CSIRO PUBLISHING
Research Paper
www.publish.csiro.au/journals/sh
Sexual Health, 2008, **5**, 169–187

Using mathematical modelling to help explain the differential increase in HIV incidence in New South Wales, Victoria and Queensland: importance of other sexually transmissible infections

Alexander Hoare[A], *David P. Wilson*[A,B], *David G. Regan*[A], *John Kaldor*[A] *and Matthew G. Law*[A]

[A]National Centre in HIV Epidemiology and Clinical Research, Faculty of Medicine, University of New South Wales, Level 2, 376 Victoria Street, Sydney, NSW 2010, Australia.
[B]Corresponding author. Email: dwilson@nchecr.unsw.edu.au

Abstract. ***Background*:** Since 1999 there has been an increase in the number of HIV diagnoses in Australia, predominantly among men who have sex with men (MSM), but the magnitude of increase differs between states: ~7% rise in New South Wales, ~96% rise in Victoria, and ~68% rise in Queensland. ***Methods*:** Epidemiological, clinical, behavioural and biological data were collated into a mechanistic mathematical model to explore possible reasons for this increase in HIV notifications in MSM. The model was then used to make projections to 2015 under various scenarios. ***Results*:** The model suggests that trends in clinical and behavioural parameters, including increases in unprotected anal intercourse, cannot explain the magnitude of the observed rise in HIV notifications, without a substantial increase in a 'transmission-increasing' factor. We suggest that a highly plausible biological factor is an increase in the prevalence of other sexually transmissible infections (STI). It was found that New South Wales required an ~2-fold increase in other STI to match the data, Victoria needed an ~11-fold increase, and Queensland required an ~9-fold increase. This is consistent with observed trends in Australia for some STI in recent years. Future projections also indicate that the best way to control the current rise in HIV notifications is to reduce the prevalence of other STI and to promote condom use, testing for HIV, and initiation of early treatment in MSM diagnosed during primary infection. ***Conclusions*:** Our model can explain the recent rise in HIV notifications with an increase in the prevalence of other STI. This analysis highlights that further investigation into the causes and impact of other STI is warranted in Australia, particularly in Victoria.

Additional keywords: Australia, men who have sex with men.

Introduction

After a steady decline in HIV notifications during the 1990s in Australia, this current decade has seen an increase in the number of notifications, with the majority of cases involving men who have sex with men (MSM). Since 1999 there has been an ~44% increase in notifications among MSM. However, this trend is not uniform across all Australian states. For example, in New South Wales (NSW) there has been an ~7% rise, in Victoria (Vic.) there has been an ~96% increase, and an ~68% increase has been observed in Queensland (Qld).[1] We seek to provide possible explanations for the differences in notifications between these three states, and to predict the future course of the HIV epidemic in these locations. To investigate the differences, we compiled available data from a variety of sources into a single mechanistic framework to understand how the various factors interact, and then estimated their relative importance in yielding an increase in new HIV infections. We developed a mathematical model to evaluate the HIV epidemics in MSM populations in NSW, Vic. and Qld, and incorporated data on time trends in various factors. These factors included: condom use, proportion of individuals diagnosed in primary HIV infection who received treatment upon diagnosis, proportion of MSM who test for HIV each year, proportion of treated patients with undetectable viral load, average number of sexual partners, and the proportion of MSM who disclose their serostatus. The model also considered other factors such as post-diagnosis behaviour change (possible increase or reduction in the number of casual partnerships), the frequency of sexual acts, and the increase in transmission due to the presence of other sexually transmissible infections (STI). We calibrated the model to match the observed number of HIV notifications in each state in 1999 and conducted rigorous uncertainty and sensitivity analyses.

Methods

Model structure

We constructed a deterministic compartmental model,[2] formulated as a system of ordinary differential equations, to simulate the HIV epidemic in the MSM population in each state. The modelled population was divided into four main groups: uninfected with HIV (susceptible), HIV-infected but undiagnosed, diagnosed with HIV infection, and HIV-infected people on antiretroviral therapy. The HIV-infected

10.1071/SH07099 1448-5028/08/020169

population in our model progresses through three stages of disease: from primary infection to chronic infection and eventually to AIDS (see Fig. 1). In our model each stage of infection was associated with a different viral load, which differentially determined the probability of transmission to a susceptible person[3] during an act of penile–anal intercourse. We assumed that most Australian MSM will engage in both insertive and receptive acts. Thus, we assumed an average transmission probability per act that reflects both insertive and receptive penile–anal intercourse. The model thus comprised 10 groups in total (see Fig. 1 for a schematic illustration of the model showing the 'flow' of the population between the various disease states).

Parameter estimation and assumptions

We modelled the population of MSM in Australia, assuming a population size of 150 000–175 000 MSM nationally (~1–2% of the male population; see Appendix 1 for the proportion distributed among each state). Data were gathered on treatment in primary infection,[4] HIV testing rates,[5–7] number of casual partners,[8–10] condom use,[5–7,11] prevalence of other STI,[12,13] and the rates of disclosure of serostatus among partners as reported in behavioural surveys conducted in each state,[5–7,11,14,15] for the years 1999 to 2006 (see Table 1). We also included other important factors that were not time dependent and remained constant over the period being modelled. Behaviour change post-diagnosis was one such factor; in this case, a multiplying factor acting on the number of sexual partners (range 0.4–1.1[9,16–23]) was applied. This range specifies that there may be an increase or decrease in choosing new partners after HIV diagnosis, but on average there is a decrease in sexual partner acquisition. The frequency of sexual acts between regular partners was also important and ranged between 80 and 120 acts per year.[24] A complete listing of parameters is given in Table A1 in the Appendix. Available

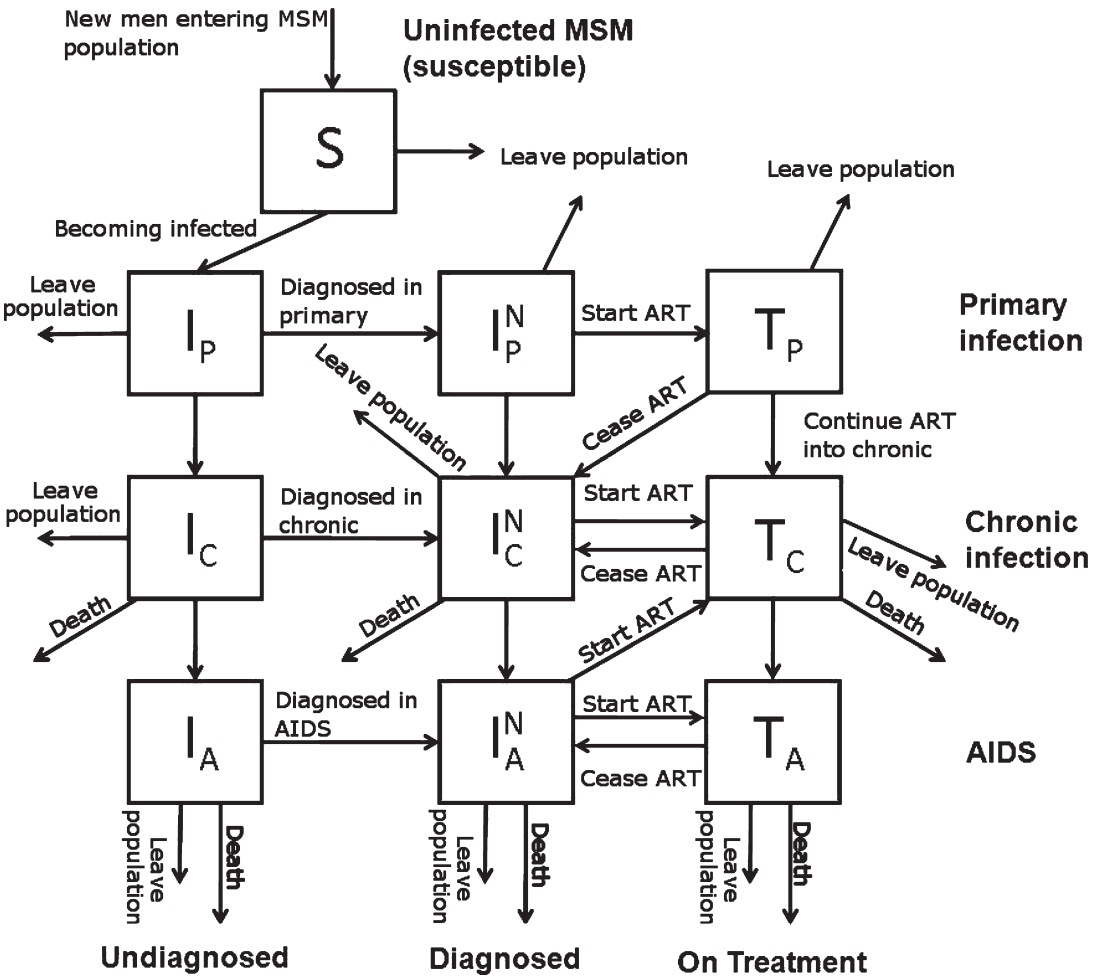
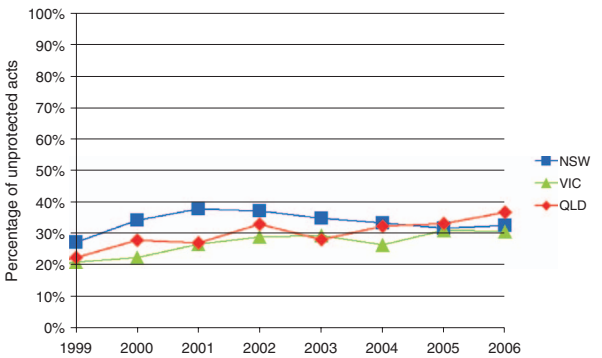
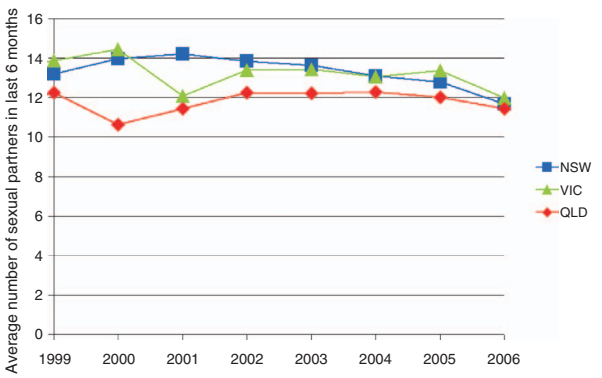
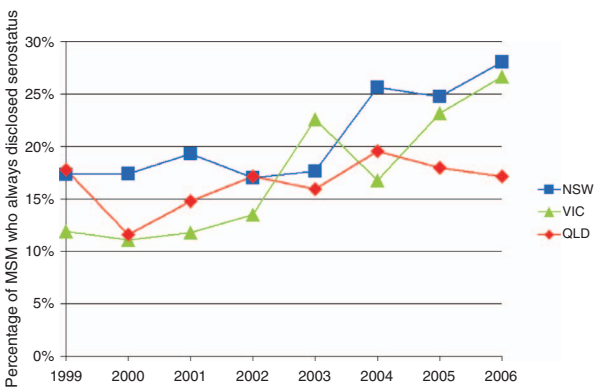
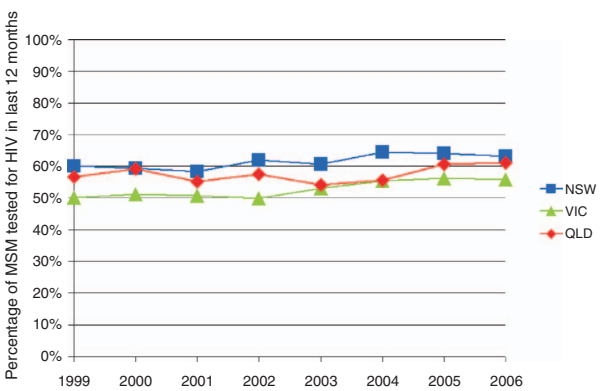


