these strategies into their national HIV strategy[24, 25], and scaled-up free testing and treatment[26], have made great progress in HIV/AIDS prevention. In 2014, the Joint United Nations Programme on HIV/AIDS (UNAIDS) launched the 90–90–90 targets[27], which provide a framework to end the AIDS epidemics with TasP as the cornerstone. The aim of these targets is to diagnose 90% of all HIV-positive persons, provide ART for 90% of those diagnosed, and achieve viral suppression for 90% of those treated by 2020, increasing to 95% by 2030.

Even through yearly universal HIV testing with immediate treatment can effectively reduce the spread of HIV, this strategy may encounter huge implementation challenges due to resource limitations, and mathematical modeling has found much less effect of this strategy in populations with heterogeneous risk behaviors[28]. When isolated or simple strategies encounter such barriers to effectiveness, combination preventions, which use a mixed tool of behavioural and biomedical preventions supported by structural interventions, are essential[29]. However, understanding the effectiveness of different strategies and identifying the best combination of methods for different risk groups and populations remains a major challenge in the HIV response.

1.1.2 HIV prevention strategies for MSM population

MSM are a key population listed by WHO[3], and are 26 times more likely to be infected with HIV than the general population[2]. In 2019, 23% of new adult HIV infections were among MSM[30]. This proportion was much higher in concentrated epidemic regions, with more than 40% in Asia and the pacific and Latin America, and 64% in western and central Europe and North America[30]. Because of sexual identity- and HIV-related stigma and discrimination, MSM may be reluctant to seek health care and disclose their sexual behaviours to health care providers, making them hard to reach with TasP strategies[31], and leading to continued high prevalence and incidence in many MSM populations.

Some specific prevention strategies are available to break these barriers for MSM. Network-based interventions have played a role in preventing and controlling HIV epidemic in MSM populations in many countries. Network interventions rely on the "social networks" of MSM population, reaching hidden members through identified individuals who then engage their peers with sexual health services and link them to sexual education by trained educators[32]. HIV self-testing is a relatively new testing service recommended by WHO which offers another option for people to test themselves without fear of stigma or discrimination[16]. However, only 77 countries had officially approved HIV self-testing policy by 2019, most of them European [33].

Pre-exposure prophylaxis (PrEP) is another new prevention measure that shows promise in MSM populations. People who do not have HIV but who are at high risk of HIV infection take HAART every day to prevent HIV infection through their risk behavior. The high

effectiveness of PrEP under good adherence has been shown through randomized controlled trials[34, 35]. In 2015, PrEP was incorporated into WHO prevention recommendations for people at high risk of HIV[36]. However, like HIV self-testing, during the implementation of PrEP prevention, it still faces the problem that many countries have not officially approved this prevention strategy, and in these countries it remains expensive and difficult to obtain[37]. This means that for many countries decisions about which mix of new strategies for HIV prevention to use in MSM populations have not been finalized, and deciding on the correct balance of policy requires modeling and other policy studies that can inform these decisions. Japan is one such country.

1.1.3 HIV burden in Japan

HIV/AIDS surveillance in Japan started in September 1984. Annual reports notifying HIV/AIDS cases for that year are released by the National AIDS Surveillance Committee[38]. The number of new HIV/AIDS cases notified annually has been increasing since 1985 and peaked at 1,590 in 2013[38], with a declining trend since then. In 2018, 1317 HIV/AIDS cases (940 HIV cases and 377 AIDS cases) were notified.

HIV is a typical concentrated epidemic in Japan, with the highest disease burden among MSM. The number of new notified cases among the MSM population dramatically increased and has outpaced all other routes of infection since the early 2000s, and has been on a flat to slightly decreasing trend since 2015 but still is the most common route of infection[39]. The MSM population was estimated to account for around 2.9% to 4.6% of the male population in Japan[40-42], but disproportionately accounted for 75.4% (670/889) of male HIV cases, 58.1%

(205/353) of male AIDS cases and 66% (875/1317) of new infections in 2018[43], which was much higher than the average level (30% of new HIV infections) in Asia[44]. Therefore, the key to the ultimate goal of eliminating HIV/AIDS in Japan lies in reducing the transmission of HIV/AIDS among MSM populations.

1.1.4 Japanese HIV Policy

Japanese HIV policy is a mixture of TasP principles and behavioral change, and slightly lags European and Australian best practice. Japan has established a scheme for free and anonymous testing at public health centers through the country, with some HIV testing also conducted in private clinics and hospitals. At the time of writing, there were 653 available institutions offering HIV testing (free: 600, charge: 53)[45]. However, HIV testing is still insufficient in Japan, which delays diagnosis. In 2018, among newly diagnosed cases, 28.6% were already in the most serious stage of AIDS[38] due to this late diagnosis. The love life and sexual health (LASH) survey of treatment and prevention intentions targeting the MSM population, found 62% of respondents have ever had an HIV test and 55.4% of those respondents had their test in the past year[46], which was far from the guidelines of many countries recommending at least annual screening for MSM populations[47, 48]. In order to increase HIV testing, some testing convenience and access promotion measures have been implemented, such as rapid testing and out-of-working-hours testing services. Until now, among the 653 institutions offering HIV testing, most (75.2%) of the institutions have an appointment requirement, 30.6% of these institutions cannot provide rapid testing with same-day results, and around half (48.7%) of these institutions provide services only on weekday

daytimes[45]. HIV testing at institutions decreased after peaking in 2008 and then stagnated. Self-collecting HIV testing as a new way allowing people find out their results without time and place restrictions, is much easier to reach hidden PLWH than institutional testing but has not yet been officially approved in Japan. Japan also lacks specific sexual health clinics targeting sexual minorities and young people, which are common in countries such as the UK and Australia and form a cornerstone of their HIV prevention activities, making testing services inconvenient to access, and MSM may experience stigma and discrimination that discourages them from accessing needed services.

HIV treatment is not free in Japan. Although 70% of the medical cost can be covered by health insurance, the remaining cost presents a large financial burden and increases the difficulty of sustainable treatment. Although Japanese treatment guidelines are consistent with UNAIDS recommendations, the Japanese insurance system does not support funding for immediate entry into treatment. The Japanese government has started a disability certificate policy for PLWH with financial difficulty[49], which enables PLWH who are eligible to receive another subsidy which reduces the maximum out-of-pocket payment for treatment to less than JPY 20,000 per month[50]. However, some restrictions on clinical indicators in the application for the disability certification make the patients in the early stage of HIV infection ineligible[51, 52], and the enrolment process is bureaucratic and cumbersome[51], which slows the rapid access to treatment required to ensure TasP and testing and treatment goals are met. The proportion of eligible applicants between 2010 to 2015 has declined by 40% from the late 1990s[53].

Japan does not provide PrEP through the national health insurance program, but it is legally possible to buy the drug for PrEP online from overseas and import it into Japan if the purchaser is able to bear the out of pocket costs[37]. The original PrEP drug Truvada (TDF/FTC) is expensive, costing around 116, 000 JPY for one month [54], and although generic drugs are much cheaper and affordable at around 6,000 JPY per month[55], only one month's usage per import is allowed. In the 2017 LASH report, 63.1% of respondents would like to take anti-HIV drugs (PrEP) to prevent HIV infection, while the top concern with using PrEP was cost[46]. The same concerns were also identified with HIV treatment, and financial burden may still be a barrier for some PLWH in Japan, especially younger PLWH who may also be the most at-risk.

The Japan Foundation for AIDS Prevention (JFAP) has established various prevention campaigns to raise public awareness of HIV, including activities for the general population like theme concerts and speeches by famous people[49]. Gay community centres (such as bars, clubs and saunas) collaborating with non-government organizations (NGOs) have taken a great role in operating campaigns targeting the MSM population. In these sites NGOs provide outreach services including HIV/safe sex education and free condom distribution to increase HIV awareness of gay customers[41]. However, these community-based activities are limited and many of the MSM population cannot be reached, so there remains a substantial proportion of the MSM population using condoms inconsistently[56] and having multiple sexual partners[46]. Research is therefore still needed to identify the extent of improvement that is needed in services, the role of combined behavioral and biomedical interventions, and

the potential impact of new strategies such as PrEP, in eliminating HIV in Japan.

1.2 Objectives

In order to reduce and eliminate the burden of HIV infection among the Japanese MSM population, it is helpful to assess the potential role of enhanced behavioural and biomedical interventions. However, quantitative research in Japan is limited. The previous research published by our team mainly focused on the impact of strengthening testing and treatment on future trends[57]. This previous research estimated the trends in HIV among MSM in Japan through enhanced TaSP measures including PrEP but did not include behavioral interventions and did not describe in detail the changes in policy required to achieve elimination of HIV. In this study, I used mathematical modelling to explore the effect of the number of sexual partners, condom use rate, testing rate, treatment rate and PrEP coverage rate on the Japanese HIV epidemic among MSM and forecast the time required to eliminate HIV if policies are enhanced, with four specific objectives:

1. Estimate and project prevalence, number of new cases and incidence of HIV in MSM from 2010 to 2050 under the status quo of current policies.

2. Explore whether HIV will be eliminated in MSM under scenarios with different numbers of sexual partners, condom use rate, testing rate and treatment rate and PrEP coverage rate.

3. Estimate how long it will take to eliminate HIV under these different scenarios.

4. Provide suggestions for policy change to achieve HIV elimination.

2 METHODS

2.1 A deterministic compartmental model of HIV

A deterministic compartmental model was built to reflect the mechanism of HIV progression, running on the Japanese MSM population aged 15-59 years old. This population was further divided into two groups-low risk MSM (LRMSM) and high risk MSM (HRMSM) based on the number of sexual partners they had in the past year. The model was applied to both LRMSM and HRMSM and used a mixing parameter to allow sexual interactions between them.

2.1.1 Model structure

I used the same deterministic compartmental model structure as Jinghua Li that has been used in research targeting Chinese MSM[58], which divides the MSM population into 15 compartments based on their HIV serostatus, CD4 count, knowledge of HIV serostatus and treatment activity. The structure of the model is shown in Figure 3.

Five columns represent one uninfected stage and four different progressive stages of HIV infection. Acute infection is the earliest stage of HIV infection, in which the virus is multiplying rapidly so the newly-infected person will be highly infectious during this time. This stage is followed by a long asymptomatic period during which HIV multiplication will be slower, CD4 cell counts decrease but remain over 500 cells/mm3. When the CD4 cell counts keep declining, the infected person will move into an asymptomatic stage with CD4 counts between 200 and 500 cells/mm3. When the CD4 cell become depleted (under 200

cells/mm3), it reaches the final AIDS stage, where the infected person is vulnerable to a wide range of opportunistic infections. In this model all stages of HIV after the acute stage are defined in terms of CD4 count, with assumptions made about the time required for CD4 count to decline when untreated.

Three rows represent knowledge of HIV serostatus and treatment activity. From top to bottom these are untested, tested but not in treatment and in treatment, respectively. Note that for the first column in the last row, “treatment” represents PrEP.

Arrows are another important component of the deterministic compartmental model, with key parameters indicating the transition rates. Arrows between compartments represent people transferring from one compartment to another compartment because of their HIV status change. Arrows pointing to the outside indicate mortality and population maturation (older than 59 years old) and arrows pointing to the compartments from the outside indicate population entry (maturation of 15 years old). The rate of change of the number of people in each compartment is described by an ordinary differential equation (ODE), which can be calculated by subtracting the number of people leaving each compartment (represented by outward arrows) from the number of entrants (represented by the inward arrows).

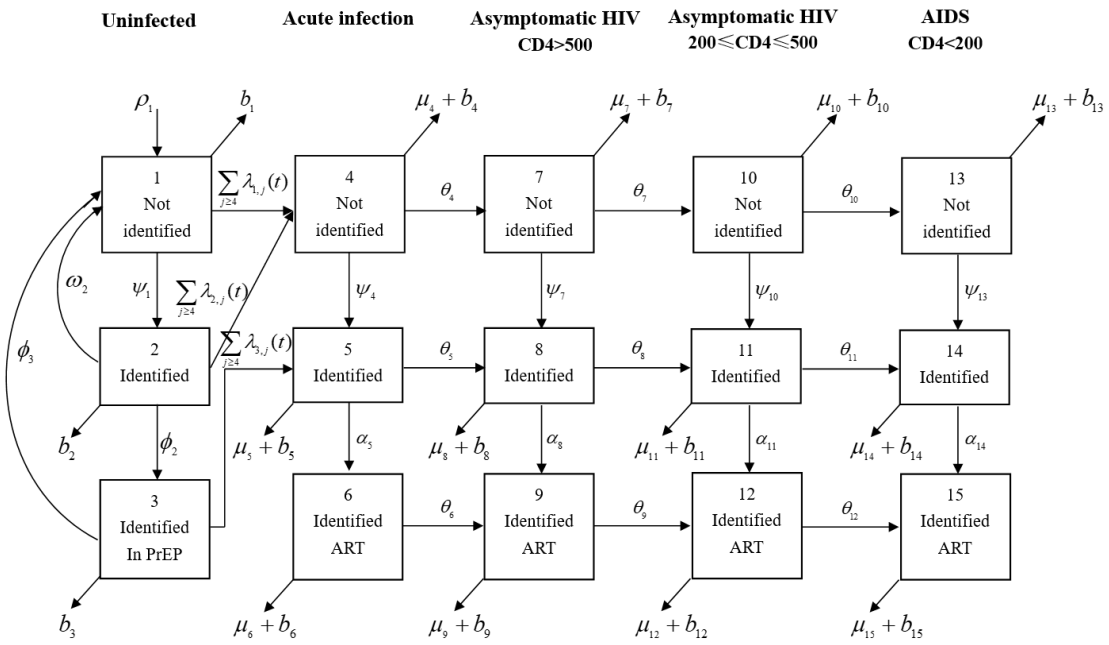

Figure 3 Deterministic compartmental model structure.