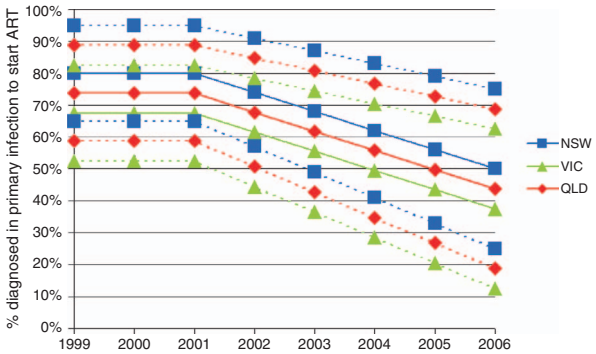
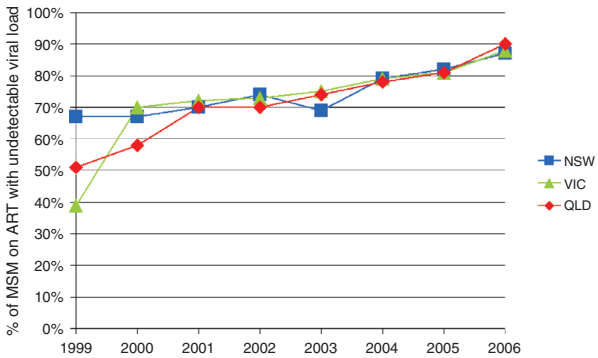
Fig. 1. Schematic diagram of our compartmental model structure. Uninfected men who have sex with men (MSM) enter the model as susceptible (*S*). Upon infection, they move from the susceptible group into undiagnosed primary infection (I_P). From here a certain proportion will get tested and will then move into the diagnosed arm (to I^N_P, I^N_C or I^N_A, depending on disease stage). Those who are not diagnosed will continue to progress through the different disease stages (I_C or I_A). Once they eventually become diagnosed, a proportion will begin treatment (T_P, T_C or T_A; the proportion varies depending on the stage of infection). People can leave each group by 'ageing' out of the population or AIDS-related death once in AIDS stage (or at lower rates in chronic stage).

Table 1. List of time-dependent parameters used in our mathematical model including graphs of changes in these parameters for New South Wales (squares), Victoria (triangles) and Queensland (diamonds)

Time-dependent parameter	Graph	References
Reported cases of unprotected acts with casual partners		5–7,11
Change in number of sexual partners		8–10
Disclosure of serostatus		5–7,11,14,15
Testing rates		5–7

(*Continued next page*)

Table 1. (*Continued*)

Time-dependent parameter	Graph	References
Treatment during primary infection		4
Proportion treated who achieve viral suppression		23,42,43

data were insufficient to enable precise estimation of the prevalence of individual STI in each of the states, and to quantify the impact of these on HIV transmission. Therefore, we did not model STI individually but made the assumption that a certain proportion of MSM would have another STI, and that the presence of an STI would increase their susceptibility to HIV acquisition. There is strong evidence that both ulcerative and non-ulcerative STI can increase the probability of HIV transmission by augmenting HIV infectiousness and susceptibility; reciprocally, HIV infection can enhance the transmission of other STI.[25–31] Several studies (in heterosexuals) estimate the relative risks of HIV infection due to infection with other STI in the range 2–24, but largely clustering between 2 and 5. We assume that this relative risk is equivalent in MSM and include a 'transmission-increasing' factor of 2–5 if another STI is present.[25–31]

In order to model the impact of STI on HIV transmission, it was necessary to estimate the proportion of MSM with other STI as well as trends over time and by state. This was problematic for several reasons. First, although there have been indications that the prevalence of some STI, notably syphilis, have been increasing in MSM in Australia, most data are reported only as notifications, not as the proportion of tests that are positive. Furthermore, the National Centre for HIV Social Research reported significant increases in testing (10–20%) in the past few years. Second, much of the published data on STI in MSM in Australia is from the 'Health in Men' (HIM) study and the incidence of STI has decreased in this highly tested, Sydney-based, HIV-negative cohort over the past few years.[14] Third, there is little data on trends in STI incidence and prevalence in MSM for the other states. Fourth, the most prevalent STI associated with HIV transmission is herpes simplex virus (HSV)-2 with prevalence in the HIM cohort estimated at ~23%, masking any trends that might be occurring with other STI. Of course, HSV-2 is latent for significant proportions of the time in infected people and virus is shed periodically; thus, the effective prevalence of HSV-2 in terms of increasing HIV transmissibility is likely to be lower. Given the uncertainty, we assumed that the average proportion of MSM with STI (ulcerative or non-ulcerative that contribute to increasing HIV transmissibility) is in the range 5–15% initially (that is, at 1999). To investigate national HIV trends, we did not distinguish STI rates between states. There is strong evidence of a significant rise in the incidence (and prevalence) of STI in recent years.[12,13,32]

Sampling and sensitivity analysis

Each parameter used in the model was assigned a uniform distribution between a minimum and maximum value, and Latin Hypercube Sampling[33] was used to generate 10 000 samples from each distribution for each state. These parameter sets became input values for our model and Monte Carlo filtering was used to remove all parameter sets that could not generate the number of observed notifications in 1999 for

each state. This left 4247 simulations for NSW, 3120 for Vic. and 3970 for Qld. These parameter sets then constituted the baseline for running simulations under several scenarios. Sensitivity analyses were carried out to determine important factors involved in the epidemic. The SaSAT software package[34] was used to generate samples and to carry out the sensitivity analyses.

Further filtering was conducted for projecting the HIV epidemic over the next 10 years. A regression line was fitted to the notifications data, and only simulations that were within 10% of the regression line at 2006 were selected for projections. This left 1482 simulations for NSW, 443 for Vic. and 799 for Qld. A range of scenarios was simulated to predict the future dynamics of the epidemic including: (1) all parameters remaining constant at their 2006 values; (2) all parameters continuing on their current trend; and (3) all parameters returning to the 1999 values. We also investigated changes in STI prevalence, HIV testing rates, condom use, and rates of early treatment of MSM diagnosed in primary infection.

Results

Without a change in the prevalence of other STI, but using the available time-dependent data for all other parameters, our model indicated that the number of HIV diagnoses should have actually decreased in all three states since 1999 (Fig. 2). This is due to increases in the effectiveness of treatment, increases in testing rates, and a slight decrease in the average number of casual partners, but offset slightly by decreases in condom use.

During the period 1999–2006, NSW experienced an 7.25% increase in notifications (see Table 2). Without an increase in other STI, our model suggested that observed changes in condom use directly resulted in an increase in HIV notifications of 5.23% and changes in patterns of treatment during primary infection resulted in an 1.01% increase. That is, these two factors account for a large proportion of the HIV increase in NSW. However, the model indicated that these factors were offset by changes in testing rates, average number of casual partnerships, disclosure of serostatus, and most importantly the proportion of treated MSM that achieve viral suppression. Each of these factors reduces the number of new infections leading to an overall decline in HIV notifications as seen in Fig. 2*a*.

Similarly, in Vic. the model suggested that a decline in condom use and treatment in primary infection, and changes in testing rates contributed positively to the number of HIV notifications. In contrast to NSW, however, these three factors accounted for a very small proportion of the large observed increase in HIV notifications (Table 2); the impact of these factors was also found to be largely outweighed by the proportion of treated people achieving viral suppression and other key parameters. Overall, without an increase in other STI, our model yielded a decrease in the number of HIV notifications, in contrast with the observed trend (Fig. 2*b*).

Qld also experienced a large increase in notifications between 1999 and 2006. In the absence of an increase in other STI, the most important factors contributing to the rise in Qld were again found to be declines in condom use and trends in treatment during primary infection. The model also suggested that changes in testing rates and disclosure of serostatus contributed positively to the rise in HIV notifications. Condom use was the most influential of these factors, contributing to an 9.45% rise, followed by change in testing rates (1.73%), treatment during primary infection (0.69%) and disclosure of serostatus (0.01%) (Table 2). But when other factors such as treatment effectiveness were included, as for the other states, our model showed that overall Qld should have experienced a decline in HIV cases (Fig. 2*c*), if the prevalence of other STI had not risen.

Because our model simulations could not directly account for the number of HIV notifications in all three states without changes in other STI, we investigated the extent of the change required to match the notification data. Although the data on the prevalence of STI among MSM in each state are incomplete, there are clear indications of increases in the incidence of infectious syphilis, chlamydia and gonorrhoea in the past few years.[12,13,32] Therefore, we used our model to estimate the magnitude of the increase in prevalence of other STI that would be required in order to match the observed data for each state. We implemented a linear increase in STI prevalence into the model. Figure 3 shows the adjusted simulations with an increasing STI factor. For NSW, we found that a 2-fold increase

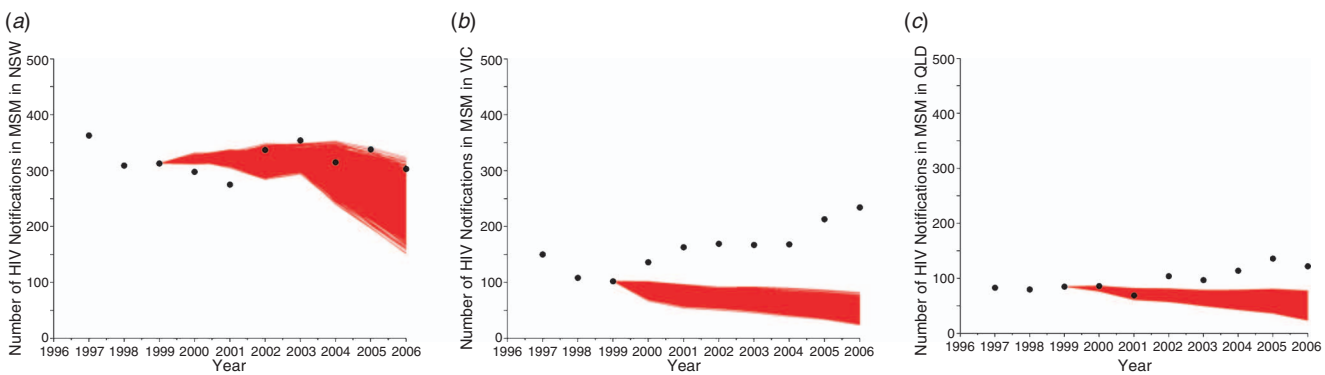


Fig. 2. Uncertainty analysis epidemic trajectories of the modelled number of HIV diagnoses if changes in the prevalence of other sexually transmissible infections are not considered. The black dots indicate the number of HIV diagnoses based on the surveillance data, and the red curves represent all simulated time courses for: (*a*) New South Wales, (*b*) Victoria and (*c*) Queensland. MSM, men who have sex with men.

Table 2. Percentage change in HIV notifications (from 1999 to 2006) that are attributable to various factors
MSM, men who have sex with men; NSW, New South Wales; Qld, Queensland; STI, sexually transmissible infection; Vic., Victoria

Factor	NSW	Vic.	Qld
Number of HIV notifications among MSM in 1999	313	102	85
Increase in notifications data from 1999 to 2006 (linear regression)	7.25%	96.43%	67.69%
Increase in HIV notifications due to factor			
Change in condom usage	5.23% (4.48, 6.03)	7.89% (6.78, 9.13)	9.45% (8.04, 10.97)
Change in casual partners	−0.45% (−2.20, −0.74)	−1.23% (−0.86, −1.62)	−0.57% (−0.39, −0.75)
Change in disclosure of serostatus	−0.11% (−0.33, 0.07)	−0.14% (−0.42, 0.12)	0.01% (0.01, 0.03)
Change in testing rates	−0.31% (−0.18, −0.46)	0.17% (0.03, 0.41)	1.73% (1.04, 2.52)
Change in treatment during primary infection	1.01% (0.43, 1.99)	0.52% (0.16, 1.15)	0.69% (0.45, 2.25)
Change in proportion treated that achieve viral suppression	−25.81% (−32.56, −20.26)	−56.13% (−62.2, −49.3)	−47.01% (−54.45, −39.97)
Change in other STI required to explain data	~2-fold increase	~11-fold increase	~9-fold increase

in the prevalence of other STI from 1999 to 2006 was required to appropriately match the data. Victoria required an increase of ~11-fold for the model simulations to match the data. Queensland required an ~9-fold increase in the prevalence of other STI for the model simulations to match the data. These required increases are not inconsistent with the trends in notifications of other STI.[12,13,32]

We then used our model to predict the number of new HIV infections, HIV diagnoses and AIDS deaths until 2015 by simulating the epidemic over this period under a variety of scenarios. We found that if all parameters remained constant at the 2006 values, there would be an increase in the number of HIV diagnoses in Vic. and Qld, whereas there would be a decrease in NSW (Fig. 4). The same qualitative result was found if the parameters did not remain constant but continued in the direction of their current trends (Fig. 5); however, if the current trends continued there would be even greater increases in HIV notifications in Vic. and Qld (Fig. 5).

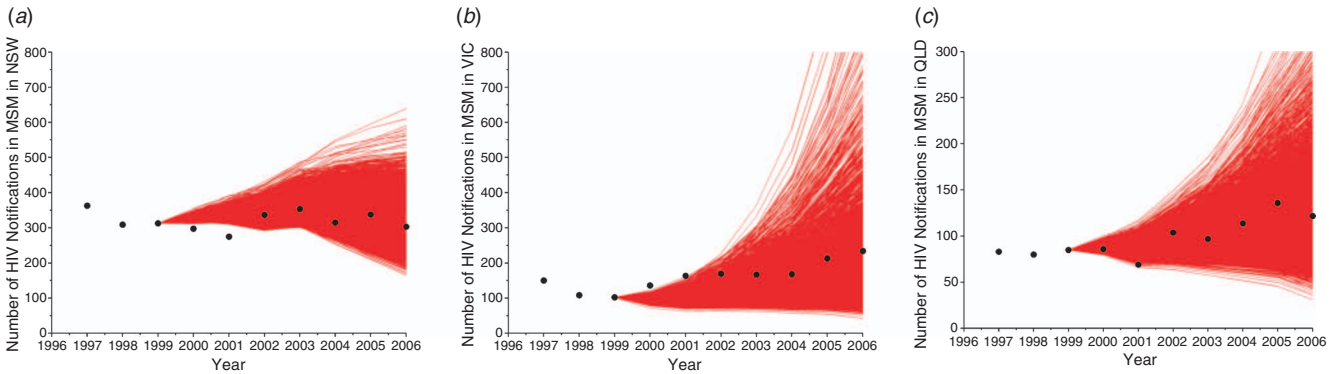


Fig. 3. Uncertainty analysis epidemic trajectories of the modelled number of HIV diagnoses if changes in sexually transmissible infections (STI) are adjusted for each state. The black dots indicate the number of HIV diagnoses based on the surveillance data, and the red curves represent all simulated time courses for: (*a*) New South Wales – with a 2-fold increase in other STI, (*b*) Victoria – 11-fold increase in other STI, and (*c*) Queensland – 9-fold increase in other STI. MSM, men who have sex with men.

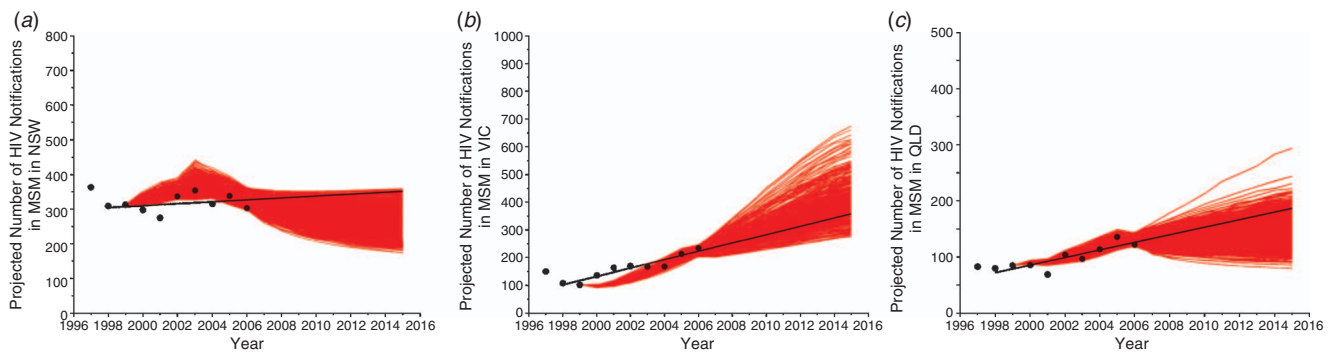


Fig. 4. Projected number of HIV notifications to 2015 in the case of parameters remaining constant at 2006 levels. The black dots indicate the surveillance data points, and the black line represents the best-fitting linear regression line through the data points for: (*a*) New South Wales, (*b*) Victoria and (*c*) Queensland. MSM, men who have sex with men.

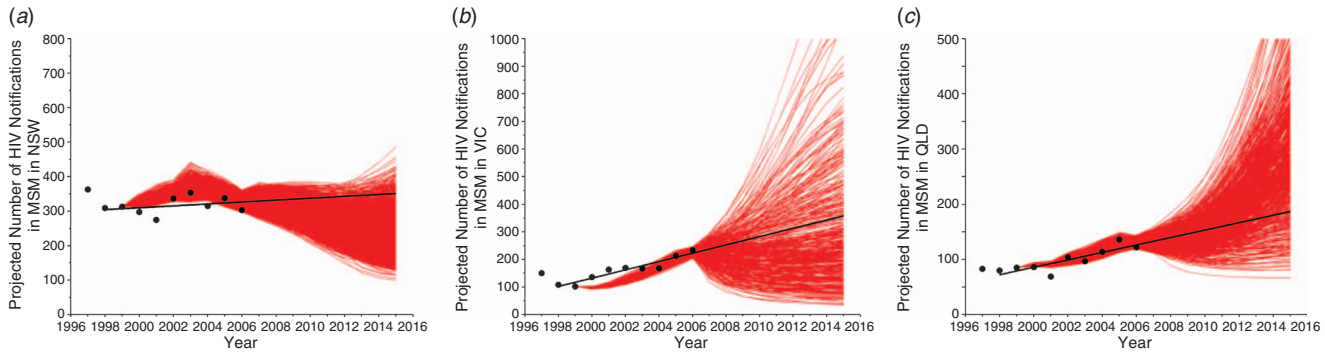


Fig. 5. Projected number of HIV notifications to 2015 in the case of all parameters continuing their current trends. The black dots indicate the surveillance data points, and the black line represents the best-fitting linear regression line through the data points for: (*a*) New South Wales, (*b*) Victoria and (*c*) Queensland. MSM, men who have sex with men.

We compared the expected impact of different interventions on the projected number of new HIV infections (as distinct from HIV notifications) in 2015 in all three states (Fig. 6). We found that the most effective way to reduce the number of new HIV infections was to reduce the prevalence of other STI. If the prevalence of other STI was changed immediately to 60%, then NSW would see a large increase in new infections, Vic. would see a decrease, and Qld would see a slight increase over the number expected if all parameters were maintained at their 2006 values. If reduced to 5%, then the epidemic is predicted to decline substantially in all states (Fig. 6). Not surprisingly, changes in condom use were also found to be highly influential in determining the future epidemic trajectories. Our projections indicated that if condoms were used in an average of 90% of acts (currently condom use is ~68% in NSW, ~69% in Vic. and ~63% in Qld[5–7]), significant declines in HIV cases would be observed in NSW and Qld, but there would still be an increase in HIV cases in Vic. (Fig. 6).