2.1.2 Parameters in the model

Table 1 shows the parameters involved in my study, including the notation, values and sources. Description of the calculations of some specific parameters are given below.

Size of the MSM population

This is calculated based on several previous surveys of the proportion of the adult population who are MSM. Ezoe et al. used a network scale-up method to obtain an estimate of 2.9%[40], while Ichikawa (2011) used a nationally representative survey to obtain an estimate of 2.0%[59], and Ichikawa (2017) reported a figure of 4.6% and 4.1% from internet surveys in 2012 and 2013 by a commercial company[42]. Given these numbers use different methods of varying quality, I use the median value of the most recent four estimates, giving a value of 3.5%.

Initial HIV prevalence among MSM and initial values for population

A survey in 2018 by Takano found 3.0% prevalence of HIV among MSM mailed a test kit[60]. I calculated the prevalence using the total number of HIV/AIDS cases in Japan in 2017. I found the total number of new HIV and AIDS cases diagnosed each year to that point, summed them and subtracted the deaths. Assuming all AIDS cases were diagnosed, I divided those surviving AIDS cases amongst the high- and low-risk population at a 20/80 ratio, and assigned them to different compartments of the model. I then multiplied the number of HIV cases by 1.17, to reflect that 14.4% of all HIV cases are likely undiagnosed[61]. The resulting number was also divided amongst the high- and low-risk groups at the 20/80 ratio and divided amongst compartments. Within the compartmental structure of each high- and low-risk population, the prevalent cases were divided between identified and unidentified groups following the proportion of unidentified PLWH in Japan. Prevalent cases were then assigned into CD4 stages based on clinical evidence for the proportion of people newly-diagnosed with HIV in each stage, using data obtained from the National Center for Global Health and Medicine EACH Cohort study. Unidentified cases were assigned into the acute and asymptomatic stages only in these proportions, on the assumption that AIDS cases in Japan are always identified through passive case-finding. The final prevalence assumed in this study is lower than that in the Takano paper but likely reflects over-representation in this paper since it is a mail-in survey.

Annual mortality rate without ART

Because treatment entry before AIDS is almost universal in Japan it was difficult to find specific information on mortality in untreated Japanese patients. Studies from Africa were used to estimate these rates instead. For mortality during acute infection the data from Lundgren (2015) was used for patients with CD4>800 and delayed treatment initiation[62]. Mortality rates for patients with CD4>500 were approximated from data on those with CD4>350 of 0.03[63]. For CD4 counts between 200 and 500, a mortality rate of 10 per 100 person years was obtained from a study of adults in Uganda[64]. For AIDS (defined as CD4<200), the same paper gave a rate of 0.48[64].

Annual mortality rate with ART

Mortality rates for patients in HAART were taken from Palella[65] and Lundgren[62]. I also used an estimate of approximate AIDS mortality based on Ministry of Health, Labour and Welfare (MHLW) notifications and deaths. Acute infection was treated as a CD4>800.

Progression rates

Disease progress rates were estimated from clinical data obtained from the EACH Cohort of PLWH at the AIDS Clinical Center, the National Center of Global Health Medicine using survival analysis to time from entering a CD4 stage to entering the following stage. This data was analyzed for a ministry of health project and is not publicly available.

Annual number of partners and proportion of LRMSM/HRMSM

The 2017 LASH report provides data on the number of partners from a large survey of MSM in Tokyo, as well as the proportion of partners with whom anal sex occurred (tables 16 and 25)[46]. The number of partners is reported in categories, so I estimated the average number of partners as the lowest number in the category multiplied by the proportion of people in the category, summed over all categories. LRMSM were defined as all men up to the 80th percentile of partner numbers, and HRMSM the men in the highest quintile of partner numbers. Average numbers of partners among the HRMSM were estimated using the same method, and then the number of low-risk partners was calculated to balance the average number of partners for the whole population. The number of partners was then multiplied by the proportion having anal sex in order to give the number of risky sexual encounters. This gave an estimate of 4.1 partners per year for the whole population, and 14.1 for HRMSM.

Condom use

This is calculated based on several previous surveys of the condom use rates among MSM population. The condom use rate in this study refers to the proportion of people responding always in surveys. Adam O Hill (2018) used a gay app-based survey to obtain an estimate of 31.5% with regular partners and an estimate of 45.8% with casual partners[56], while Yoharu Hidaka reported a figure of 32% and 30.4% from internet surveys in 2011 and 2012[66]. Given these numbers use different methods of varying quality, I use the mean value of the four estimates, setting the condom use rate at 35%.

HIV Testing

The 2017 LASH report finds 62% of respondents have ever had an HIV test (table 46) and 55.4% of those respondents had their test in the past year (table 47), suggesting that 34.3% of MSM had been tested in the past year[46]. Ichikawa (2017) reported similar level testing rate in 2012 and 2013[42]. Thus, 35% might be a reasonable value to set this at, with no evidence of increases over time.

Table 1 Model parameters

Variable[a]	Definition	Value	References
Demographic			
	Initial population (age 18-59)		
	Men	35763734	
	MSM (%)	3.5%	[40, 42, 59]
	Low-risk MSM (%)	0.8	[46]
	High-risk MSM (%)	0.2	[46]
	Background maturation, entry and mortality rates		
b_j^i	Annual maturation rate, male	0.0271	[57]
ρ_1^i	Annual entry rate, male	0.0167	[57]
μ_j^i	Annual mortality rate, male (background)	0.00486	[57]
	Annual mortality rate without ART		
	Acute	0.003	[62]
	Asymptomatic (CD>500)	0.03	[63]
	Asymptomatic (200<=CD4<=500)	0.1	[64]
	AIDS (CD4<200)	0.48	[64]
	Annual mortality rate with ART		
	Acute	0.002	[62, 65]
	Asymptomatic (CD>500)	0.002	[62, 65]
	Asymptomatic (200<=CD4<=500)	0.01	[62, 65]
	AIDS (CD4<200)	0.02	[62, 65]
Biological			
	Duration of HIV progression status converted to months		
$1/\theta_j^i$	Acute to CD4>500	3	[67]
	CD4>500 to 200<=CD4<=500	14.3	[67]
	200<=CD4<=500 to CD4<200	80.33	[67]
	Probability of HIV transmission per partnership, where z= acute, asymptomatic HIV, symptomatic HIV, and AIDS		
σ^z	Acute (within 3 months)	0.21	[58]
	Asymptomatic (CD>500)	0.003	[58]
	Asymptomatic (200<=CD4<=500)	0.045	[58]
	AIDS (CD4<200)	0.12	[58]
r_2	**Reduction in infectivity (multiplicative) due to ART**	0.99	[68]
Behavioral			
	Annual number of partners		

	MSM, total	4.1	[46]
η_1	Low risk MSM	1.6	Calculated[b] [46]
η_2	High risk MSM	14.1	[46]
	Condom use (% of sexual encounters)		
$u_{i,j}$	Condom use rate (%)	35%	[56, 66]
κ	Condom effectiveness	0.9	[69, 70]
	Others		
ε	Proportion of members of one group having sexual interaction with members of the other group	0.3	Assumed
r_1	Reduction in sexual behavior after HIV diagnosis	0.2	Assumed
$r_1^{'}$	Reduction in sexual behavior among AIDS patients	0.9	Assumed
Biomedical			
	HIV testing		
ψ_j^i	Proportion of population tested in past 12 months, %	35%	[42, 46]
	Rate of detection of HIV through passive case-finding	0.1	Assumed
	Rate of detection of AIDS through passive case-finding	1	Assumed
$1/\omega_2^i$	Average duration that uninfected individuals remain identified after testing in risk	12 months	
	Monthly entry rate to ART		
α_j^i	Acute	0.2	Calculated[c]
	Asymptomatic (CD>500)	0.29	Calculated[c]
	Asymptomatic (200<=CD4<=500)	0.38	Calculated[c]
	AIDS (CD4<200)	0.43	Calculated[c]
	Pre-exposure prophylaxis		
ϕ_2^i	Rate of uninfected people start taking PrEP	-	Based on the scenarios
ϕ_3^i	Rate of PrEP dropout	0	100% adherence
r_3	PrEP Effectiveness	0.9 under 100% adherence	[71]
Transmission force[d]			
$\sum_{j\geq 4}\lambda_{k,j}^i(t)$	Transmission force (k=1,2 means not in PrEP, k=3 means in PrEP)	-	[58]

NOTE: i indicates risk group, $i=1$:LRMSM, $i=2$: HRMSM; $j\left(j=1,2,\cdots,15\right)$ indicates HIV status. Variable[a]: variables with no notation were not directly used but were

involved in the calculations of other variables. Calculated[b]: Annual number of partners in LRMSM was calculated coordinated with the proportion of people in each group and the annual number of partners in HRMSM to ensure the annual number of partners of 4.1 in the whole population. Calculated[c]: Obtained using survival analysis of the data obtained from the clinic cohort at AIDS Clinical Center. Transmission force[d]: Transmission force represents the rate of uninfected people $(j=1,2,3)$ entering the infected population $(j=4,5)$, which is the sum of force of infections with each infectious compartment $(j=4,5,\cdots,15)$. The detailed calculations are shown in later sub-section 2.2.3.

2.2 Model equations

In this section, I will show the 15 ODEs and two key components in these equations: mixing between two groups and the force of infection.

2.2.1 Ordinary differential equations

For each risk group, there are 15 ODEs describing the rate of change in the number of people in each compartment, the detailed equations are shown below. $X_{i,j}$ is initial value for the population of risk group i in compartment j.

$$\frac{dX_{i,1}}{dt}=\rho_1^i\sum_{\forall j}X_{i,j}+\omega_2^iX_{i,2}+\phi_3^iX_{i,3}-\left(\sum_{j\geq 4}\lambda_{1,j}^i(t)\right)X_{i,1}-(\psi_1^i+b_1^i)X_{i,1} \tag{1}$$

$$\frac{dX_{i,2}}{dt}=\psi_1^iX_{i,1}-\left(\sum_{j\geq 4}\lambda_{2,j}^i(t)\right)X_{i,2}-(\omega_2^i+\phi_2^i+b_2^i)X_{i,2} \tag{2}$$

$$\frac{dX_{i,3}}{dt} = \phi_2^i X_{i,2} - \left(\sum_{j \geq 4} \lambda_{3,j}^i (t) \right) X_{i,3} - (\phi_3^i + b_3^i) X_{i,3} \tag{3}$$

$$\frac{dX_{i,4}}{dt} = \left(\sum_{j \geq 4} \lambda_{1,j}^i (t) \right) X_{i,1} + \left(\sum_{j \geq 4} \lambda_{2,j}^i (t) \right) X_{i,2} - (\psi_4^i + \theta_4^i + \mu_4^i + b_4^i) X_{i,4} \tag{4}$$

$$\frac{dX_{i,5}}{dt} = \left(\sum_{j \geq 4} \lambda_{3,j}^i (t) \right) X_{i,3} + \psi_4^i X_{i,4} - (\theta_5^i + \alpha_5^i + \mu_5^i + b_5^i) X_{i,5} \tag{5}$$

$$\frac{dX_{i,6}}{dt} = \alpha_5^i X_{i,5} - (\theta_6^i + \mu_6^i + b_6^i) X_{i,6} \tag{6}$$

$$\frac{dX_{i,7}}{dt} = \theta_4^i X_{i,4} - (\psi_7^i + \theta_7^i + \mu_7^i + b_7^i) X_{i,7} \tag{7}$$

$$\frac{dX_{i,8}}{dt} = \theta_5^i X_{i,5} + \psi_7^i X_{i,7} - (\theta_8^i + \alpha_8^i + \mu_8^i + b_8^i) X_{i,8} \tag{8}$$

$$\frac{dX_{i,9}}{dt} = \theta_6^i X_{i,6} + \alpha_8^i X_{i,8} - (\theta_9^i + \mu_9^i + b_9^i) X_{i,9} \tag{9}$$

$$\frac{dX_{i,10}}{dt} = \theta_7^i X_{i,7} - (\psi_{10}^i + \theta_{10}^i + \mu_{10}^i + b_{10}^i) X_{i,10} \tag{10}$$

$$\frac{dX_{i,11}}{dt} = \theta_8^i X_{i,8} + \psi_{10}^i X_{i,10} - (\theta_{11}^i + \alpha_{11}^i + \mu_{11}^i + b_{11}^i) X_{i,11} \tag{11}$$

$$\frac{dX_{i,12}}{dt} = \theta_9^i X_{i,9} + \alpha_{11}^i X_{i,11} - (\theta_{12}^i + \mu_{12}^i + b_{12}^i) X_{i,12} \tag{12}$$

$$\frac{dX_{i,13}}{dt} = \theta_{10}^i X_{i,10} - (\psi_{13}^i + \mu_{13}^i + b_{13}^i) X_{i,13} \tag{13}$$

$$\frac{dX_{i,14}}{dt} = \theta_{11}^{i} X_{i,11} + \psi_{13}^{i} X_{i,13} - (\alpha_{14}^{i} + \mu_{14}^{i} + b_{14}^{i}) X_{i,14} \tag{14}$$

$$\frac{dX_{i,15}}{dt} = \theta_{12}^{i} X_{i,12} + \alpha_{14}^{i} X_{i,14} - (\mu_{15}^{i} + b_{15}^{i}) X_{i,15} \tag{15}$$

2.2.2 Mixing between LRMSM and HRMSM

The model was applied to LRMSM and HRMSM, respectively. People in each group have a chance to interact with people in the other group. To model the chance, a mixing parameter ε was introduced, with $1-\varepsilon$ representing the fraction of partnerships occurring within one's own group. The proportion of the partnerships that members of LRMSM have with members of LRMSM is:

$$\eta_{1,1} = (1-\varepsilon) + \varepsilon \frac{TP1}{TP1+TP2} \tag{16}$$

The proportion of the partnerships that members of LRMSM have with members of HRMSM is:

$$\eta_{1,2} = \varepsilon \frac{TP2}{TP1+TP2} \tag{17}$$

The proportion of the partnerships that members of HRMSM have with members of LRMSM is:

$$\eta_{2,1} = \varepsilon \frac{TP1}{TP1+TP2} \tag{18}$$

The proportion of the partnerships that members of HRMSM have with members of HRMSM is:

$$\eta_{2,2} = (1-\varepsilon) + \varepsilon \frac{TP2}{TP1+TP2} \tag{19}$$

Where, $TP1$ and $TP2$ are the total numbers of partnerships of LRMSM and HRMSM

respectively.

$$TP1=\sum_{i=1}\left[\left(\sum_{j=1,2,3,4,7,10}X_{i,j}\right)n_i+\left(\sum_{j=5,6,8,9,11,12}X_{i,j}\right)n_i(1-r_1)+\left(\sum_{j=13,14,15}X_{i,j}\right)n_i(1-r_1')\right] \tag{20}$$

$$TP2=\sum_{i=2}\left[\left(\sum_{j=1,2,3,4,7,10}X_{i,j}\right)n_i+\left(\sum_{j=5,6,8,9,11,12}X_{i,j}\right)n_i(1-r_1)+\left(\sum_{j=13,14,15}X_{i,j}\right)n_i(1-r_1')\right] \tag{21}$$

2.2.3 Transmission force

Transmission force represents the rate of uninfected people $(j=1,2,3)$ entering the infected population $(j=4,5)$, which is the sum of force of infections with each infectious compartment $(j=4,5,\cdots,15)$. The detailed calculations are described in a previous paper[58].

Transmission forces for LRMSM that are not in PrEP are:

$$\sum_{j\geq4}\lambda_{1,j}^{1}(t)=\sum_{j\geq4}\lambda_{2,j}^{1}(t)=\sum_{j\geq4}\left\{1-N\_LRMSM_j^{\eta_{1,1}n_1(1-u_1\kappa)}\right\}+\sum_{j\geq4}\left\{1-N\_HRMSM_j^{\eta_{1,2}n_1(1-u_1\kappa)}\right\} \tag{22}$$

Transmission force for LRMSM that are in PrEP is:

$$\sum_{j\geq4}\lambda_{3,j}^{1}(t)=\sum_{j\geq4}\left\{1-N\_prepLRMSM_j^{\eta_{1,1}n_1(1-u_1\kappa)}\right\}+\sum_{j\geq4}\left\{1-N\_prepHRMSM_j^{\eta_{1,2}n_1(1-u_1\kappa)}\right\} \tag{23}$$

Transmission forces for HRMSM that are not in PrEP are:

$$\sum_{j\geq4}\lambda_{1,j}^{2}(t)=\sum_{j\geq4}\lambda_{2,j}^{2}(t)=\sum_{j\geq4}\left\{1-N\_LRMSM_j^{\eta_{2,1}n_2(1-u_2\kappa)}\right\}+\sum_{j\geq4}\left\{1-N\_HRMSM_j^{\eta_{2,2}n_2(1-u_2\kappa)}\right\} \tag{24}$$

Transmission force for HRMSM that are in PrEP is:

$$\sum_{j\geq4}\lambda_{3,j}^{2}(t)=\sum_{j\geq4}\left\{1-N\_prepLRMSM_j^{\eta_{2,1}n_2(1-u_2\kappa)}\right\}+\sum_{j\geq4}\left\{1-N\_prepHRMSM_j^{\eta_{2,2}n_2(1-u_2\kappa)}\right\} \tag{25}$$

Where $N\_LRMSM_j\ (j=4,5,\cdots,15)$ is the probability that MSM without PrEP are not infected by LRMSM in compartment j in one partnership.

$$N\_LRMSM_4=\left[1-\left(\frac{X_{1,4}n_1}{TP1}\sigma^{acute}\right)\right];N\_LRMSM_{10}=\left[1-\left(\frac{X_{1,10}n_1}{TP1}\sigma^{asym}\right)\right];$$
$$N\_LRMSM_5=\left[1-\left(\frac{X_{1,5}n_1(1-r_1)}{TP1}\sigma^{acute}\right)\right];N\_LRMSM_{11}=\left[1-\left(\frac{X_{1,11}n_1(1-r_1)}{TP1}\sigma^{asym}\right)\right];$$
$$N\_LRMSM_6=\left[1-\left(\frac{X_{1,6}n_1(1-r_1)}{TP1}\sigma^{acute}(1-r_2)\right)\right];N\_LRMSM_{12}=\left[1-\left(\frac{X_{1,12}n_1(1-r_1)}{TP1}\sigma^{asym}(1-r_2)\right)\right];$$
$$N\_LRMSM_7=\left[1-\left(\frac{X_{1,7}n_1}{TP1}\sigma^{asym}\right)\right];N\_LRMSM_{13}=\left[1-\left(\frac{X_{1,13}n_1(1-r_1^{'})}{TP1}\sigma^{AIDS}\right)\right];$$
$$N\_LRMSM_8=\left[1-\left(\frac{X_{1,8}n_1(1-r_1)}{TP1}\sigma^{asym}\right)\right];N\_LRMSM_{14}=\left[1-\left(\frac{X_{1,14}n_1(1-r_1^{'})}{TP1}\sigma^{AIDS}\right)\right];$$
$$N\_LRMSM_9=\left[1-\left(\frac{X_{1,9}n_1(1-r_1)}{TP1}\sigma^{asym}(1-r_2)\right)\right];N\_LRMSM_{15}=\left[1-\left(\frac{X_{1,15}n_1(1-r_1^{'})}{TP1}\sigma^{AIDS}(1-r_2)\right)\right] \quad (26)$$

$N\_prepLRMSM_j\left(j=4,5,\cdots,15\right)$ is the probability that MSM with PrEP are not infected by LRMSM in compartment j in one partnership.

$$N\_prepLRMSM_4=\left[1-\left(\frac{X_{1,4}n_1}{TP1}\sigma^{acute}(1-r_3)\right)\right];N\_prepLRMSM_{10}=\left[1-\left(\frac{X_{1,10}n_1}{TP1}\sigma^{asym}(1-r_3)\right)\right];$$
$$N\_prepLRMSM_5=\left[1-\left(\frac{X_{1,5}n_1(1-r_1)}{TP1}\sigma^{acute}(1-r_3)\right)\right];N\_prepLRMSM_{11}=\left[1-\left(\frac{X_{1,11}n_1(1-r_1)}{TP1}\sigma^{asym}(1-r_3)\right)\right];$$
$$N\_prepLRMSM_6=\left[1-\left(\frac{X_{1,6}n_1(1-r_1)}{TP1}\sigma^{acute}(1-r_2)(1-r_3)\right)\right];N\_prepLRMSM_{12}=\left[1-\left(\frac{X_{1,12}n_1(1-r_1)}{TP1}\sigma^{asym}(1-r_2)(1-r_3)\right)\right];$$
$$N\_prepLRMSM_7=\left[1-\left(\frac{X_{1,7}n_1}{TP1}\sigma^{asym}(1-r_3)\right)\right];N\_prepLRMSM_{13}=\left[1-\left(\frac{X_{1,13}n_1(1-r_1^{'})}{TP1}\sigma^{AIDS}(1-r_3)\right)\right];$$
$$N\_prepLRMSM_8=\left[1-\left(\frac{X_{1,8}n_1(1-r_1)}{TP1}\sigma^{asym}(1-r_3)\right)\right];N\_prepLRMSM_{14}=\left[1-\left(\frac{X_{1,14}n_1(1-r_1^{'})}{TP1}\sigma^{AIDS}(1-r_3)\right)\right];$$
$$N\_prepLRMSM_9=\left[1-\left(\frac{X_{1,9}n_1(1-r_1)}{TP1}\sigma^{asym}(1-r_2)(1-r_3)\right)\right];N\_prepLRMSM_{15}=\left[1-\left(\frac{X_{1,15}n_1(1-r_1^{'})}{TP1}\sigma^{AIDS}(1-r_2)(1-r_3)\right)\right] \quad (27)$$

$N\_HRMSM_j\left(j=4,5,\cdots,15\right)$ is the probability that MSM without PrEP are not infected by HRMSM in compartment j in one partnership.

$$N\_HRMSM_4=\left[1-\left(\frac{X_{2,4}n_2}{TP2}\sigma^{acute}\right)\right];N\_HRMSM_{10}=\left[1-\left(\frac{X_{2,10}n_2}{TP2}\sigma^{asym}\right)\right];$$
$$N\_HRMSM_5=\left[1-\left(\frac{X_{2,5}n_2(1-r_1)}{TP2}\sigma^{acute}\right)\right];N\_HRMSM_{11}=\left[1-\left(\frac{X_{2,11}n_2(1-r_1)}{TP2}\sigma^{asym}\right)\right];$$
$$N\_HRMSM_6=\left[1-\left(\frac{X_{2,6}n_2(1-r_1)}{TP2}\sigma^{acute}(1-r_2)\right)\right];N\_HRMSM_{12}=\left[1-\left(\frac{X_{2,12}n_2(1-r_1)}{TP2}\sigma^{asym}(1-r_2)\right)\right];$$
$$N\_HRMSM_7=\left[1-\left(\frac{X_{2,7}n_2}{TP2}\sigma^{asym}\right)\right];N\_HRMSM_{13}=\left[1-\left(\frac{X_{2,13}n_2(1-r_1^{'})}{TP2}\sigma^{AIDS}\right)\right];$$
$$N\_HRMSM_8=\left[1-\left(\frac{X_{2,8}n_2(1-r_1)}{TP2}\sigma^{asym}\right)\right];N\_HRMSM_{14}=\left[1-\left(\frac{X_{2,14}n_2(1-r_1^{'})}{TP2}\sigma^{AIDS}\right)\right];$$
$$N\_HRMSM_9=\left[1-\left(\frac{X_{2,9}n_2(1-r_1)}{TP2}\sigma^{asym}(1-r_2)\right)\right];N\_HRMSM_{15}=\left[1-\left(\frac{X_{2,15}n_2(1-r_1^{'})}{TP2}\sigma^{AIDS}(1-r_2)\right)\right] \quad (28)$$

$N\_prepHRMSM_j\ (j=4,5,\cdots,15)$ is the probability that MSM with PrEP are not infected by HRMSM in compartment j in one partnership.

$$N\_prepHRMSM_4=\left[1-\left(\frac{X_{2,4}n_2}{TP2}\sigma^{acute}(1-r_3)\right)\right];N\_prepHRMSM_{10}=\left[1-\left(\frac{X_{2,10}n_2}{TP2}\sigma^{asym}(1-r_3)\right)\right];$$
$$N\_prepHRMSM_5=\left[1-\left(\frac{X_{2,5}n_2(1-r_1)}{TP2}\sigma^{acute}(1-r_3)\right)\right];N\_prepHRMSM_{11}=\left[1-\left(\frac{X_{2,11}n_2(1-r_1)}{TP2}\sigma^{asym}(1-r_3)\right)\right];$$
$$N\_prepHRMSM_6=\left[1-\left(\frac{X_{2,6}n_2(1-r_1)}{TP2}\sigma^{acute}(1-r_2)(1-r_3)\right)\right];N\_prepHRMSM_{12}=\left[1-\left(\frac{X_{2,12}n_2(1-r_1)}{TP2}\sigma^{asym}(1-r_2)(1-r_3)\right)\right];$$
$$N\_prepHRMSM_7=\left[1-\left(\frac{X_{2,7}n_2}{TP2}\sigma^{asym}(1-r_3)\right)\right];N\_prepHRMSM_{13}=\left[1-\left(\frac{X_{2,13}n_2(1-r_1^{'})}{TP2}\sigma^{AIDS}(1-r_3)\right)\right];$$
$$N\_prepHRMSM_8=\left[1-\left(\frac{X_{2,8}n_2(1-r_1)}{TP2}\sigma^{asym}(1-r_3)\right)\right];N\_prepHRMSM_{14}=\left[1-\left(\frac{X_{2,14}n_2(1-r_1^{'})}{TP2}\sigma^{AIDS}(1-r_3)\right)\right];$$
$$N\_prepHRMSM_9=\left[1-\left(\frac{X_{2,9}n_2(1-r_1)}{TP2}\sigma^{asym}(1-r_2)(1-r_3)\right)\right];N\_prepHRMSM_{15}=\left[1-\left(\frac{X_{2,15}n_2(1-r_1^{'})}{TP2}\sigma^{AIDS}(1-r_2)(1-r_3)\right)\right] \quad (29)$$

2.3 Effective reproduction number of HIV

Reproduction number (R) is an important concept in the field of epidemiology and

infectious diseases study. R is the average number of secondary cases that one case would produce in her/his/its lifetime. When R >1, the epidemic will continue, while when R <1, the epidemic will slow down and can be expected to end in the future. The basic reproduction number R_0 is the reproduction number in a completely susceptible population[72], while the effective reproduction number R_t at time t is used when there is a certain amount of infections in the population or some interventions have been implemented[73].

In this section, first I used the next generation matrix method to obtain the formula of R_0^i for each group without considering the interaction between two groups, and then applied a meta-population approach to obtain a formula of R_0 for the whole MSM population by incorporating the mixing function. Finally, I derived the effective reproduction number R_t by applying the formula of R_0 but using the parameter values in year t.

2.3.1 Next generation matrix method

The next generation matrix method was applied to the deterministic compartment model for each group[74]. In this method each of the ODE of each infected compartment is divided into two processes: new infections in group i and infected compartment j, f_j^i and transition in group i in infected compartments j, v_j^i.

$$\frac{dX_{i,j}}{dt} = f_j^i(\boldsymbol{X}_0^i) - v_j^i(\boldsymbol{X}_0^i),\ j=4,5,\cdots,15 \tag{30}$$

Where $\boldsymbol{X}_0^i$ is the disease-free equilibrium (DFE), which assumes there is no infected cases in the population, and the number of people in uninfected status is equal to the population. The next generation matrix for group i is defined as

$$\mathcal{N} = F^i(V^i)^{-1} \tag{31}$$

where Jacobian matrices F^i and V^i are:

$$F^i = \left[\frac{\partial f_j^i(\boldsymbol{X}_0^i)}{\partial X_{i,k}} \right] \tag{32}$$

$$V^i = \left[\frac{\partial v_j^i(\boldsymbol{X}_0^i)}{\partial X_{i,k}} \right] \tag{33}$$

Where $j,k=4,5,\cdots,15$. The basic reproduction number R_0^i is the maximum eigenvalue of the next generation matrix in equation 31.