We also investigated the effect of patterns in the treatment of people diagnosed during the primary stage of HIV infection. Although the majority of seroconverters will not be detected with infection during primary infection, if early detection does

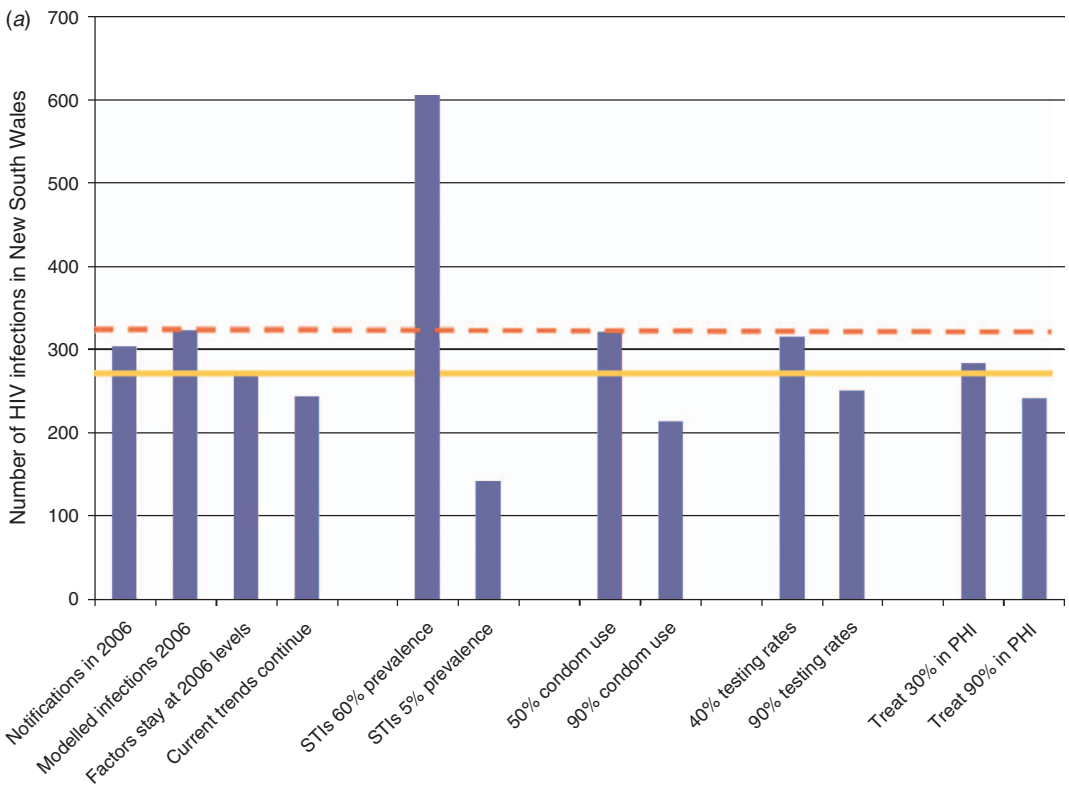
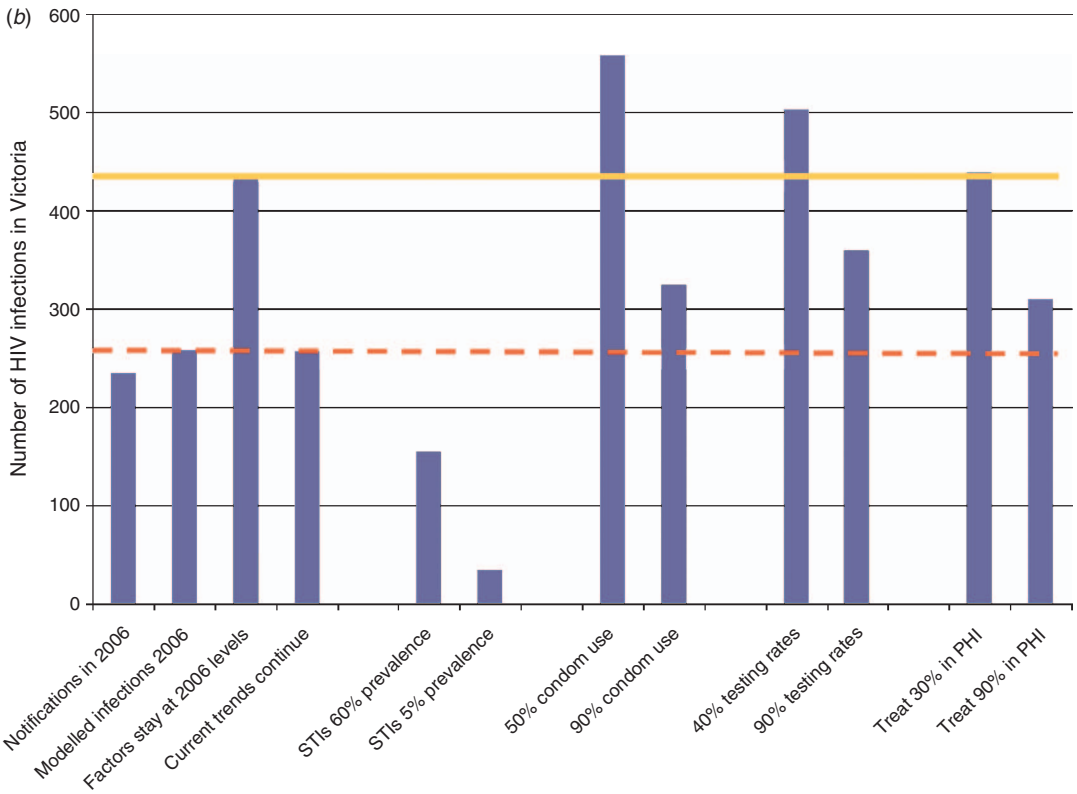


Fig. 6. Histograms showing the median number of projected HIV infections (as distinct from notifications) in 2015 for each scenario. The dashed red line corresponds to the number of infections simulated in 2006, and the solid orange line corresponds to the projected number of infections in 2015 if all parameters remain constant at their 2006 values.



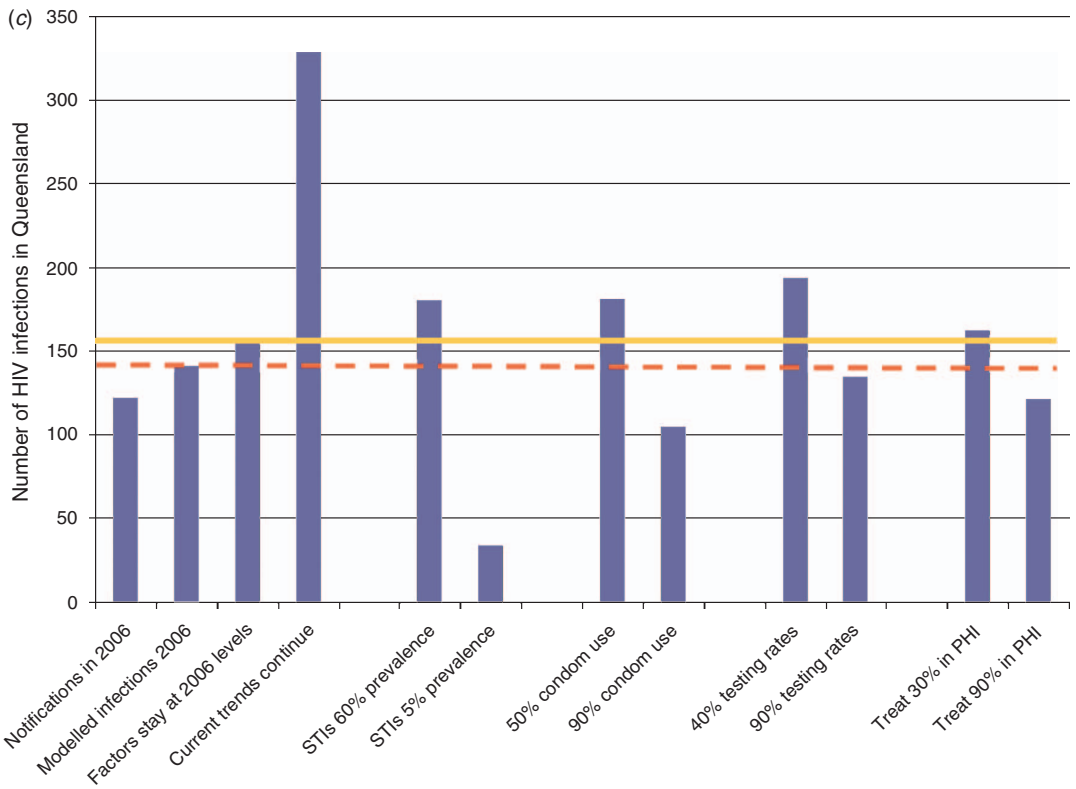


Fig. 6. (*Continued*)

occur and early treatment is provided then it has the effect of significantly reducing the high viral loads associated with primary infection, and this in turn reduces secondary transmission to others. Our findings indicate that increasing the proportion of people diagnosed in primary infection who receive treatment will lead to reductions in the number of new HIV cases. We investigated several coverage levels of treatment of people diagnosed in primary infection. Currently, ~30–50% of people diagnosed in primary infection receive treatment. If this was increased to 90%, then decreases would be seen in both NSW and Qld. Victoria would still see an increase over the number of infections in 2006, but the numbers would be considerably lower than if all parameters were to remain constant. Treating 90% of people diagnosed in primary infection may be feasible; high treatment in primary infection was achieved in Australia during the late 1990s. The qualitative implications of this result are that any effort to increase treatment during primary HIV infection is likely to be beneficial at the population level. Of course, the degree of success in treating early infection is dependent on the number of people that are diagnosed early in their infection. Therefore, the rate of testing for HIV is highly important.

Increasing testing for HIV is beneficial in reducing further HIV transmissions because sexual behaviour generally changes upon diagnosis (to decrease transmission to partners). We found that increasing testing rates decreases the incidence of HIV. Currently ~63% of MSM in NSW test for HIV each year, ~56% in Vic. and ~61% in Qld; testing rates have increased in all states since the levels in 1999 (of 60, 50 and 56%, respectively). This suggests that it is feasible to continue to increase testing rates. However, the maximum increase attainable is unknown. We investigated testing rates of 40, 50, 60, 70, 80 and 90%. Although testing 90% of MSM each year is likely to be unfeasible, we found that increasing testing has the potential to be highly beneficial in reducing the overall incidence of HIV in Australia (see Fig. 6).

Discussion

It was found that changes in condom use contributed to increases in HIV notifications in all three states. According to the data gathered from the Gay Periodic Surveys,[5–7] in all three states there has been a slight increase in the percentage of unprotected acts during the period 1999–2006. However, this decline in condom use cannot completely explain the rise in notifications. Treatment during primary infection has decreased in each state during the studied time period. Because viral loads are very high in primary infection,[35–40] the trends away from treatment during primary infection account for some of the rise in HIV notifications but are also unable to account for the magnitude of the observed rise. Indeed, the combination of changes in all variables could not account for the large rise in HIV notifications.

Testing rates in each state have recently increased modestly in all states. Our simulations suggested that the increased testing rates in NSW actually had a negative effect (–0.31%) on the number of HIV notifications (Table 2). In contrast, in Vic. and Qld the increases in testing had a small positive effect on HIV notifications, of 0.17 and 1.73%, respectively. Our model suggested that increasing testing can be beneficial in reducing the incidence of HIV. MSM diagnosed with HIV are likely to take behavioural measures to reduce their risk of transmission to other people, and if they receive treatment then their infectiousness will decrease substantially (especially if their infection is detected early). We have modelled a variety of testing levels and presented a ‘maximum’ achievable impact of increasing testing rates (to 90% of MSM each year). Although on its own such a high level of testing cannot turn the trends in HIV notifications in all states, our results suggest that testing is highly important and should be promoted further.