Next generation matrix for LRMSM

The new infection vector f^1 has 12 elements, which can be expressed as:

$$f^1 = \left[\sum_{j\geq 4} \lambda_{1,j}^1(t)(X_{1,1} + X_{1,2}), \sum_{j\geq 4} \lambda_{3,j}^1(t) X_{1,3}, 0, 0, \cdots, 0 \right] \tag{34}$$

Interactions between two groups are not considered in the calculation of a single group. Therefore, the transmission force (equations 22 and 23) can be rewritten as

$$\sum_{j\geq 4} \lambda_{1,j}^1(t) = \sum_{j\geq 4} \left\{ 1 - N\_LRMSM_j^{\,n_1(1-u_1\kappa)} \right\} \tag{35}$$

$$\sum_{j\geq 4} \lambda_{3,j}^1(t) = \sum_{j\geq 4} \left\{ 1 - N\_prepLRMSM_j^{\,n_1(1-u_1\kappa)} \right\} \tag{36}$$

According to equations 26 and 27, the simplified form of N_LRMSM_j and $N\_prepLRMSM_j$ can be rewritten as $1-\frac{LR(X_{1,j})}{TP_1}$ and $1-\frac{prepLR(X_{1,j})}{TP_1}$ respectively. When the system is at DFE, $TP_1 = (X_{1,1} + X_{1,2} + X_{1,3})n_1 = N_1 n_1$, N_1 is the number of LRMSM. In order to obtain the new infection Jacobian matrix F^1, we need to calculate the partial derivative of each element of f^1 with respect to every $X_{1,j}$ $(j=4,5,\cdots,15)$, and the key to calculate the partial derivatives lies in the first two elements of f^1, because the partial derivatives for third to twelfth elements are 0 (see equation 34). The partial derivative of

$\sum_{j\geq 4}\lambda_{1,j}^{1}(t)$:

$$
\begin{aligned}
&\frac{\partial}{\partial X_{1,k}}\sum_{j\geq 4}\left\{1-N\_LRMSM_{j}^{\,n_1(1-u_1\kappa)}\right\}\\
&=\sum_{j\geq 4}\frac{\partial}{\partial X_{1,k}}\left\{1-N\_LRMSM_{j}^{\,n_1(1-u_1\kappa)}\right\}\\
&=\sum_{j\geq 4}\frac{\partial}{\partial X_{1,k}}\left\{1-\left(1-\frac{LR(X_{1,j})}{TP_1}\right)^{n_1(1-u_1\kappa)}\right\}\\
&=-\sum_{j\geq 4}\frac{\partial}{\partial X_{1,k}}\left(1-\frac{LR(X_{1,j})}{TP_1}\right)^{n_1(1-u_1\kappa)}\\
&=-\sum_{j\geq 4}\left(n_1(1-u_1\kappa)\left(1-\frac{LR(X_{1,j})}{TP_1}\right)^{n_1(1-u_1\kappa)-1}\right)\left(-\frac{\frac{\partial LR(X_{1,j})}{\partial X_{1,k}}TP_1-LR(X_{1,j})\frac{\partial TP_1}{\partial X_{1,k}}}{TP_1^{2}}\right)
\end{aligned}
\tag{37}
$$

The partial derivative of $\sum_{j\geq 4}\lambda_{3,j}^{1}(t)$:

$$
\begin{aligned}
&\frac{\partial}{\partial X_{1,k}}\sum_{j\geq 4}\left\{1-N\_prepLRMSM_{j}^{\,n_1(1-u_1\kappa)}\right\}\\
&=\sum_{j\geq 4}\frac{\partial}{\partial X_{1,k}}\left\{1-N\_prepLRMSM_{j}^{\,n_1(1-u_1\kappa)}\right\}\\
&=\sum_{j\geq 4}\frac{\partial}{\partial X_{1,k}}\left\{1-\left(1-\frac{prepLR(X_{1,j})}{TP_1}\right)^{n_1(1-u_1\kappa)}\right\}\\
&=-\sum_{j\geq 4}\frac{\partial}{\partial X_{1,k}}\left(1-\frac{prepLR(X_{1,j})}{TP_1}\right)^{n_1(1-u_1\kappa)}\\
&=-\sum_{j\geq 4}\left(n_1(1-u_1\kappa)\left(1-\frac{prepLR(X_{1,j})}{TP_1}\right)^{n_1(1-u_1\kappa)-1}\right)\left(-\frac{\frac{\partial prepLR(X_{1,j})}{\partial X_{1,k}}TP_1-prepLR(X_{1,j})\frac{\partial TP_1}{\partial X_{1,k}}}{TP_1^{2}}\right)
\end{aligned}
\tag{38}
$$

Because both $LR(X_{1,j})$ and $prepLR(X_{1,j})$ only depend on the number of people in compartment j, $LR(X_{1,j})\propto X_{1,j}$ and $prepLR(X_{1,j})\propto X_{1,j}$, therefore,

$$\frac{\partial LR(X_{1,j})}{\partial X_{1,k}} = 0, \forall j \neq k \tag{39}$$

$$\frac{\partial prepLR(X_{1,j})}{\partial X_{1,k}} = 0, \forall j \neq k \tag{40}$$

Applying equations 39 and 40 to equations 37 and 38, I can simplify equations 37 and 38 to

$$\begin{aligned} &\frac{\partial}{\partial X_{1,k}} \sum_{j \geq 4} \left\{ 1 - N\_LRMSM_j^{\,n_1(1-u_1\kappa)} \right\} \\ &= \frac{n_1(1-u_1\kappa)\dfrac{\partial LR(X_{1,k})}{\partial X_{1,k}}}{N_1 n_1} \\ &= \frac{(1-u_1\kappa)\dfrac{\partial LR(X_{1,k})}{\partial X_{1,k}}}{N_1} \end{aligned} \tag{41}$$

$$\begin{aligned} &\frac{\partial}{\partial X_{1,k}} \sum_{j \geq 4} \left\{ 1 - N\_prepLRMSM_j^{\,n_1(1-u_1\kappa)} \right\} \\ &= \frac{n_1(1-u_1\kappa)\dfrac{\partial prepLR(X_{1,k})}{\partial X_{1,k}}}{N_1 n_1} \\ &= \frac{(1-u_1\kappa)\dfrac{\partial prepLR(X_{1,k})}{\partial X_{1,k}}}{N_1} \end{aligned} \tag{42}$$

According to equations 26 and 27, $\frac{\partial LR(X_{1,k})}{\partial X_{1,k}}$ and $\frac{\partial prepLR(X_{1,k})}{\partial X_{1,k}}$ are easy to calculate.

According to the calculation process above, define the Jacobian matrix F^1 as:

$$F^1_{j-3,k-3} = \left[\frac{\partial f^1_{j-3}}{\partial X_{1,k}} \right] = \begin{cases} \beta^1_{j-3,k-3}, if & 4 \leq j \leq 5 \\ 0, \quad if & 5 < j \leq 15 \end{cases}, \quad k \in (4,15) \tag{43}$$

Where β^1 is:

$$\beta^1_{1,1}=\frac{(1-u_1\kappa)n_1\sigma^{acute}}{N_1}(X_{1,1}+X_{1,2});\beta^1_{1,7}=\frac{(1-u_1\kappa)n_1\sigma^{sym}}{N_1}(X_{1,1}+X_{1,2});$$

$$\beta^1_{1,2}=\frac{(1-u_1\kappa)n_1(1-r_1)\sigma^{acute}}{N_1}(X_{1,1}+X_{1,2});\beta^1_{1,8}=\frac{(1-u_1\kappa)n_1(1-r_1)\sigma^{sym}}{N_1}(X_{1,1}+X_{1,2});$$

$$\beta^1_{1,3}=\frac{(1-u_1\kappa)n_1(1-r_1)\sigma^{acute}(1-r_2)}{N_1}(X_{1,1}+X_{1,2});\beta^1_{1,9}=\frac{(1-u_1\kappa)n_1(1-r_1)\sigma^{sym}(1-r_2)}{N_1}(X_{1,1}+X_{1,2});$$

$$\beta^1_{1,4}=\frac{(1-u_1\kappa)n_1\sigma^{asym}}{N_1}(X_{1,1}+X_{1,2});\beta^1_{1,10}=\frac{(1-u_1\kappa)n_1(1-r_1^{'})\sigma^{AIDS}}{N_1}(X_{1,1}+X_{1,2});$$

$$\beta^1_{1,5}=\frac{(1-u_1\kappa)n_1(1-r_1)\sigma^{asym}}{N_1}(X_{1,1}+X_{1,2});\beta^1_{1,11}=\frac{(1-u_1\kappa)n_1(1-r_1^{'})\sigma^{AIDS}}{N_1}(X_{1,1}+X_{1,2});$$

$$\beta^1_{1,6}=\frac{(1-u_1\kappa)n_1(1-r_1)\sigma^{asym}(1-r_2)}{N_1}(X_{1,1}+X_{1,2});\beta^1_{1,12}=\frac{(1-u_1\kappa)n_1(1-r_1^{'})\sigma^{AIDS}(1-r_2)}{N_1}(X_{1,1}+X_{1,2})$$

(44)

$$\beta^1_{2,1}=\frac{(1-u_1\kappa)n_1\sigma^{acute}(1-r_3)}{N_1}X_{1,3};\ \beta^1_{2,7}=\frac{(1-u_1\kappa)n_1\sigma^{sym}(1-r_3)}{N_1}X_{1,3};$$

$$\beta^1_{2,2}=\frac{(1-u_1\kappa)n_1(1-r_1)\sigma^{acute}(1-r_3)}{N_1}X_{1,3};\ \beta^1_{2,8}=\frac{(1-u_1\kappa)n_1(1-r_1)\sigma^{sym}(1-r_3)}{N_1}X_{1,3};$$

$$\beta^1_{2,3}=\frac{(1-u_1\kappa)n_1(1-r_1)\sigma^{acute}(1-r_2)(1-r_3)}{N_1}X_{1,3};\beta^1_{2,9}=\frac{(1-u_1\kappa)n_1(1-r_1)\sigma^{sym}(1-r_2)(1-r_3)}{N_1}X_{1,3};$$

$$\beta^1_{2,4}=\frac{(1-u_1\kappa)n_1\sigma^{asym}(1-r_3)}{N_1}X_{1,3};\ \beta^1_{2,10}=\frac{(1-u_1\kappa)n_1(1-r_1^{'})\sigma^{AIDS}(1-r_3)}{N_1}X_{1,3};$$

$$\beta^1_{2,5}=\frac{(1-u_1\kappa)n_1(1-r_1)\sigma^{asym}(1-r_3)}{N_1}X_{1,3};\ \beta^1_{2,11}=\frac{(1-u_1\kappa)n_1(1-r_1^{'})\sigma^{AIDS}(1-r_3)}{N_1}X_{1,3};$$

$$\beta^1_{2,6}=\frac{(1-u_1\kappa)n_1(1-r_1)\sigma^{asym}(1-r_2)(1-r_3)}{N_1}X_{1,3};\beta^1_{2,12}=\frac{(1-u_1\kappa)n_1(1-r_1^{'})\sigma^{AIDS}(1-r_2)(1-r_3)}{N_1}X_{1,3}$$

(45)

The transition vector v^1 consists of the differentiation part of each infected compartments (equation 4 to equation 15), except for the new infection parts. Because annual maturation rate b^i_j, annual mortality rate μ^i_j, HIV progression rate θ^i_j, HIV testing rate ψ^i_j are treated as same in two risk groups, I omitted the superscript in the formula. The equation for transition vector v^1 is shown in equation 46.

$$v^1=\begin{bmatrix}
\left(\psi_4+\theta_4+\mu_4+b_4\right)X_{1,4}\\
-\psi_4X_{1,4}+\left(\theta_5+\alpha_5+\mu_5+b_5\right)X_{1,5}\\
-\alpha_5X_{1,5}+(\theta_6+\mu_6+b_6)X_{1,6}\\
-\theta_4X_{1,4}+(\psi_7+\theta_7+\mu_7+b_7)X_{1,7}\\
-\theta_5X_{1,5}-\psi_7X_{1,7}+(\theta_8+\alpha_8+\mu_8+b_8)X_{1,8}\\
-\theta_6X_{1,6}-\alpha_8X_{1,8}+(\theta_9+\mu_9+b_9)X_{1,9}\\
-\theta_7X_{1,7}+(\psi_{10}+\theta_{10}+\mu_{10}+b_{10})X_{1,10}\\
-\theta_8X_{1,8}-\psi_{10}X_{1,10}+(\theta_{11}+\alpha_{11}+\mu_{11}+b_{11})X_{1,11}\\
-\theta_9X_{1,9}-\alpha_{11}X_{1,11}+(\theta_{12}+\mu_{12}+b_{12})X_{1,12}\\
-\theta_{10}X_{1,10}+(\psi_{13}+\mu_{13}+b_{13})X_{1,13}\\
-\theta_{11}X_{1,11}-\psi_{13}X_{1,13}+(\alpha_{14}+\mu_{14}+b_{14})X_{1,14}\\
-\theta_{12}X_{1,12}-\alpha_{14}X_{1,14}+(\mu_{15}+b_{15})X_{1,15}
\end{bmatrix} \tag{46}$$

The transition Jacobian matrixs V^1 is derived from this vector, as the matrix of partial derivatives:

$$V^1=\begin{bmatrix}
\psi_4+\theta_4+\mu_4+b_4 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0\\
-\psi_4 & \theta_5+\alpha_5+\mu_5+b_5 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0\\
0 & -\alpha_5 & \theta_6+\mu_6+b_6 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0\\
-\theta_4 & 0 & 0 & \psi_7+\theta_7+\mu_7+b_7 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0\\
0 & -\theta_5 & 0 & -\psi_7 & \theta_8+\alpha_8+\mu_8+b_8 & 0 & 0 & 0 & 0 & 0 & 0 & 0\\
0 & 0 & -\theta_6 & 0 & -\alpha_8 & \theta_9+\mu_9+b_9 & 0 & 0 & 0 & 0 & 0 & 0\\
0 & 0 & 0 & -\theta_7 & 0 & 0 & \psi_{10}+\theta_{10}+\mu_{10}+b_{10} & 0 & 0 & 0 & 0 & 0\\
0 & 0 & 0 & 0 & -\theta_8 & 0 & -\psi_{10} & \theta_{11}+\alpha_{11}+\mu_{11}+b_{11} & 0 & 0 & 0 & 0\\
0 & 0 & 0 & 0 & 0 & -\theta_9 & 0 & -\alpha_{11} & \theta_{12}+\mu_{12}+b_{12} & 0 & 0 & 0\\
0 & 0 & 0 & 0 & 0 & 0 & -\theta_{10} & 0 & 0 & \psi_{13}+\mu_{13}+b_{13} & 0 & 0\\
0 & 0 & 0 & 0 & 0 & 0 & 0 & -\theta_{11} & 0 & -\psi_{13} & \alpha_{14}+\mu_{14}+b_{14} & 0\\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -\theta_{12} & 0 & -\alpha_{14} & \mu_{15}+b_{15}
\end{bmatrix} \tag{47}$$

The basic reproduction number for the LRMSM group, R_0^1, is the maximum eigenvalue of $F^1(V^1)^{-1}$.

Next generation matrix for HRMSM

The new infection vector f^2 has 12 elements, which can be written as:

$$f^2=\left[\sum_{j\geq 4}\lambda_{1,j}^2(t)(X_{2,1}+X_{2,2}),\sum_{j\geq 4}\lambda_{3,j}^2(t)X_{2,3},0,0,\cdots,0\right] \tag{48}$$

Interactions between two groups are not considered in the calculation of a single group. Therefore, the transmission force (equations 24 and 25) can be rewritten as

$$\sum_{j\geq 4}\lambda_{1,j}^2(t)=\sum_{j\geq 4}\left\{1-N\_HRMSM_j{}^{n_2(1-u_2\kappa)}\right\} \tag{49}$$

$$\sum_{j\geq 4}\lambda_{3,j}^2(t)=\sum_{j\geq 4}\left\{1-N\_prepHRMSM_j{}^{n_2(1-u_2\kappa)}\right\} \tag{50}$$

According to equations 28 and 29, the simplified form of N_HRMSM_j and $N\_prepHRMSM_j$ can be rewritten as $1-\frac{HR(X_{2,j})}{TP_2}$ and $1-\frac{prepHR(X_{2,j})}{TP_2}$ respectively.

When the system is at DFE, $TP_2=(X_{2,1}+X_{2,2}+X_{2,3})n_2=N_2n_2$, where N_2 is the number of LRMSM. In order to obtain new infection Jacobian matrix F^2, we need to calculate the partial derivative of each element of f^2 with respect to every $X_{2,j}$ (j=4,5,$\cdots$,15), and the key to calculate the partial derivatives lies in the first two elements of f^2, because the derivatives for third to twelfth elements are 0 (see equation 48). The partial derivative of $\sum_{j\geq 4}\lambda_{1,j}^2(t)$:

$$\begin{aligned}
&\frac{\partial}{\partial X_{2,k}}\sum_{j\geq 4}\left\{1-N_HRMSM_j{}^{n_2(1-u_2\kappa)}\right\}\\
&=\sum_{j\geq 4}\frac{\partial}{\partial X_{2,k}}\left\{1-N_HRMSM_j{}^{n_2(1-u_2\kappa)}\right\}\\
&=\sum_{j\geq 4}\frac{\partial}{\partial X_{2,k}}\left\{1-\left(1-\frac{HR(X_{2,j})}{TP_2}\right)^{n_2(1-u_2\kappa)}\right\}\\
&=-\sum_{j\geq 4}\frac{\partial}{\partial X_{2,k}}\left(1-\frac{HR(X_{2,j})}{TP_2}\right)^{n_2(1-u_2\kappa)}\\
&=-\sum_{j\geq 4}\left(n_2(1-u_2\kappa)\left(1-\frac{HR(X_{2,j})}{TP_2}\right)^{n_2(1-u_2\kappa)-1}\right)\left(-\frac{\frac{\partial HR(X_{2,j})}{\partial X_{2,k}}TP_2-HR(X_{2,j})\frac{\partial TP_2}{\partial X_{2,k}}}{TP_2{}^2}\right)
\end{aligned} \tag{51}$$

The partial derivative of $\sum_{j\geq 4}\lambda_{3,j}^{2}(t)$:

$$\frac{\partial}{\partial X_{2,k}}\sum_{j\geq 4}\left\{1-N\_prepHRMSM_{j}^{\,n_2(1-u_2\kappa)}\right\}$$
$$=\sum_{j\geq 4}\frac{\partial}{\partial X_{2,k}}\left\{1-N\_prepHRMSM_{j}^{\,n_2(1-u_2\kappa)}\right\}$$
$$=\sum_{j\geq 4}\frac{\partial}{\partial X_{2,k}}\left\{1-\left(1-\frac{prepHR(X_{2,j})}{TP_2}\right)^{n_2(1-u_2\kappa)}\right\}$$
$$=-\sum_{j\geq 4}\frac{\partial}{\partial X_{2,k}}\left(1-\frac{prepHR(X_{2,j})}{TP_2}\right)^{n_2(1-u_2\kappa)}$$
$$=-\sum_{j\geq 4}\left(n_2(1-u_2\kappa)\left(1-\frac{prepHR(X_{2,j})}{TP_2}\right)^{n_2(1-u_2\kappa)-1}\right)\left(-\frac{\frac{\partial prepHR(X_{2,j})}{\partial X_{2,k}}TP_2-prepHR(X_{2,j})\frac{\partial TP_2}{\partial X_{2,k}}}{TP_2^{\,2}}\right) \tag{52}$$

Because both $HR(X_{2,j})$ and $prepHR(X_{2,j})$ only depend on the number of people in compartment j, $HR(X_{2,j})\propto X_{2,j}$ and $prepHR(X_{2,j})\propto X_{2,j}$, therefore,

$$\frac{\partial HR(X_{2,j})}{\partial X_{2,k}}=0,\forall j\neq k \tag{53}$$

$$\frac{\partial prepHR(X_{2,j})}{\partial X_{2,k}}=0,\forall j\neq k \tag{54}$$

Applying equations 53 and 54 to equations 51 and 52, equations 51 and 52 can be simplified to

$$\frac{\partial}{\partial X_{2,k}}\sum_{j\geq 4}\left\{1-N\_HRMSM_{j}^{\,n_2(1-u_2\kappa)}\right\}$$
$$=\frac{n_2(1-u_2\kappa)\frac{\partial HR(X_{2,k})}{\partial X_{2,k}}}{N_2n_2}$$
$$=\frac{(1-u_2\kappa)\frac{\partial HR(X_{2,k})}{\partial X_{2,k}}}{N_2} \tag{55}$$

$$\frac{\partial}{\partial X_{2,k}}\sum_{j\geq 4}\left\{1-N\_prepHRMSM_j^{\,n_2(1-u_2\kappa)}\right\}$$
$$=\frac{n_2(1-u_2\kappa)\dfrac{\partial prepHR(X_{2,k})}{\partial X_{2,k}}}{N_2 n_2}$$
$$=\frac{(1-u_2\kappa)\dfrac{\partial prepHR(X_{2,k})}{\partial X_{2,k}}}{N_2} \tag{56}$$

According to equations 28 and 29, $\dfrac{\partial HR(X_{2,k})}{\partial X_{2,k}}$ and $\dfrac{\partial prepHR(X_{2,k})}{\partial X_{2,k}}$ are easy to calculate.

According to the calculation process above, define Jacobian matrix F^2 as:

$$F^2_{j-3,k-3}=\left[\frac{\partial f^{\,2}_{j-3}}{\partial X_{2,k}}\right]=\begin{cases}\beta^2_{j-3,k-3}, if & 4\leq j\leq 5\\ 0, \quad if & 5<j\leq 15\end{cases},\ k\in(4,15) \tag{57}$$

Where β^2 is:

$$\beta^2_{1,1}=\frac{(1-u_2\kappa)n_2\sigma^{acute}}{N_2}(X_{2,1}+X_{2,2});\beta^2_{1,7}=\frac{(1-u_2\kappa)n_2\sigma^{sym}}{N_2}(X_{2,1}+X_{2,2});$$
$$\beta^2_{1,2}=\frac{(1-u_2\kappa)n_2(1-r_1)\sigma^{acute}}{N_2}(X_{2,1}+X_{2,2});\beta^2_{1,8}=\frac{(1-u_2\kappa)n_2(1-r_1)\sigma^{sym}}{N_2}(X_{2,1}+X_{2,2});$$
$$\beta^2_{1,3}=\frac{(1-u_2\kappa)n_2(1-r_1)\sigma^{acute}(1-r_2)}{N_2}(X_{2,1}+X_{2,2});\beta^2_{1,9}=\frac{(1-u_2\kappa)n_2(1-r_1)\sigma^{sym}(1-r_2)}{N_2}(X_{2,1}+X_{2,2});$$
$$\beta^2_{1,4}=\frac{(1-u_2\kappa)n_2\sigma^{asym}}{N_2}(X_{2,1}+X_{2,2});\beta^2_{1,10}=\frac{(1-u_2\kappa)n_2(1-r_1^{'})\sigma^{AIDS}}{N_2}(X_{2,1}+X_{2,2});$$
$$\beta^2_{1,5}=\frac{(1-u_2\kappa)n_2(1-r_1)\sigma^{asym}}{N_2}(X_{2,1}+X_{2,2});\beta^2_{1,11}=\frac{(1-u_2\kappa)n_2(1-r_1^{'})\sigma^{AIDS}}{N_2}(X_{2,1}+X_{2,2});$$
$$\beta^2_{1,6}=\frac{(1-u_2\kappa)n_2(1-r_1)\sigma^{asym}(1-r_2)}{N_2}(X_{2,1}+X_{2,2});\ \beta^2_{1,12}=\frac{(1-u_2\kappa)n_2(1-r_1^{'})\sigma^{AIDS}(1-r_2)}{N_2}(X_{2,1}+X_{2,2}) \tag{58}$$

$$\beta_{2,1}^2=\frac{(1-u_2\kappa)n_2\sigma^{acute}(1-r_3)}{N_2}X_{2,3};\ \beta_{2,7}^2=\frac{(1-u_2\kappa)n_2\sigma^{sym}(1-r_3)}{N_2}X_{2,3}$$

$$\beta_{2,2}^2=\frac{(1-u_2\kappa)n_2(1-r_1)\sigma^{acute}(1-r_3)}{N_2}X_{2,3};\ \beta_{2,8}^2=\frac{(1-u_2\kappa)n_2(1-r_1)\sigma^{sym}(1-r_3)}{N_2}X_{2,3}$$

$$\beta_{2,3}^2=\frac{(1-u_2\kappa)n_2(1-r_1)\sigma^{acute}(1-r_2)(1-r_3)}{N_2}X_{2,3};\beta_{2,9}^2=\frac{(1-u_2\kappa)n_2(1-r_1)\sigma^{sym}(1-r_2)(1-r_3)}{N_2}X_{2,3};$$

$$\beta_{2,4}^2=\frac{(1-u_2\kappa)n_2\sigma^{asym}(1-r_3)}{N_2}X_{2,3};\ \beta_{2,10}^2=\frac{(1-u_2\kappa)n_2(1-r_1^{'})\sigma^{AIDS}(1-r_3)}{N_2}X_{2,3}$$

$$\beta_{2,5}^2=\frac{(1-u_2\kappa)n_2(1-r_1)\sigma^{asym}(1-r_3)}{N_2}X_{2,3};\ \beta_{2,11}^2=\frac{(1-u_2\kappa)n_2(1-r_1^{'})\sigma^{AIDS}(1-r_3)}{N_2}X_{2,3}$$

$$\beta_{2,6}^2=\frac{(1-u_2\kappa)n_2(1-r_1)\sigma^{asym}(1-r_2)(1-r_3)}{N_2}X_{2,3};\beta_{2,12}^2=\frac{(1-u_2\kappa)n_2(1-r_1^{'})\sigma^{AIDS}(1-r_2)(1-r_3)}{N_2}X_{2,3} \tag{59}$$

Transition vector v^2 is the same as v^1, which does not change with the group. Therefore, $V^2=V^1$, and the basic reproduction number of HRMSM R_0^2 is the maximum eigenvalue of $F^2(V^2)^{-1}$.

2.3.2 Meta-population reproduction number calculation approach

When the whole population is divided into several sub-populations, and there are interactions among these sub-populations, the meta-population reproduction number approach is needed. The approach of van den Driessche and Watmough was used to formulate the next generation matrix K for the whole population in the study[75], considering the mixing between LRMSM and HRMSM, based on the following formula:

$$K=\begin{bmatrix} R_0^1\eta_{1,1} & R_0^1\eta_{1,2} \\ R_0^2\eta_{2,1} & R_0^2\eta_{2,2} \end{bmatrix} \tag{60}$$

The basic reproduction number R_0 for the whole population is the maximum eigenvalue of K, where $\eta_{i,j}$ (equations 16 to 19) is the proportion of the partnerships that members of

group i have with members of group j.