One factor that we have not attempted to model separately by state is serosorting, whereby MSM engage in unprotected anal intercourse only with men of the same serostatus as themselves. If successful, serosorting would reduce the risk of HIV transmission despite apparent increases in rates of unprotected anal intercourse. There are some data that suggest that serosorting may have been more successful in NSW than in Vic. or Qld.[41] It is possible that this has contributed to differences in trends in HIV notifications by state, and currently this has not been captured in the models. If serosorting was more successful in NSW than the other states, then it is likely that less-dramatic differences in trends in rates of STI would be required to reproduce the observed trends in HIV notifications by state. However, we have considered differences between states in the trends in disclosure of serostatus in established sexual partnerships. It is much more likely that negotiated protection, based on serostatus, within partnerships will occur than the establishment of partnerships on the basis of serostatus (G. Prestage, National Centre in HIV Epidemiology and Clinical Research, pers. comm). It is also known that serosorting is more common among HIV-infected MSM than HIV-negative MSM. Thus, including serosorting is not likely to alter the incidence of new HIV infections. Of course, the impact of any serosorting among HIV-negative men is only as reliable as the frequency of HIV testing and degree of monogamy.

We have shown that the prevalence of other STI is a more important factor underlying the recent increase in HIV notifications than perhaps previously thought. Other STI may have had the greatest direct impact on the recent increase in HIV trajectories in Australia. It should be noted that our model did not link STI prevalence with condom use. In our model these factors have been decoupled, such that any changes in condom use and the prevalence of STI are independent. This is a limitation in our model. Future work will extend this analysis to model interacting infections and allow investigation of the indirect effects of condoms on reducing HIV by reducing the incidence (and thus prevalence) of other STI. However, our model indicates that the decrease in condom use alone (i.e. its direct effect in reducing HIV transmission) is not enough to account for the increases in HIV notifications. Our projections show that targeting STI in the community will be the most effective way to alter the epidemic trajectories. Condom use is also very important: our projections show that if condom use increased even moderately, then declines in new HIV infections would be observed. Of course, increasing condom use will also reduce the transmission of many other STI. We also suggest that increasing testing rates and subsequent early treatment of individuals diagnosed in primary infection will

have secondary benefits beyond the newly infected individuals in averting significant numbers of onward transmissions.

Acknowledgements

The authors thank the members of the Reference Group that provided advice and guidance through the development of this report. Members of the Reference Group, and the bodies they represented, were: Professor Frank Bowden, HIV/AIDS and STI Subcommittee of the Ministerial Advisory Committee on AIDS, Sexual Health and Hepatitis; Ms Sharon Flanagan and Ms Karen Fox, Australian Government Department of Health and Ageing; Associate Professor John Imrie, National Centre in HIV Social Research, University of New South Wales; Mr Philip Keen, AIDS Council of New South Wales; Dr Rosemary Lester, Communicable Diseases Network Australia; Dr Kelly Shaw, Blood Borne Virus Surveillance System; and Mr Bill Whittaker, National Association of People living With HIV/AIDS. The authors also thank the following colleagues and collaborators at the National Centre in HIV Epidemiology and Clinical Research for making data available, and also for numerous discussions and advice on interpretation: Dr Handan Wand, Ms Linda Gelgor, Ms Kathleen Falster, Professor Andrew Grulich, Associate Professor Anthony Kelleher, Professor John Kaldor, Ms Ann McDonald, Ms Melanie Middleton and Dr Garrett Prestage. The National Centre in HIV Epidemiology and Clinical Research is funded by the Australian Government Department of Health and Ageing, and is affiliated with the Faculty of Medicine, University of New South Wales. Dr David Wilson is funded by a Vice Chancellor's Fellowship from the University of New South Wales and by grant number DP0771620 from the Australian Research Council; Mr Alex Hoare is funded by a University Postgraduate Award from the University of New South Wales; Dr David Regan is funded by grant number 358425 from the Australian National Health and Medical Research Council; Associate Professor Matthew Law is funded by grant numbers 1-U01-AI6994-01, 1-U01-AI068641, 1-U01-A1069907-01 and 5-U19-AI05371 from the National Institutes of Health, USA.

References

1 National Center in HIV Epdemiology and Clinical Research. HIV/AIDS, viral hepatitis and sexually transmissible infections in Australia Annual Surveillance Report 2007. National Centre in HIV Epidemiology and Clinical Research, The University of New South Wales, Sydney, NSW; Australian Institute of Health and Welfare, Canberra, ACT; 2007.

2 Anderson RM, May RM. Infectious diseases of humans. Oxford: Oxford University Press; 1991.

3 Quinn TC, Wawer MJ, Sewankambo N, Serwadda D, Li C, Wabwire-Mangen F, *et al*. Viral load and heterosexual transmission of human immunodeficiency virus type 1. *N Engl J Med* 2000; 342: 921–9. doi: 10.1056/NEJM200003303421303

4 Falster K, Gelgor L, Shaik A, Zablotska I, Prestage G, Grierson J, *et al*. HIV antiretroviral treatment differences by state in Australia. *Sex Health* 2007; 5: 141–54. doi: 10.1071/SH07082

5 Zablostska I, Prestage G, Frankland A, Chong S, Sutherland R, Corrigan N, Honnor G, Kippax S. Gay Community Periodic Survey: Sydney, February 2007. Sydney: National Centre in HIV Social Research, The University of New South Wales; 2007.

6 Frankland A, Zablotska I, Prestage G, Batrouney C, Clift P, Nixon R, Kippax S. Gay Community Periodic Survey: Melbourne 2007 (GCPS Report 4/2007). Syndney: National Centre in HIV Social Research, The University of New South Wales; 2007

7 Zablotska I, Prestage G, Imrie J, Kippax S, Hakala T, Martin P, O'Connor S. Gay Community Periodic Survery: Queensland 2006. (GCPS Report 1/2007). Sydney: National Centre in HIV Social Research, The University of New South Wales; 2007.

8 Satter M, Fitzherbert S (eds). National Centre in HIV Social Research annual report. Sydney: University of New South Wales; 2006.

9 National Centre in HIV Social Research annual report of trends in behaviour. Sydney: University of New South Wales; 2006.

10 Richters J (ed.) HIV/AIDS, hepatitis and sexually transmissible infections in Australia: annual report of trends in behaviour 2006 (Monograph 3/2006). Sydney: National Centre in HIV Social Research, The University of New South Wales; 2006.

11 Grierson J, Thorpe R, Pitts M. HIV futures 5: Life as we know it, monograph series number 60. Melbourne: The Australian Research Centre in Sex, Health and Society, Latrobe University; 2006.

12 Grulich AE, Cunningham P, Munier M-L, Prestage G, Amin J, Ringland C, *et al*. Sexual behaviour and human herpesvirus infection in homosexual men in Australia. *Sex Health* 2005; 2: 13–8. doi: 10.1071/SH04029

13 Jin F, Prestage GP, Kippax SC, Pell CM, Donovan BJ, Kaldor JM, *et al*. Epidemic syphilis among homosexually active men in Sydney. *Med J Aust* 2005; 183: 179–83.

14 Fogarty A, Mao L, Zablotska I, Salter M, Santana H, Prestage G, *et al*. The health in men and positive health cohorts: a comparison of trends in the health and sexual behaviour of HIV-negative and HIV-positive gay men, 2002–2005, National Centre in HIV Social Research annual report of trends in behaviour. Sydney: University of New South Wales; 2006.

15 Mao L, Crawford JM, Hospers HJ, Prestage GP, Grulich AE, Kaldor J, *et al*. 'Serosorting' in casual anal sex of HIV-negative gay men is noteworthy and is increasing in Sydney, Australia. *AIDS* 2006; 20: 1204–6. doi: 10.1097/01.aids.0000226964.17966.75

16 Cleary PD, Van Devanter N, Rogers TF, Singer E, Shipton-Lery R, Steilen M, *et al*. Behavior changes after notification of HIV infection. *Am J Public Health* 1991; 81: 1586–90.

17 Colfax GN, Buchbinder SP, Cornelisse PGA, Vittinghoff E, Mayer K, Celum C, *et al*. Sexual risk behaviors and implications for secondary HIV transmission during and after HIV seroconversion. *AIDS* 2002; 16: 1529–35. doi: 10.1097/00002030-200207260-00010

18 Marks G, Crepaz N, Senterfitt JW, Janssen RS. Meta-analysis of high-risk sexual behavior in persons aware and unaware they are infected with HIV in the United States: implications for HIV prevention programs. *J Acquir Immune Defic Syndr* 2005; 39: 446–53. doi: 10.1097/01.qai.0000151079.33935.79

19 McCusker J, Stoddard AM, Mayer KH, Zapka J, Morrison C, Saltzman SP, *et al*. Effects of HIV antibody test knowledge on subsequent sexual behaviors in a cohort of homosexually active men. *Am J Public Health* 1988; 78: 462–7.

20 Saah AJ, Hoover DR, Weng S, Carrington M, Mellors J, Rinaldo CR Jr, *et al*. Association of HLA profiles with early plasma viral load, CD4+ cell count and rate of progression to AIDS following acute HIV-1 infection. Multicenter AIDS Cohort Study. *AIDS* 1998; 12: 2107–13. doi: 10.1097/00002030-199816000-00005

21 Smith DK, Warren DL, Valhov D, Schuman P, Stein MD, Greenberg BL, *et al*. Design and baseline participant characteristics of the Human Immunodeficiency Virus Epidemiology Research (HER) Study: a prospective cohort study of human immunodeficiency virus infection in US women. *Am J Epidemiol* 1997; 146: 459–69.

22 Valleroy LA, MacKellar DA, Karon JM, Rosen DH, McFarland W, Shehan DA, *et al*. HIV prevalence and associated risks in young men who have sex with men. Young Men's Survey Study Group. *JAMA* 2000; 284: 198–204. doi: 10.1001/jama.284.2.198

23 Van de Ven P, Mao L, Fogarty A, Rawstorne P, Crawford J, Prestage G, *et al*. Undetectable viral load is associated with sexual risk taking in HIV serodiscordant gay couples in Sydney. *AIDS* 2005; 19: 179–84.

24 Crawford JM, Kippax SC, Mao L, Van de Ven PG, Prestage GP, Grulich AE, *et al*. Number of risk acts by relationship status and partner serostatus: findings from the HIM cohort of homosexually active men in Sydney, Australia. *AIDS Behav* 2006; 10: 325–31. doi: 10.1007/s10461-005-9057-3

25 Bautista CT, Sanchez JL, Montano SM, Laguna-Torres VA, Lama JR, Sanchez JL, *et al*. Seroprevalence of and risk factors for HIV-1 infection among South American men who have sex with men. *Sex Transm Infect* 2004; 80: 498–504. doi: 10.1136/sti.2004.013094

26 Fleming DT, Wasserheit JN. From epidemiological synergy to public health policy and practice: the contribution of other sexually transmitted diseases to sexual transmission of HIV infection. *Sex Transm Infect* 1999; 75: 3–17.