2.3.3 Effective reproduction number

According to sub-section 2.3.1 and 2.3.2, I obtained the formula of basic reproduction number R_0. The effective reproduction number R_t can be obtained by applying the formula of R_0 but using the parameter values in year t. I calculated R_t under staus quo and different intervention scenarios in the first year of interventions. The detailed information of parameter values of intervention is described in section 2.4.

2.4 Intervention scenarios

In this study, I changed the values of the annual number of sexual partners, condom use rate, testing rate and treatment rate and PrEP coverage rate in the compartmental model from 2022 to model interventions that will be implemented from 2022, and then explored the effects of single measure behavioral and biomedical interventions and comprehensive multiple measures interventions on the Japanese HIV epidemic among MSM and forecasted the time required to eliminate HIV under these intervention scenarios. The specific scenarios are as follows.

- Scenario 0 (Status Quo): No intervention, under the status quo of current policies.

Behavioral interventions

- Scenario 1 (Partner reduction): Control the annual number of sexual partners per capita of HRMSM no more than 14 (i.e., between 1 to 14), while all other conditions

maintain the status quo level.

- Scenario 2 (Increased condom use rate): Increase the overall condom use rate to over 40% (i.e., between 40% to 100%), with 90% condom effectiveness, other conditions maintain the status quo.

Biomedical interventions

- Scenario 3 (Enhanced testing and treatment): Increase both the overall testing rate and treatment rate to over 50% (i.e., between 50% to 100%), representing interventions in terms of TasP and testing and treatment strategy, other conditions maintain the status quo.
- Scenario 4 (Introducing PrEP): Introduce PrEP to both LRMSM and HRMSM, with coverage rate between 10% to 100%, with 90% effectiveness under 100% adherence, other conditions maintain the status quo.

Comprehensive behavioral and biomedical interventions

- Scenario 5 (Weak comprehensive intervention): Reduce 10% of the sexual partners in HRMSM group (HRMSM:14*0.9=12.6), increase the overall condom use rate to 40%, with 50% overall testing rate, 50% overall treatment rate and 10% PrEP coverage rate, other conditions maintain the status quo.
- Scenario 6 (Moderate comprehensive intervention): Reduce 20% of the sexual partners in HRMSM group (HRMSM:14*0.8=11.2), increase the overall condom use rate to 50%, with 70% overall testing rate, 70% overall treatment rate and 20% PrEP

coverage rate, other conditions maintain the status quo.

- Scenario 7 (Strong comprehensive intervention): Reduce 30% of the sexual partners in HRMSM group (HRMSM:14*0.7=9.8), increase the overall condom use rate to 60%, with 90% overall testing rate, 90% overall treatment rate and 30% PrEP coverage rate, other conditions maintain the status quo.

2.5 Model outcomes

This study estimated and forecasted the epidemic of HIV in Japan under status quo and different scenarios. I calculated prevalence, number of new cases, incidence rate, and the relative time required to eliminate HIV. The time unit of the model was month, the parameter values given by year were unified into month by dividing by 12, and outcomes were aggregated to yearly values for final analyses.

2.5.1 Epidemiological outcomes

Prevalence

The prevalence in group i in year t is:

$$P_i(t) = \sum_{j=4}^{15} X_{i,j}(t) \Big/ \sum_{\forall j} X_{i,j}(t) \tag{61}$$

The prevalence of the whole MSM population in year t is:

$$P(t) = \left(\sum_{j=4}^{15} X_{1,j}(t) + \sum_{j=4}^{15} X_{2,j}(t) \right) \Big/ \left(\sum_{\forall j} X_{1,j}(t) + \sum_{\forall j} X_{2,j}(t) \right) \tag{62}$$

Number of new cases

The number of new cases in group i in year t is:

$$NI_i(t) = \sum_{j\geq 4} \lambda_{1,j}^{i}(t) \times X_{i,1}(t) + \sum_{j\geq 4} \lambda_{2,j}^{i}(t) \times X_{i,2}(t) + \sum_{j\geq 4} \lambda_{3,j}^{i}(t) \times X_{i,3}(t) \tag{63}$$

The number of new cases of the whole MSM population in year t is:

$$NI\ (t) = NI_1(t) + NI_2(t) \tag{64}$$

Incidence rate

The incidence rate in group i in year t is:

$$I_i(t) = NI_i(t) \Big/ \sum_{\forall j} X_{i,j}(t) \tag{65}$$

The incidence rate of the whole MSM population in year t is:

$$I\ (t) = \left(NI_1(t) + NI_2(t)\right) \Big/ \left(\sum_{\forall j} X_{1,j}(t) + \sum_{\forall j} X_{2,j}(t) \right) \tag{66}$$

2.5.2 Elimination analysis

I used effective reproduction number R_{2022} in 2022 as a necessary precondition for elimination, with R_{2022}<1 representing HIV epidemic will slowing down since 2022, and incidence rate<1/1000 person-year as the threshold for HIV elimination, based on Granich's previous work published in *the Lancet*[21]. Therefore, the time required to eliminate HIV is:

$$t_e = min\left\{t : I\left(t\right) < 0.001\right\} - 2022 \tag{67}$$

I also calculated the time of achieving 90-90-90/95-95-95 targets under different scenarios to reflect the elimination progress in a similar way. The percentage of diagnosed people among all PLWH in year t is:

$$Test\ (t) = 1 - \left(\sum_{j=4,7,10,13} X_{1,j}(t) + \sum_{j=4,7,10,13} X_{2,j}(t) \right) \Bigg/ \left(\sum_{j=4}^{15} X_{1,j}(t) + \sum_{j=4}^{15} X_{2,j}(t) \right) \quad (68)$$

And the percentage of people entering into treatment after diagnosis in year t is:

$$Treat\ (t) = \left(\sum_{j=6,9,12,15} X_{1,j}(t) + \sum_{j=6,9,12,15} X_{2,j}(t) \right) \Bigg/ \left(\sum_{j=5,6,8,9,11,12,14,15} X_{1,j}(t) + \sum_{j=5,6,8,9,11,12,14,15} X_{2,j}(t) \right) \quad (69)$$

The number of required test/treatment/people taking PrEP in the first year of the intervention (i.e., 2022) is:

$$n.testing = rate.test \times \left(\sum_{j=4,7,10,13} X_{1,j}(t) + \sum_{j=4,7,10,13} X_{2,j}(t) \right) \quad (70)$$

$$n.treatment = rate.treat \times \left(\sum_{j=6,9,12,15} X_{1,j}(t) + \sum_{j=6,9,12,15} X_{2,j}(t) \right) \quad (71)$$

$$n.PrEP = coverage.PrEP \times \left(\sum_{j=3} X_{1,j}(t) + \sum_{j=3} X_{2,j}(t) \right) \quad (72)$$

Where *rate.test*, *rate.treat* and *coverage.PrEP* are annual testing rate, annual treatment rate and coverage of PrEP, respectively.

2.6 Model calibration

The parameter values were mostly extracted from published academic papers, survey reports, government data and reports by international organizations. The data from these sources have some degree of uncertainty because of the limitations of the original studies. Therefore, model calibration was conducted to select the most reliable model by sampling the key parameters within their possible range.

Key parameters were sampled by using a $Beta$ distribution. Here, for each key parameter, $Beta(2,2)$ was used and shifted and scaled to control the range of the possible

value. Table 2 shows the list of the key parameters and their corresponding distributions.

Sensitivity analysis was conducted by randomly sampling the key parameters from their corresponding distributions simultaneously. I sampled 1000 times to obtain 1000 key parameter sets. Each set was combined with the other fixed parameters as a complete parameter set, and the model run with this complete parameter set to obtain one set of annual prevalence estimates. Ultimately, 1000 models with 1000 estimations were generated.

The estimations of the prevalence were calibrated against the prevalence from 2010 to 2016. A deviance-based loss was calculated using the following formula:

$$D_s = 2\sum_{t=2010}^{2016}\left(P_t \ln\left(P_t/\hat{P}_{t,s}\right) - P_t + \hat{P}_{t,s}\right) \quad (73)$$

Where D_s is the deviance of the s*th* sampling, $\hat{P}_{t,s}$ is the estimated prevalence in sample s year t, and P_t is the prevalence in year t. The 400 models with the lowest deviance were retained as the final model set. The weighted mean of the 400 model was the final estimation, and the range of the 400 models formed the uncertainty range.

Table 2 Sensitivity distributions of key parameters

Variable	Definition	Value	Range	Distribution
Demographic				
	Initial population (age 18-59)			
	MSM (%)	3.5%	3% – 4%	0.01*Beta(2,2)+0.03
Behavioral				
	Annual number of partners			
	MSM, total	4.1	3 – 5	2*Beta(2,2)+3
n_2	High risk MSM	14.1	13 – 15	13*Beta(2,2)+2
	Condom use (% of sexual encounters)			
$u_{i,j}$	Condom use rate	35%	32% – 39%	[0.2*Beta(2,2)+0.9]*35%
	Others			
ε	Proportion of members of one group having sexual interaction with members of the other group	0.3	0.27 – 0.33	[0.2*Beta(2,2)+0.9]*0.3
Biomedical				
	HIV testing			
ψ_j^i	Proportion of population tested in past 12 months, %	35%	32% – 39%	[0.2*Beta(2,2)+0.9]*35%
	Monthly entry rate to ART			
α_j^i	Acute	0.2	0.18 – 0.22	[0.2*Beta(2,2)+0.9]*0.2
	Asymptomatic (CD>500)	0.29	0.26 – 0.32	[0.2*Beta(2,2)+0.9]*0.29
	Asymptomatic (200<=CD4<=500)	0.38	0.34 – 0.42	[0.2*Beta(2,2)+0.9]*0.38
	AIDS (CD4<200)	0.43	0.39 – 0.47	[0.2*Beta(2,2)+0.9]*0.43

3 RESULTS

3.1 HIV epidemic forecast under status quo

Figure 4 shows the change trend in prevalence and incidence rates under current policies. The incidence rate among the Japanese MSM population has been increasing since 2010 and will peak at 10.60 per 1000 person-years in 2030, with a declining trend after this point. The incidence rate will still be greater than the threshold for HIV elimination of 1 per 1000 person-years in 2050. Prevalence has a similar trend to the incidence rate, increasing since 2010 and peaking at 10.24% in 2043 - 13 years after the incidence peak, followed by a gradual decrease. Without other interventions, neither the 90-90-90 targets nor the 95-95-95 targets can be achieved on schedule under the status quo. Based on model estimates, the testing target of 90-90-90 will be achieved with a big delay in 2045 (sensitivity range 2040 to 2050), and treatment targets will be achieved at the same year in 2045 (sensitivity range 2040 to 2048), however, neither testing nor treatment can reach the 95% level before 2050 (Table 4). Under the status quo, the reproduction number in 2022 (R_{2022}) is expected to be 1.41 (sensitivity range 1.33 to 1.49), indicating the HIV epidemic will persist for a long time if policies are unchanged, which is consistent with the model projection.

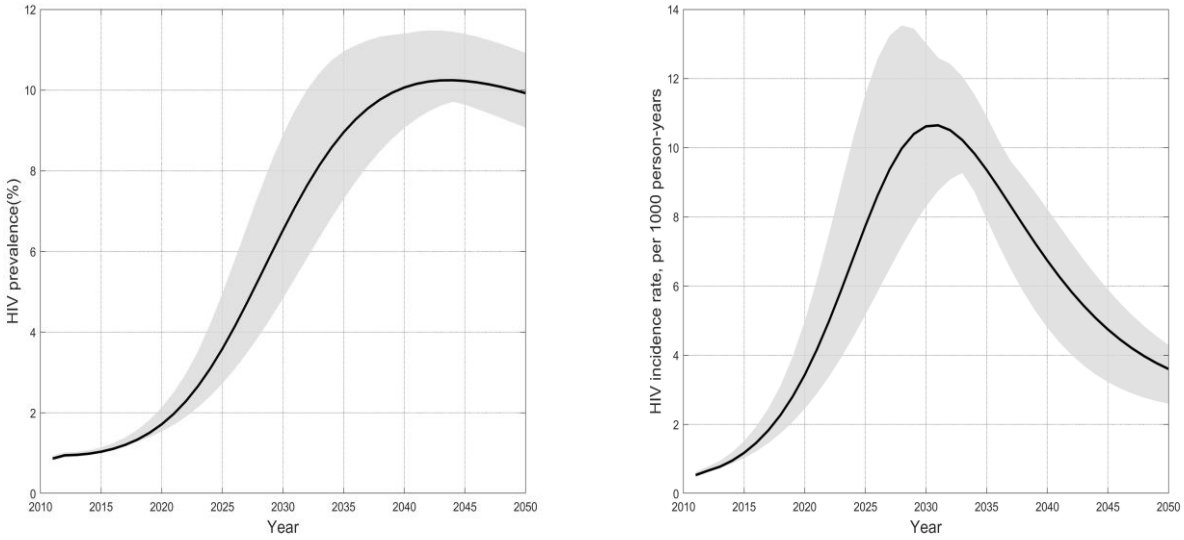

Figure 4 HIV prevalence and HIV incidence rate under status quo of current policies.

3.2 Effect of behavioral interventions

In this section, I explored the effect of two behavioral interventions implemented separately from 2022. These interventions are either a partner reduction intervention or an increased condom use intervention. For each intervention I calculated the reproduction number R_{2022} and the time required to eliminate HIV. R_{2022} is used to reflect the impact of interventions.

Figure 5 shows the trend in R_{2022} and time required to eliminate HIV under different numbers of sexual partners in HRMSM group. The value of R_{2022} decreases with reduction in the number of sexual partners, and the time required for HIV elimination is shortened as R_{2022} declines. When the number of sexual partners in HRMSM is reduced to less than 10, R_{2022} will be less than 1, meaning each person with HIV will infect on average less than one person, and HIV will be eliminated by 2050 when the annual number of sexual partners in

HRMSM can be controlled under 9.

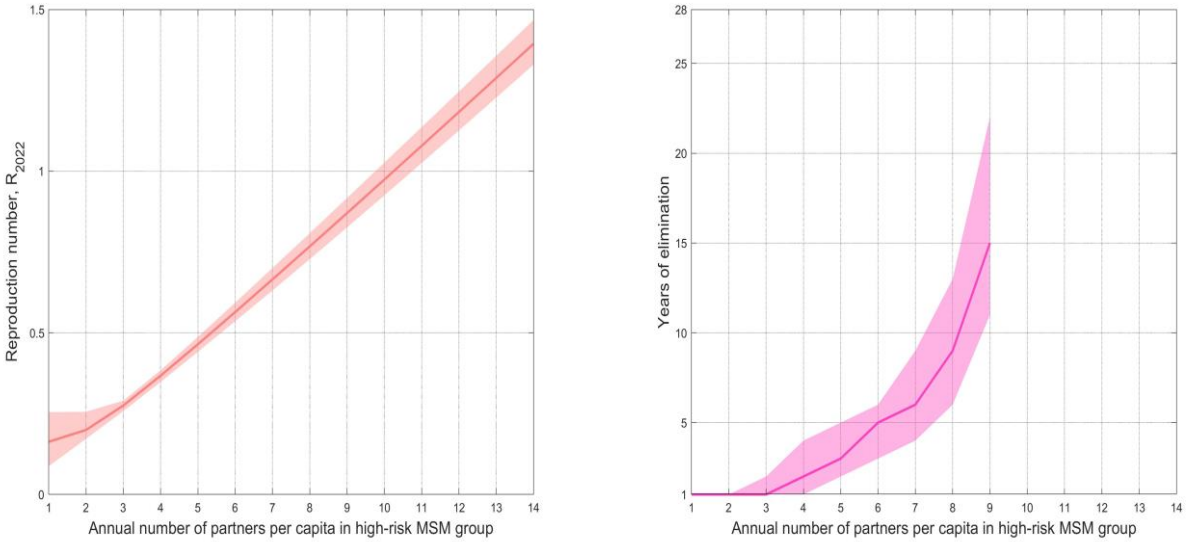

Figure 5 Reproduction number R_{2022} (left) and the time required to eliminate HIV (right) under partner reduction intervention. (The blank for values above 9 in the right panel indicates failure to achieve HIV elimination within 28 years).

Figure 6 shows the trend in R_{2022} and time required to eliminate HIV under different condom use rates. The condom use rate has a linear relationship with R_{2022}. If overall condom use rates increase from 40% to 100%, R_{2022} will decrease from 1.30 to less than 0.2. HIV cannot be eliminated by 2050 when condom use rate is less than 65%, but rapid elimination can be achieved when the condom use rate is higher than 80%.

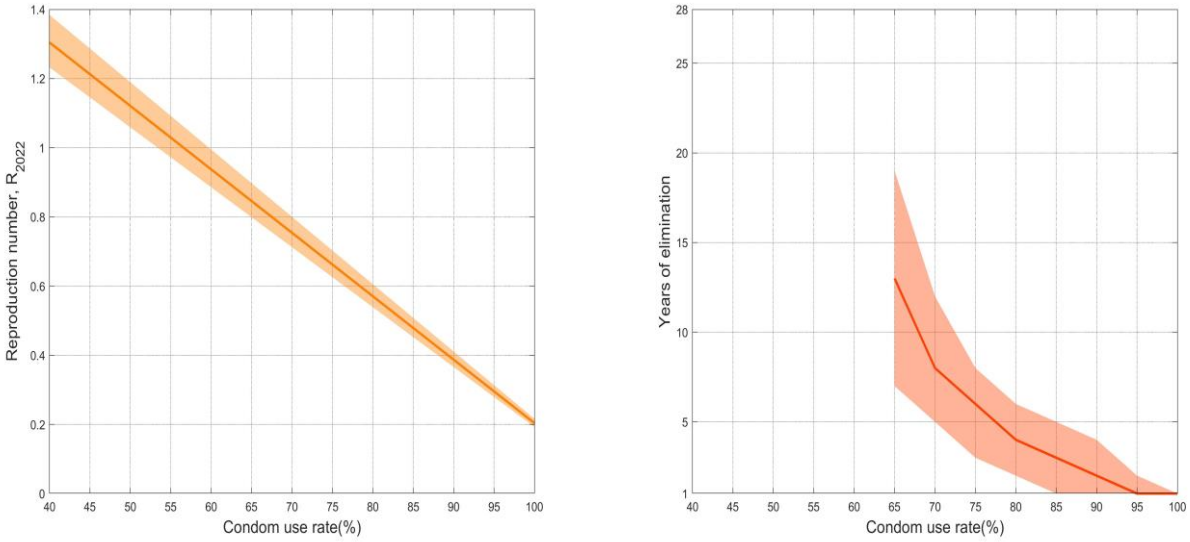

Figure 6 Reproduction number R_{2022} (left) and the time required to eliminate HIV (right) under increased condom use intervention. (The blank for values below 65% in the right panel indicates failure to achieve HIV elimination within 28 years).

3.3 Effect of biomedical interventions

In this section, I explore the effect of two single biomedical interventions implemented from 2022. The two biomedical interventions are enhanced testing and treatment and introducing PrEP. Because testing is the first step of entering into treatment, testing and treatment are treated as a single intervention measure.

Enhanced testing and treatment is an effective method to control the HIV epidemic since Japan is still at a relatively low testing and treatment level. Figure 7 shows the trend in R_{2022} and time required to eliminate HIV under different testing rates and treatment rates. The range of R_{2022} is from 1.22 to 0.88 coresponding to the annual testing rate and treatment rate from 50% to 100%. R_{2022} will be less than 1 if both annual testing rate and annual treatment

rate are over approximately 75%. However, that still requires a long time to achieve HIV elimination, and much higher testing and treatment rates are needed to shorten the elimination time. For example, testing rate and treatment rate over 95% can achieve HIV elimination within 10 years.

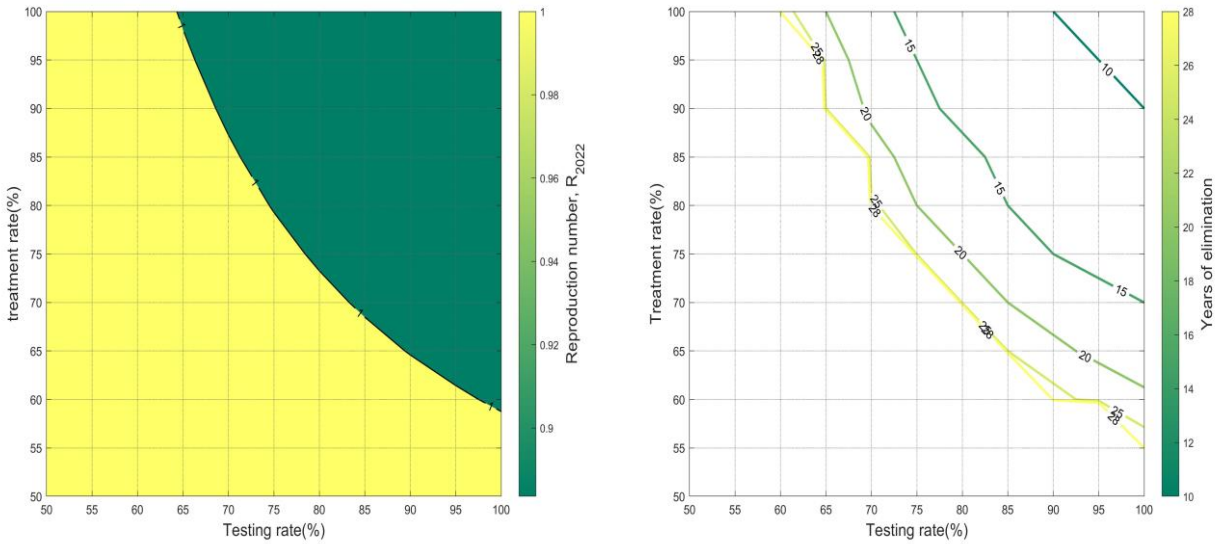

Figure 7 Reproduction number R_{2022} (left) and the time required to eliminate HIV (right) under enhanced testing and treatment intervention.

Figure 8 shows the trend in R_{2022} and time required to eliminate HIV under different PrEP coverage rates. The PrEP coverage rate also has a linear relationship with R_{2022}. As overall PrEP coverage rate increases from 10% to 100% with 100% adherence rate, R_{2022} will decrease from 1.36 to 0.94. HIV will be eliminated after 26 years (sensitivity range 25 to 28 years) when there is 10% PrEP coverage rate, and the time required of elimination is decreased to 9 years (sensitivity range 8 to 11 years) when there is 70% coverage. After that, the effect of increasing PrEP coverage rate begins to be not significant.

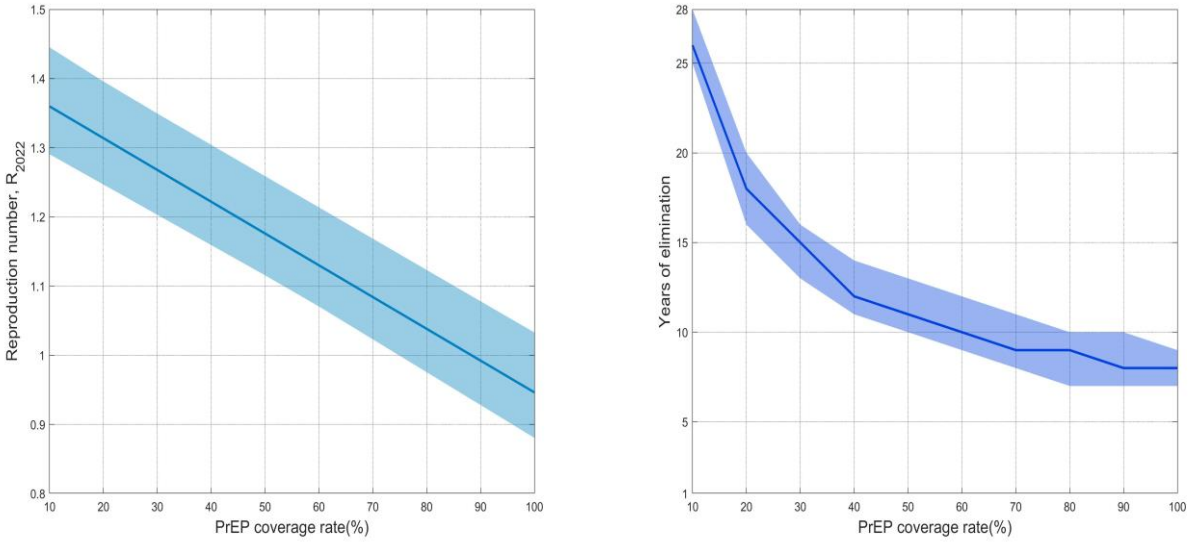

Figure 8 Reproduction number R_{2022} (left) and the time required to eliminate HIV (right) under introducing PrEP.

3.4 Effect of comprehensive interventions

In section 3.2 and section 3.3 I showed that each single intervention can achieve HIV elimination by 2050, with different intervention intensities requiring different time to achieve elimination. In this section, I explore the effect of combining both behavioral and biomedical interventions at three possible intensities. The prevalence and incidence rate under three intensities of combined intervention are shown in Figure 9. All three interventions can drastically reduce the incidence rate that is expected to continue to rise under the current policies, thereby rapidly reducing the prevalence rate. Even weak intervention, with only minor interventions for each dimension, can play a great role in the control of HIV epidemic. The years of elimination under different intervention scenarios are shown in Table 3, and in all cases the time required for comprehensive interventions is much less than the time

required in each single intervention, with HIV elimination achieved in 2033 (sensitivity range 2032 to 2034), 2026 (sensitivity range 2025 to 2027) and 2024 (sensitivity range 2024 to 2025) under weak, moderate and strong interventions, respectively.

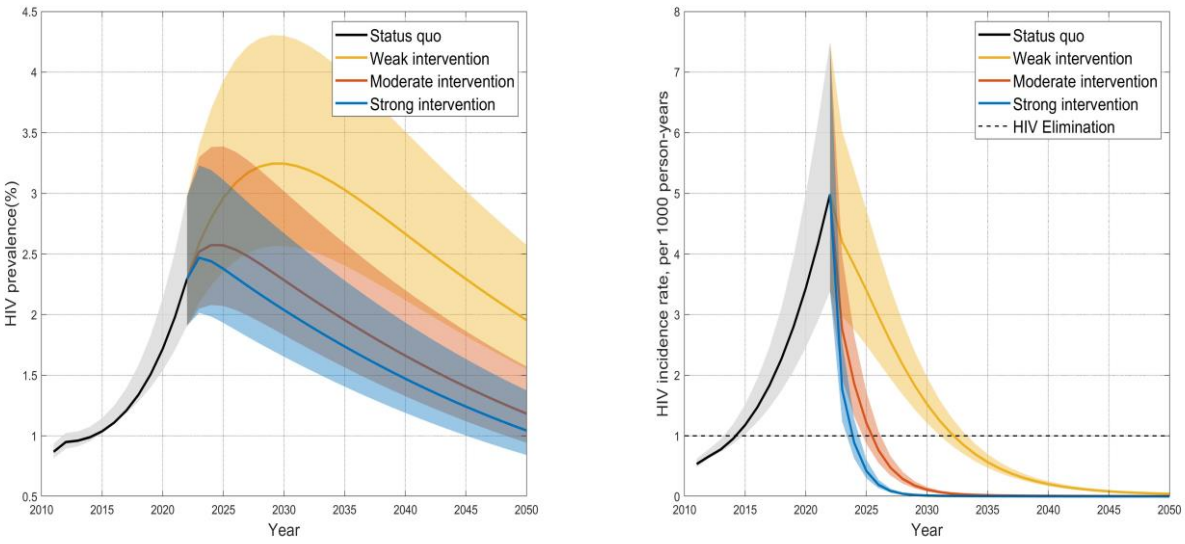

Figure 9 HIV prevalence and HIV incidence rate under three kinds of comprehensive behavior and biomedical interventions

Table 4 shows the epidemiological impact, the years taken to achieve 90-90-90/95-95-95 targets and the number of tests/treatments/people taking PrEP required under three levels of comprehensive interventions. Comprehensive interventions can prevent 83.97% to 97.96% new HIV infections from 2022 to 2050. Three comprehensive interventions can accelerate the pace of achieving 90-90-90 targets with shorter delay, and moderate and strong comprehensive interventions can achieve the 95-95-95 targets on schedule by 2030. I also calculated the number of tests/treatments/people taking PrEP needed in each comprehensive intervention to provide references for intervention preparation.