27 Galvin SR, Cohen MS. The role of sexually transmitted diseases in HIV transmission. *Nat Rev Microbiol* 2004; 2: 33–42. doi: 10.1038/nrmicro794

28 Piot P, Laga M. Genital ulcers, other sexually transmitted diseases, and the sexual transmission of HIV. *BMJ* 1989; 298: 623–4.

29 Read TRH, Hocking J, Sinnott V, Hellard M. Rick factors for incident HIV infection in men having sex with men: a case-control study. *Sex Health* 2007; 4: 35–9. doi: 10.1071/SH06043

30 Rottingen JA, Cameron DW, Garnett GP. A systematic review of the epidemiologic interactions between classic sexually transmitted diseases and HIV: how much really is known? *Sex Transm Dis* 2001; 28: 579–97. doi: 10.1097/00007435-200110000-00005

31 Simonsen JN, Cameron DW, Gakinya MN, Ndinya-Achola JO, D'Costa LJ, Karasira P, *et al*. Human immunodeficiency virus infection among men with sexually transmitted diseases. Experience from a center in Africa. *N Engl J Med* 1988; 319: 274–8.

32 Middleton MG, McDonald AM, Grulich AE, Donovan B, Kaldor JM. Could sexually transmissible infections be contributing to the increase in HIV infections among men who have sex with men in Australia? *Sex Health* 2008; 5: 131–40. doi: 10.1071/SH07086

33 Blower SM, Dowlatabadi H. Sensitivity and uncertainty analysis of complex models of disease transmission: an HIV model, as an example. *Int Stat Rev* 1994; 62: 229–43.

34 Hoare A, Regan DG, Wilson DP. Sampling and sensitivity analyses tools (SaSAT) for computational modelling. *Theor Biol Med Model* 2008; 5: 4. doi: 10.1186/1742-4682-5-4

35 Bonjoch A, Paredes R, Domingo P, Cervantes M, Pedrol E, Ribera E, *et al*. Long-term safety and efficacy of nevirapine-based approaches in HIV type 1-infected patients. *AIDS Res Hum Retroviruses* 2006; 22: 321–9. doi: 10.1089/aid.2006.22.321

36 Rangsin R, Chiu J, Khamboonruang C, Sirisopana N, Eiumtrakul S, Brown AE, *et al*. The natural history of HIV-1 infection in young Thai men after seroconversion. *J Acquir Immune Defic Syndr* 2004; 36: 622–9. doi: 10.1097/00126334-200405010-00011

37 Richardson BA, Mbori-Ngacha D, Lavreys L, John-Stewart GC, Nduati R, Panteleeff DD, *et al*. Comparison of human immunodeficiency virus type 1 viral loads in Kenyan women, men, and infants during primary and early infection. *J Virol* 2003; 77: 7120–3. doi: 10.1128/JVI.77.12.7120-7123.2003

38 Sabin CA, Devereux H, Phillips AN, Hill A, Janossy G, Lee CA, *et al*. Course of viral load throughout HIV-1 infection. *J Acquir Immune Defic Syndr* 2000; 23: 172–7.

39 Simon V, Ho DD, Abdool Karim Q. HIV/AIDS epidemiology, pathogenesis, prevention, and treatment. *Lancet* 2006; 368: 489–504. doi: 10.1016/S0140-6736(06)69157-5

40 Yozviak JL, Doerfler RE, Woodward WC. Effectiveness and tolerability of nevirapine, stavudine, and lamivudine in clinical practice. *HIV Clin Trials* 2001; 2: 474–6. doi: 10.1310/T0RR-TGY0-8QWB-8YT2

41 Zablotska I, Prestage G, Grulich AE, Imrie J. Differing trends in sexual risk behaviours in three Australian states: New South Wales, Victoria and Queensland, 1998–2006. *Sex Health* 2008; 5: 125–30. doi: 10.1071/SH07076

42 Glenday K. Australian HIV Observational Database annual report 2006. Sydney: National Centre in HIV Epidemiology and Clinical Research; 2006.

43 Zhang H, Dornadula G, Beumont M, Livornese L, Van Uitert B, Henning K, *et al*. Human immunodeficiency virus type 1 in the semen of men receiving highly active antiretroviral therapy. *N Engl J Med* 1998; 339: 1803–9. doi: 10.1056/NEJM199812173392502

Manuscript received 17 December 2007, accepted 16 April 2008

Appendix:

Transmission model equations

The dynamic transmission model is represented by 10 ordinary differential equations. The mathematical description of our model is described here. In our model, we track the number of individuals to enter the susceptible men who have sex with men (MSM) population (S) at a rate of π per year. These individuals enter into the 'pool' of MSM, choosing sexual partners from the population. On average they leave the population of those choosing new sexual partners after an average of $1/\mu$ years. Thus, out of each compartment we include an outflow at rate μ. The other means by which susceptible individuals can leave this compartment is by becoming HIV-infected. The rate of flow in the number of people who become infected – that is, the force of infection (λ) – is defined below. Then, the rate of change in the total number of susceptible men at time t is given by

$$\frac{dS}{dt} = \pi - (\mu + \lambda(t))S(t).$$

Once an individual has become infected with HIV, he will initially have the status of undiagnosed with primary HIV infection (I_P). Thus, the number of MSM who leave the susceptible population per year, λS, becomes the source for the I_P compartment. There are three ways in which men can leave the undiagnosed primary HIV infection compartment: (i) become diagnosed as HIV-positive (at a rate γ_P), (ii) remain undiagnosed and progress in disease to chronic infection stage (at a rate ω_P), or (iii) leave the sexually active population (at rate μ). Accordingly, the rate of change in the total number of undiagnosed HIV-positive men in primary infection at time t is given by

$$\frac{dI_P}{dt} = \lambda(t)S(t) - I_P(t)(\mu + \gamma_P + \omega_P).$$

Similarly, the rate of change in the total number of undiagnosed HIV-positive men in chronic and AIDS stage infection at time t is given by

$$\frac{dI_C}{dt} = \omega_P I_P(t) - I_C(t)(\mu + \gamma_C + \omega_C + \delta_C)$$

and

$$\frac{dI_A}{dt} = \omega_C I_C(t) - I_A(t)(\mu + \gamma_A + \delta_A),$$

respectively, where the subscripts refer to the different disease stages and people in AIDS stage die of AIDS-related illnesses at a rate δ_A (we also include an HIV-related death rate, δ_C, for people in the chronic stage of HIV infection).

Rates of movement out of compartments of untreated HIV-infected and diagnosed men can be due to (i) disease progression (at rate ω), (ii) commencing antiretroviral therapy (at rate η), (iii) death (at rate δ), or (iv) leaving the sexually active population (at rate μ). Rates of movement into compartments of untreated HIV-infected and diagnosed men can be due to (i) newly diagnosed as HIV-infected (at rate γ) or (ii) previously treated men stopping antiretroviral therapy (at rate ν). Then, the rate of change in the total numbers of diagnosed but untreated HIV-positive men in primary, chronic, and AIDS stages of infection at time t are given by

$$\frac{dI_P^N}{dt} = \gamma_P I_P(t) - I_P^N(t)(\mu + \omega_P + \eta_P),$$

$$\frac{dI_C^N}{dt} = \gamma_C I_C(t) + \omega_P I_P^N(t) + \nu_C T_C(t) + \nu_P T_P(t) - I_C^N(t)(\mu + \omega_C + \eta_C + \delta_C),$$

and

$$\frac{dI_A^N}{dt} = \gamma_A I_A(t) + \nu_A T_A(t) + \omega_C I_C^N(t) - I_A^N(t)(\mu + \eta_A + \delta_A),$$

where the subscripts refer to the respective disease stages.

Individuals diagnosed with HIV have the option of initiating antiretroviral therapy (ART). Based on the proportion of HIV-infected MSM who are on ART or initiate ART each year we determine the rate of movement from untreated diagnosed compartments to treatment compartments (denoted by η). The rates of initiating therapy are different for each stage of disease. Individuals on therapy can cease therapy until a later time (due to toxicities etc.), and we define the rate of ceasing treatment as ν (individuals treated in primary infection could initiate an early treatment schedule and upon ceasing ART would move into chronic infection (at rate ν_P)). Treatment will delay the progression of disease, but HIV-infected patients on ART can still progress in their infection (at rates τ) and if

in AIDS-stage can still die of AIDS-related illnesses at a slower rate to untreated people (due to ineffective treatment for various possible reasons including drug resistance). Then, the rate of change in the total numbers of treated HIV-positive men in primary, chronic, and AIDS stages of infection at time t are given by

$$\frac{dT_P}{dt} = \eta_P I_P^N(t) - T_P(t)(\mu + \nu_P + \tau_P)$$

$$\frac{dT_C}{dt} = \eta_C I_C^N + \tau_P T_P(t) + (1 - p_A)\eta_A I_A^N(t) - T_C(t)(\mu + \nu_C + \tau_C + \delta_C^T),$$

and

$$\frac{dT_A}{dt} = p_A \eta_A I_A^N(t) + \tau_C T_C(t) - T_A(t)(\mu + \nu_A + \delta_T).$$

Table A1 gives a full description of all of the parameters mentioned above, along with values that were used in the model.

Force of infection

The force of infection, λ, is the dynamic rate at which susceptible individuals become infected with HIV. This function contains many of the factors that contribute to HIV transmission. Typically λ is calculated as the average number of sexual partners each susceptible person has per year, multiplied by the probability that each new partner is HIV-positive, multiplied by the probability of HIV transmission occurring per partnership per year. Various factors contribute to each of these components.

Number of sexual partners

We distinguish between the numbers of casual sexual partners and the numbers of regular partners MSM are likely to have, on average, each year. We let c_{cas} represent the number of casual partners and c_{reg} represent the number of casual partners. We use behavioural data[1–3] on the proportion of men who have 0, 1, 2–10, 11–50, >50 partners to calculate a weighted average at each available time point, to obtain the following trends. We also make the assumption that one partner is regular, on average, and the remaining partners are casual partners.

Probability that new sexual partner is HIV-positive

If there was homogeneous non-differential mixing and no change in sexual behaviour between any categories of MSM in our model, then the probability that a new partner is HIV-positive is simply the ratio of the number of HIV-infected men to the total number of men in the population. There is evidence of change in behaviour upon diagnosis and men in AIDS stage disease are likely to have reduced numbers of partners due to their sickness. If healthy undiagnosed and susceptible men have partners per year, then we model the number of partners per year that men with AIDS have as $\theta_{\text{AIDS}} \cdot c$, where θ_{AIDS} is a multiplying factor for the reduction in sexual activity due to the effect of illness. We model the number of partners that diagnosed men have per year as $f \cdot c$. Here, f refers to the multiplicative increase or decrease in sexual activity; we consider both the possibility of increase or decrease since HIV-positive men may reduce risky sex to avoid infecting others or they may increase risky sex as they are no longer at risk of seroconverting. Thus, the probability of a new partner being HIV-positive is

$$\frac{I_P + I_C + \theta_{\text{AIDS}} I_A + f(I_P^N + I_C^N + \theta_{\text{AIDS}} I_A^N + T_P + T_C + \theta_{\text{AIDS}} T_A)}{S + I_P + I_C + \theta_{\text{AIDS}} I_A + I_P^N + f(I_C^N + \theta_{\text{AIDS}} I_A^N + T_P + T_C + \theta_{\text{AIDS}} T_A)}.$$

Sexual partnerships are likely to be formed irrespective of HIV serology status. A proportion of men will disclose their HIV serostatus to their partner (which is generally reciprocated). We denote the proportion of men who disclose their serostatus to their partner as p_{disclose}. If serostatus is disclosed and a partnership is serodiscordant then we assume that condoms are used in the majority of acts, but if the partnership is thought to be seroconcordant then we assume that condom use will be low.[4] The risk of transmission in the relationships thought to be seroconcordant is due to partners that are undiagnosed but HIV-infected. If serostatus is not disclosed, then we assume that there is average condom use (at the average level reported in survey studies) and that partners of any status/compartment can be chosen.

Serosorting for the formation of partnerships is rare; particularly among HIV-negative MSM (it is more common among HIV-positive MSM) (G. Prestage, pers. comm., National Centre in HIV Epidemiology and Clinical Research). Therefore, we simplify our model by not including serosorting for the establishment of partners. Negotiating condom use based on disclosure of serostatus is relatively common and is an important aspect retained in our model.

Table A1. Definitions, ranges and references for input parameters used in our mathematical model
ART, antiretroviral treatment; MSM, men who have sex with men; STI, sexually transmissible infections

Parameter	Description		Value	Ref.
c	Average number of sexual partnerships per year (undiagnosed MSM)		1–3[C]	
θ_{AIDS}	Multiplying factor for the reduction in number of sexual partners for men in AIDS stage disease		0.1–0.4	
p_{anal}	Percentage of sexual partnerships in which penile–anal intercourse occurs		10–40%	6
f	Multiplying factor for the average change in number of sexual partners post-diagnoses of HIV infection (this reflects a possible range from 50% decrease to 10% increase)		0.4–1.1	6–14
$p_{disclose}$	Proportion of partnerships in which serostatus is disclosed (in negotiating condom usage)	Regular	0.8–0.9	1, 4, 15, 16
		Casual	[C]	
p_{condom}	Proportion of acts in which condoms are used			1, 4[C]
ε	Efficacy of condom protection per act		0.85–0.9	17–21
W	Baseline viral load during chronic infection		10^4–10^5 copies/mL	22–26
V_{PI}	Average viral load at primary infection stage		$10^{6.5}$–10^8 copies/mL	22–24, 26, 27
V_A	Average viral load at AIDS		$10^{5.5}$–$10^{6.5}$ copies/mL	24, 28, 29
V_T	Average viral load in effectively treated individual		10–100 copies/mL	30–32
P_s	Proportion of individuals on antiretroviral therapy in which viral load is suppressed			1, 7, 33, 34[C]
β_C, β_C^N	Probability of HIV transmission per act from an individual in chronic stage of infection		0.0015–0.0025	35–40
β_P, β_P^N, β_A, β_A^N	Probability of HIV transmission per act from an individual in primary or AIDS stage of infection			5
β_P^T, β_C^T, β_A^T	Probability of HIV transmission per act from a treated individual			5, 41
P_{STI}	Proportion of HIV-negative MSM who have other STIs		0.05–0.15	42, 43
b_{STI}	The multiplicative increase in transmission probability due to the presence of other STIs		2–5	44–50
n_{reg}	Average number of anal intercourse acts per regular partner per week		1.6–2.4	51
n_{cas}	Average number of anal intercourse acts per casual partner (over duration of casual relationship)		1–2	16, 51
P_{Test}	Proportion of MSM who test for HIV infection each year			1[C]
$1/\gamma_A$	Average time from the beginning of AIDS before individual is likely to be diagnosed with infection		2–4 months	
$1/\omega_p$	Average time for untreated individuals to progress from primary infection to chronic infection		3–9 months	23, 52, 53
$1/\omega_C$	Average time for individuals to progress from chronic infection to AIDS		8–12 years	22, 28, 54–57
P_p	Proportion of people diagnosed in primary infection who will commence treatment		[A]	
$1/\nu_p$	Average time to cease treatment for individuals with primary infection		6–12 months	[A]
P_P^C	Proportion of people who started ART in primary infection and continue ART after finishing dosing schedule		65–75%	[A]
P_C	Proportion of people in chronic infection who will commence treatment		65–75%	1, 4, 58
P_A	Proportion of people with AIDS who commence treatment that experience treatment failure		0–0.1	
$1/\eta_A$	Average time before individuals with AIDS commence therapy		1–3 months	
$1/\eta_C$	Average time before diagnosed individuals in chronic infection commence therapy		2–10 years	
$1/\nu_C$	Average time to cease treatment for individuals with chronic infection		6–12 years	1
$1/\nu_A$	Average time to cease treatment for individuals with AIDS		8–14 years	1
$1/\mu$	Average time for individuals to 'retire' out of sexually active population (no longer obtaining new partners)		30–35 years	56
δ_C	Proportion of untreated MSM in chronic infection who die each year		1–2%	59–63
δ_C^T	Proportion of treated MSM in chronic infection who die each year		1–2%	59–63
$1/\delta_A$	Average time until death from the onset of AIDS for untreated individuals		0.5–1.5 years	63–66
$1/\delta_T$	Average time until AIDS-related death for individuals in AIDS stage but on ART (with treatment failure)		0.5–5 years	56, 63, 65, 67–73

Table A1. *Continued*

Parameter	Description	Value	Ref.
$1/\tau_C$	Average time of disease progression for treated individual with chronic infection to progress to AIDS	$1/\omega_C < 1/\tau_C < 20$	
π	Number of new susceptible individuals entering the MSM population per year (this is ~3–3.5% of men)		
	Nationally	2000–2500[B]	
	NSW	35–40%	
	VIC	22–27%	
	QLD	17–22%	

[A]We evaluated available data from primary infection cohorts on the percentage of HIV-infected MSM who commenced ART within 1 year of HIV diagnosis, including patients recruited to the Acute Infection and Early Disease Research Program (CORE 01) protocol established by the National Institutes of Health, and the Primary HIV and Early Disease Research: Australian Cohort (PHAEDRA) established by the National Centre in HIV Epidemiology and Clinical Research. This data has large uncertainty (summarised in reference 58), is limited in time and only includes NSW and VIC. Sample sizes are also not sufficient (as low as four in some years for VIC and six for NSW). Consequently, this has been used as a rough guide but we make assumptions in the trends in early treatment based on personal communication with clinicians (e.g. Prof. Tony Kelleher (NCHECR and Centre for Immunology at St Vincent's Hospital, t.kelleher@cfi.unsw.edu.au)). We estimate the basic anecdotal trends observed over the past few years, shown in Table 1 of the main text. However, since there are no firm data for the trends, we include greater uncertainty bounds on this time-dependent parameter than on the others (we use a multiplicative uncertainty range on these trends of 0.6–1.2). We also assume that the initial dosing schedule for these patients who commence treatment in primary infection is 6–12 months, after which time 60–70% of these patients will continue ART and the remaining patients will discontinue therapy until a later time.

[B]This leads to ~150 000–175 000 MSM nationally. The proportion of new MSM in NSW, VIC, QLD each year as a subset of the total National number are indicated.

[C]For each of these time-dependent parameters we include an uncertainty range of ±5%.

Our model requires estimates of the proportion of partnerships in which serostatus is disclosed in order to negotiate condom usage, p_{disclose} . We use data on the percentage of men who reported UAI and always disclosed serostatus,[1] and we included a ±25% uncertainty on the data.

Condom use

In regular relationships that are serodiscordant, we assume that average condom usage is high. Based on the Futures study,[4] we assume condoms are used in 75–85% of anal intercourse acts between discordant MSM. However, in regular relationships that are thought to be seroconcordant we assume that average condom usage is relatively low; we assume condoms are used in 5–10% of acts.[4] In casual relationships, serological disclosure is not as common as in regular relationships, but if the MSM in a casual relationship determines the relationship is serodiscordant then we assume condoms are used in 95–100% of acts. We assume that condoms are used more frequently in casual partnerships than in regular partnerships; thus, if it is thought that a casual relationship is seroconcordant then $p^{\text{reg}}_{\text{condom}} < p^{\text{cas}}_{\text{condom}} < 10\%$.

Probability of HIV transmission per discordant partnership per year

We denote the probability of HIV-transmission from an infected male to an uninfected male during a single unprotected act of anal intercourse by β. However, if a condom is used as protection during intercourse then the probability of transmission is reduced. If ε is the efficacy of condoms then the transmission probability per protected act is $(1-\varepsilon)\beta$. We consider the average number of coital acts per partner per unit time (η) and the proportion of these acts in which condoms are used (p_{condom}) to calculate the probability of transmission of infection per partnership over time. If β_i is the probability of HIV-transmission during a single coital act in a discordant partnership with protection type i (condom or no protection), then the probability of remaining uninfected after the single act is $(1-\beta_i)$. Since each discordant coital act results in either transmission of infection or not (two possible outcomes), we have a Bernoulli trial, assuming each act is independent and has equal transmission for each protection option.

Accordingly, the probability of remaining uninfected after all $n \cdot p_{\text{condom}}$ and $n(1-p_{\text{condom}})$ discordant sex acts that involved protection or no protection is binomial: $(1-(1-\varepsilon)\beta)^{n \cdot p_{\text{condom}}}$ and $(1-\beta)^{n(1-p_{\text{condom}})}$, respectively. Thus, together the probability of acquiring infection per discordant partnership per year is given by

$$\hat{\beta} = 1 - (1 - (1 - \varepsilon)\beta)^{n \cdot p_{\text{condom}}} (1 - \beta)^{n(1-p_{\text{condom}})}.$$

This expression is valid in the case of a standard transmission probability β. But the presence of other sexually transmissible infections, both ulcerative and non-ulcerative, can increase the transmission of HIV. Therefore, we consider the proportion of men who have other sexually transmissible infections (p_{STI}) and the multiplicative increase in the transmission

probability due to the presence of other infections(b_{STI}) . Accordingly, the probability of acquiring infection per discordant partner per year is adjusted to become

$$1-(1-(1-\varepsilon)\beta')^{n\cdot p_{\mathrm{condom}}}(1-\beta')^{n(1-p_{\mathrm{condom}})},$$

where

$$\beta'=(1-p_{\mathrm{STI}})\,\beta\;+\;p_{\mathrm{STI}}b_{\mathrm{STI}}\beta.$$

Combining factors for the resultant force of infection function

The force of infection is not as simple as multiplying each of the components together. This is because each compartment of HIV-infected person will have a different transmission probability. Average HIV viral load differs between disease stages and in individuals effectively treated with combination antiretroviral therapy. To calculate the transmission probabilities for each of these compartments we employ the relation described by Quinn *et al.*,[5] namely,

$$\hat{\beta}=2.45^{\log_{10}\left(\frac{\nu}{W}\right)}\beta_C,$$

where ν is the average viral load associated with a stage of infection, W is a baseline viral load taken at chronic infection, and β_c is the transmission probability for someone in chronic infection. That is, for each $\log_{10}$ increase in viral load there is a 2.45 times increase in the transmission probability.