Table 3 Years of elimination under different intervention scenarios

Intensity	Intervention	Year of HIV elimination				
		Scenario 1 (Sensitivity range)	**Scenario 2** (Sensitivity range)	**Scenario 3** (Sensitivity range)	**Scenario 4** (Sensitivity range)	**Comprehensive interventions** (Sensitivity range)
Weak	Partner reduction: 10%	After 2050				
	Condom use rate: 40%		After 2050			
	Testing and treatment: 50%			After 2050		2033 (2032 – 2034)
	PrEP coverage rate: 10%				2048 (2047 – 2050)	
Moderate	Partner reduction: 20%	After 2050				
	Condom use rate: 50%		After 2050			
	Testing and treatment: 70%			After 2050		2026 (2025 – 2027)
	PrEP coverage rate: 20%				2040 (2038 – 2042)	
Strong	Partner reduction:30%	After 2050				
	Condom use rate: 60%		After 2050			
	Testing and treatment: 90%			2033 (2030 – 2038)		2024 (2024 – 2025)
	PrEP coverage rate: 30%				2037 (2035 –2038)	

Table 4 HIV epidemic forecast under different intervention scenarios

	Status quo	Weak intervention	Moderate intervention	Strong intervention
Epidemiological impact				
Prevalence in 2050 (%)	9.93 (9.07, 10.92)	1.95 (1.55, 2.58)	1.18 (0.94, 1.57)	1.04 (0.84, 1.38)
Incidence rate in 2050 (/1000 person-year)	3.6 (2.6, 4.3)	0.043 (0.034, 0.057)	0.0044 (0.0033, 0.0063)	0.0017 (0.0012, 0.0024)
Total HIV infections from 2022 to 2050 (×10,000)	16.83 (11.83, 21.69)	2.72 (1.94, 3.89)	0.76 (0.52, 1.17)	0.47 (0.23, 0.53)
HIV infections prevented from 2022 to 2050 (×10,000)	-	14.11 (9.79, 17.93)	16.05 (11.30, 20.53)	16.48 (11.60, 21.16)
HIV infections prevented from 2022 to 2050 (%)	-	83.97 (79.14, 89.77)	95.44 (93.81, 97.43)	97.96 (97.21, 98.88)
Years of achievement				
Year when the testing target of 90-90-90 is achieved	2045 (2040, 2050)	2029 (2029, 2029)	2024 (2024, 2025)	2023 (2023, 2024)
Year when the treatment target of 90-90-90 is achieved	2045 (2040, 2048)	2030 (2030, 2030)	2026 (2025, 2026)	2025 (2024, 2025)
Year when the testing target of 95-95-95 is achieved	After 2050	2033 (2032, 2033)	2026 (2026, 2026)	2024 (2024, 2024)
Year when the treatment target of 95-95-95 is achieved	After 2050	2034 (2034, 2035)	2027 (2027, 2028)	2026 (2025, 2026)
Required number of tests/treatments/people taking PrEP in the first year of the intervention (i.e., 2022)				
Number of tests required (×100,000)	-	3.47 (3.15, 3.66)	4.49 (4.08, 4.74)	5.34 (4.85, 5.64)
Number of treatments required (×1000)	-	2.66 (1.65, 4.19)	3.76 (2.33, 5.92)	4.77 (2.96, 7.53)
Number of PrEP required (×10,000)	0	2.79 (2.55, 2.94)	6.27 (5.75, 6.61)	10.25 (9.41, 10.82)

4 DISCUSSION

This study used a deterministic compartmental mathematical model to reflect the mechanism of HIV progression in the Japanese MSM population. HIV epidemic trends were estimated and forecasted under the status quo of current policies, two single behavioral interventions, two single biomedical interventions, and a comprehensive behavioral and biomedical intervention with three intensities. Effective reproduction numbers in 2022 were calculated to reflect the impact of corresponding interventions.

4.1 Findings of the study

Under the status quo of current policies, my modeling found that the HIV epidemic cannot be rapidly controlled, and HIV cannot be eliminated by 2050. HIV prevalence and incidence will increase over the next 22 and 9 years respectively, which is consistent with previous research findings. Enhanced interventions are necessary to control the epidemic.

The Japanese MSM population are facing great behavioral risk due to the large number of sexual partners in the high-risk group and low condom use rates. Small reductions in partner numbers or increases in condom use rates are not enough by themselves to change the current situation. This study found that to achieve HIV elimination by 2050, the annual number of sexual partners in high-risk group needs to be reduced by at least 35% to less than 9, or condom use rates almost doubled to 65%. However, behavior change is a gradual process and requires long time commitments when the magnitude of the change is large, and encouraging a substantial reduction in sexual partners may create debate about stigmatization

of and discrimination against MSM. There is also little evidence from overseas that abstinence-based or partner reduction strategies are effective or easy to achieve.

Against this backdrop of increasing incidence in the status quo scenario, my study found that enhanced testing and treatment intervention can shorten the duration from infection to viral suppression. Under the current policy, it takes about six years for infected persons to go from infection to virus suppression. During the six years before the virus suppression, the infected persons still have the risk of infecting other people. When infected persons have high-risk behaviors, the risk of transmission will be even more exacerbated. Increasing testing and treatment rates can reduce this transmission risk by accelerating the process of achieving virus suppression. The process can be shortened to approximately two years with detection rate and treatment rate of more than 95%, greatly reducing the risk of infected persons being exposed to the population to spread disease. However, it is extremely difficult to achieve this with no change in current policies.

At present, the coverage of PrEP in Japanese MSM population is extremely low, with only 5 people taking PrEP in the 6408 respondents to the 2017 LASH report, even though most respondents would like to take PrEP to prevent HIV[46]. PrEP can protect uninfected people from being infected, and is a highly effective prevention method. My results show that only a 10% coverage rate with 100% adherence will make it possible to achieve HIV elimination by 2050, with this required time shortening rapidly with higher testing rates.

My study found combinations of behavioral and biomedical interventions were effective and could rapidly eliminate HIV with relatively small changes. A weak intervention with

approximately only 10% changes in both behavioral and biomedical interventions will prevent 83.97% new infections and achieve HIV elimination in 2033. The additional prevention benefit is decreased in higher intensity interventions. A moderate intervention with 10% more changes than weak intervention will prevent 11% more new infections and achieve elimination 7 years earlier than the weak intervention, and a strong intervention with 10% more changes than a moderate intervention will prevent 2% more new infections and achieve elimination 2 years earlier than a moderate intervention.

In summary, both behavioral and biomedical interventions are effective and could achieve HIV elimination by 2050, but isolated interventions requiring larger changes may stimulate social conflict and encounter big implementation challenges in reality. Comprehensive interventions allowing smaller changes could solve this problem by combining both behavioral and biomedical interventions, which not only reduce the difficulty of implementing each intervention, but also accelerate the realization of HIV elimination.

4.2 Policy implications

The MHLW does not report the prevalence and incidence of HIV/AIDS in the general or the MSM population, but the number of new HIV/AIDS cases notified annually has been declining since it peaked in 2013[38]. My model estimates rise annually, in contradiction to these government reports. However, yearly new notified cases are not the same as new cases, because new notified cases include the cases infected in the past few years who were not tested in time and excludes new cases happening in this year that have not been tested.

Moreover, the decreasing number of yearly new notified cases may not reflect improvements in HIV control, but may just be the result of the stagnation of HIV testing[76]. The reasons for this slowing of testing are varied, including decreased sense of alarm and reduced budgets from national and local governments[76], but my modelling results suggest that the plateau of newly notified cases in recent years does not necessarily reflect a reducing incidence of the disease, and care should be taken in assuming that HIV has begun to enter a controlled phase in Japan.

Partner reduction and increased condom use rate are key measures to reduce behavioral risk thereby achieving HIV elimination, and in Japan these are often achieved by activities conducted by gay NGOs. Previous NGO actitivites to raise public HIV awareness campaigns have the limitation that a substantial proportion of MSM cannot be reached, therefore reducing the effect of community-based educational activities. In recent years, the rise of gay apps has provided the MSM population new places to connect with each other. Gay apps have attracted a large number of users[77], basing on the Global Positioning System (GPS) in the mobile phones, which enable users to find other users nearby easily. Moreover, studies from other countries have shown that gay app users are more likely to engage in risk behaviors such as group sex[78] and have higher numbers of partners[79]. Therefore, organizing HIV education campaigns through gay apps may be a more effective way of achieving behavioral change goals, especially when the target users are at more risk.

HIV prevention in Japan should incorporate more measures to enhance the testing rate and ensure immediate and sustainable treatment options with more financial support. HIV

testing at institutions has stagnated since 2010 with 130 to 140 thousand tests per year[80]. At the same time, HIV self-testing, such as postal HIV testing, plays an increasingly important role in HIV testing in Japan, with almost one third of people tested by postal HIV testing in 2016 in one survey, although it has not been approved and covered in health insurance [60]. Postal HIV testing provides an easier way for people learn their results and is a possible method to promote the scale-up testing, which should be considered as a part of HIV testing scheme and incorporated into insurance. In addition, Japan should establish a network of free, confidential, and anonymous sexual health clinics targeting sexual minorities and young people. Through this network, testing services can be convenient to access, and stigma and discrimination can be reduced[57]. However, the effect of the scale-up testing services can only be reflected under scale-up of treatment services. More financial support is needed to ensure treatments are easier to enter and sustainable, such as lower co-payment proportion and changes in guidelines to ensure immediate entry to treatment is covered under standard insurance procedures and can be initiated without administrative delays.

In view of PrEP's high effectiveness, its low coverage rate and the strong willingness to use PrEP among the MSM population, the government should consider incorporating PrEP into health insurance and providing MSM an easier way to purchase PrEP drugs before PrEP drugs within Japan. However, in the process of PrEP policy making, actions should be taken to ensure PrEP adherence and pay attention to the possible risk compensation such as PrEP users involving an increased risk of condomless sex[81]. High adherence can alleviate the potential increase in risk compensation to ensure the effectiveness of PrEP interventions[58].

Compared with single behavioral or biomedical interventions, comprehensive interventions offer a more practical and feasible pathway to HIV elimination. Although this study cannot determine which comprehensive intervention is the most cost-effective or cost beneficial, because cost-effectiveness analyses were not been conducted, it did find decreased additional prevention benefit in higher intensity interventions, indicating that it may not be necessary to implement strong interventions to achieve elimination. Detailed cost-effectiveness and cost benefit studies are needed to identify the best trade-off between time and financial burden and explore the resource requirements of these interventions. However, it is clear from this study, that the sexual risk and treatment behavior of Japanese MSM is close to the edge of the parameter space required to maintain the HIV epidemic's growth, and small simultaneous changes in both behavioral risk behavior and biomedical interventions could be sufficient to begin the process of elimination of HIV in Japan.

4.3 Limitations

The present study has some limitations. First, the deterministic compartmental model used in this study assumes that people in each compartment are homogeneous. Further efforts should be made to address this limitation by introducing more realistic models, such as individual-based models and dynamic network models. Individual-based models do not have homogeneity assumptions, which increase their flexibity but also demands richer data[82]. Dynamic network models considering the connection pattern and linkage process between individuals are more powerful tools[82]. However, these kinds of models are difficult to

parameterize and analyze due to more complex model structures, especially when the data is limited[83].

Second, heterosexual transmission was not considered in my model, although a small portion of MSM have male and female partners[84]. However, since the majority (90%) of cases are men[38], the lack of heterosexual transmission will not have too much influence on the results, and the lack of detailed sexual behavior information on Japanese heterosexuals is also an obstacle to building a more complex model including heterosexual transmission.

Third, our model involves many parameters, the quality of which has a great impact on model outcomes. The parameter values were mostly extracted from publicly available publications, and inevitably included some degree of uncertainty because of the limitations of the original studies. I used model calibration to select the most reliable model by sampling the key parameters and assumptions within their possible range. However, multiple parameters were sampled simultaneously, with the possibility of existing combination of extremums of some parameters, which causes a relatively wide range of the uncertainty comparing with single parameter sensitivity analysis.

Fourth, my study used a definition of HIV elimination based on Granich's work that defined HIV elimination threshold as incidence reaching less than 1 per 1000 person-years[21], which might be insufficient in Japan because this threshold was set based on data in South Africa. A stricter measure in future should be explored, but it will require much more aggressive policy to reach.

Finally, this study does not include the time needed to scale up the implementation of

corresponding interventions, but assumes all interventions start from 2022. This means the corresponding measures such as testing rate and treatment rate in the intervention immediately rise to the level of the requirements in 2022. In reality the time to achieve elimination will be longer and will depend on the scale-up time, and the scale-up time will be highly depended on factors that are not easy to predict and were not included in my models.

4.4 Conclusion

HIV will not be eliminated by 2050 in the Japanese MSM population under current policies, and enhanced interventions are necessary to control the epidemic. Both behavioral interventions (partners reductions, increased condom use rate) and biomedical interventions (enhanced testing and treatment, introducing PrEP) can achieve HIV elimination by 2050, but comprehensive interventions can accelerate the realization of HIV elimination with high feasibility. By a small reduction in behavioral risk in Japan's most high-risk MSM populations, combined with improved testing infrastructure, improved treatment guidelines, and the introduction of PrEP, Japan can make the end of AIDS a reality within just one or two decades.

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