Taken together, our expression for the force of infection is given by:

$$\begin{aligned}
\lambda=c_{\mathrm{reg}}\Bigg[&p^{\mathrm{reg}}_{\mathrm{disclose}}\frac{\hat{\beta}_P^{\mathrm{reg}\,|\,\mathrm{low\,condom}}I_P+\hat{\beta}_C^{\mathrm{reg}\,|\,\mathrm{low\,condom}}I_C+\hat{\beta}_A^{\mathrm{reg}\,|\,\mathrm{low\,condom}}\theta_{\mathrm{AIDS}}I_A}{S+I_P+I_C+\theta_{\mathrm{AIDS}}I_A+f(I_P^N+I_C^N+\theta_{\mathrm{AIDS}}I_A^N+T_P+T_C+\theta_{\mathrm{AIDS}}T_A)}\\
&+p^{\mathrm{reg}}_{\mathrm{dislose}}\frac{f(\hat{\beta}_P^{\mathrm{reg}\,|\,\mathrm{high\,condom}}I_P^N+\hat{\beta}_C^{\mathrm{reg}\,|\,\mathrm{high\,condom}}I_C^N+\hat{\beta}_A^{\mathrm{reg}\,|\,\mathrm{high\,condom}}\theta_{\mathrm{AIDS}}I_A^N+\hat{\beta}_T^{\mathrm{reg}\,|\,\mathrm{high\,condom}}(T_P+T_C+\theta_{\mathrm{AIDS}}T_A))}{S+I_P+I_C+\theta_{\mathrm{AIDS}}I_A+f(I_P^N+I_C^N+\theta_{\mathrm{AIDS}}I_A^N+T_P+T_C+\theta_{\mathrm{AIDS}}T_A)}\\
&+(1-p^{\mathrm{reg}}_{\mathrm{disclose}})\frac{\hat{\beta}_P^{\mathrm{reg}\,|\,\mathrm{ave\,condom}}I_P+\hat{\beta}_C^{\mathrm{reg}\,|\,\mathrm{ave\,condom}}I_C+\hat{\beta}_A^{\mathrm{reg}\,|\,\mathrm{ave\,condom}}\theta_{\mathrm{AIDS}}I_A}{S+I_P+I_C+\theta_{\mathrm{AIDS}}I_A+f(I_P^N+I_C^N+\theta_{\mathrm{AIDS}}I_A^N+T_P+T_C+\theta_{\mathrm{AIDS}}T_A)}\\
&+(1-p^{\mathrm{reg}}_{\mathrm{disclose}})\frac{f(\hat{\beta}_P^{\mathrm{reg}\,|\,\mathrm{ave\,condom}}I_P^N+\hat{\beta}_C^{\mathrm{reg}\,|\,\mathrm{ave\,condom}}I_C^N+\hat{\beta}_A^{\mathrm{reg}\,|\,\mathrm{ave\,condom}}\theta_{\mathrm{AIDS}}I_A^N+\hat{\beta}_T^{\mathrm{reg}\,|\,\mathrm{ave\,condom}}(T_P+T_C+\theta_{\mathrm{AIDS}}T_A))}{S+I_P+I_C+\theta_{\mathrm{AIDS}}I_A+f(I_P^N+I_C^N+\theta_{\mathrm{AIDS}}I_A^N+T_P+T_C+\theta_{\mathrm{AIDS}}T_A)}\Bigg]\\
&+c_{\mathrm{cas}}\Bigg[p^{\mathrm{cas}}_{\mathrm{disclose}}\frac{\hat{\beta}_P^{\mathrm{cas}\,|\,\mathrm{low\,condom}}I_P+\hat{\beta}_C^{\mathrm{cas}\,|\,\mathrm{low\,condom}}I_C+\hat{\beta}_A^{\mathrm{cas}\,|\,\mathrm{low\,condom}}\theta_{\mathrm{AIDS}}I_A}{S+I_P+I_C+\theta_{\mathrm{AIDS}}I_A+f(I_P^N+I_C^N+\theta_{\mathrm{AIDS}}I_A^N+T_P+T_C+\theta_{\mathrm{AIDS}}T_A)}\\
&+p^{\mathrm{cas}}_{\mathrm{dislose}}\frac{f(\hat{\beta}_P^{\mathrm{cas}\,|\,\mathrm{high\,condom}}I_P^N+\hat{\beta}_C^{\mathrm{cas}\,|\,\mathrm{high\,condom}}I_C^N+\hat{\beta}_A^{\mathrm{cas}\,|\,\mathrm{high\,condom}}\theta_{\mathrm{AIDS}}I_A^N+\hat{\beta}_T^{\mathrm{cas}\,|\,\mathrm{high\,condom}}(T_P+T_C+\theta_{\mathrm{AIDS}}T_A))}{S+I_P+I_C+\theta_{\mathrm{AIDS}}I_A+f(I_P^N+I_C^N+\theta_{\mathrm{AIDS}}I_A^N+T_P+T_C+\theta_{\mathrm{AIDS}}T_A)}\\
&+(1-p^{\mathrm{cas}}_{\mathrm{disclose}})\frac{\hat{\beta}_P^{\mathrm{cas}\,|\,\mathrm{ave\,condom}}I_P+\hat{\beta}_C^{\mathrm{cas}\,|\,\mathrm{ave\,condom}}I_C+\hat{\beta}_A^{\mathrm{cas}\,|\,\mathrm{ave\,condom}}\theta_{\mathrm{AIDS}}I_A}{S+I_P+I_C+\theta_{\mathrm{AIDS}}I_A+f(I_P^N+I_C^N+\theta_{\mathrm{AIDS}}I_A^N+T_P+T_C+\theta_{\mathrm{AIDS}}T_A)}\\
&+(1-p^{\mathrm{cas}}_{\mathrm{disclose}})\frac{f(\hat{\beta}_P^{\mathrm{cas}\,|\,\mathrm{ave\,condom}}I_P^N+\hat{\beta}_C^{\mathrm{cas}\,|\,\mathrm{ave\,condom}}I_C^N+\hat{\beta}_A^{\mathrm{cas}\,|\,\mathrm{ave\,condom}}\theta_{\mathrm{AIDS}}I_A^N+\hat{\beta}_T^{\mathrm{cas}\,|\,\mathrm{ave\,condom}}(T_P+T_C+\theta_{\mathrm{AIDS}}T_A))}{S+I_P+I_C+\theta_{\mathrm{AIDS}}I_A+f(I_P^N+I_C^N+\theta_{\mathrm{AIDS}}I_A^N+T_P+T_C+\theta_{\mathrm{AIDS}}T_A)}\Bigg]
\end{aligned}$$

where the β parameters are each specified by the transmission probability per partnership per year as defined above and based on the various behavioural and biological parameters (including number of acts for each type of relationship, condom usage, and viral loads affecting the transmission probabilities).

References

1 NSW, VIC and QLD Gay Periodic Surveys. 1998–2006.
2 Richters J. *HIV/AIDS, Hepatitis C & Related Diseases in Australia: Annual Report of Behaviour* 2006, National Centre in HIV Social Research, University of New South Wales: Sydney.
3 Crawford JM, *et al*. Number of risk acts by relationship status and partner serostatus: Findings from the HIM cohort of homosexually active men in Sydney, Australia. *AIDS Behav* 2006; 10: 325–31. doi: 10.1007/s10461-005-9057-3
4 Grierson J, Thorpe R, Pitts M. *HIV Futures 5: Life as we know it, monograph series number 60*. 2006, The Australian Research Centre in Sex, Health and Society, Latrobe University, Melbourne, Australia.
5 Quinn TC, *et al*. Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai Project Study Group. *N Engl J Med* 2000; 342: 921–9. doi: 10.1056/NEJM200003303421303
6 *National Centre in HIV Social Research Annual Report of Trends in Behaviour*. 2006, University of New South Wales: Sydney.
7 Van de Ven P, *et al*. Undetectable viral load is associated with sexual risk taking in HIV serodiscordant gay couples in Sydney. *AIDS* 2005; 19: 179–84.
8 Marks G, *et al*. Meta-analysis of high-risk sexual behavior in persons aware and unaware they are infected with HIV in the United States: implications for HIV prevention programs. *J Acquir Immune Defic Syndr* 2005; 39: 446–53. doi: 10.1097/01.qai.0000151079.33935.79
9 Cleary PD, *et al*. Behavior changes after notification of HIV infection. *Am J Public Health* 1991; 81: 1586–90.
10 Colfax GN, *et al*. Sexual risk behaviors and implications for secondary HIV transmission during and after HIV seroconversion. *AIDS* 2002; 16: 1529–35. doi: 10.1097/00002030-200207260-00010
11 McCusker J, *et al*. Effects of HIV antibody test knowledge on subsequent sexual behaviors in a cohort of homosexually active men. *Am J Public Health* 1988; 78: 462–7.
12 Saah AJ, *et al*. Association of HLA profiles with early plasma viral load, CD4+ cell count and rate of progression to AIDS following acute HIV-1 infection. Multicenter AIDS Cohort Study. *AIDS* 1998; 12: 2107–13. doi: 10.1097/00002030-199816000-00005
13 Smith DK, *et al*. Design and baseline participant characteristics of the Human Immunodeficiency Virus Epidemiology Research (HER) Study: a prospective cohort study of human immunodeficiency virus infection in US women. *Am J Epidemiol* 1997; 146: 459–69.
14 Valleroy LA, *et al*. HIV prevalence and associated risks in young men who have sex with men. Young Men's Survey Study Group. *JAMA* 2000; 284: 198–204. doi: 10.1001/jama.284.2.198
15 Fogarty A , *et al.* The Health in Men and Positive Health cohorts: A comparison of trends in the health and sexual behaviour of HIV-negative and HIV-positive gay men, 2002–2005, National Centre in HIV Social Research Annual Report of Trends in Behaviour. 2006, University of New South Wales: Sydney.
16 Mao L, *et al*. "Serosorting" in casual anal sex of HIV-negative gay men is noteworthy and is increasing in Sydney, Australia. *AIDS* 2006; 20: 1204–6. doi: 10.1097/01.aids.0000226964.17966.75
17 Davis KR, Weller SC. The effectiveness of condoms in reducing heterosexual transmission of HIV. *Fam Plann Perspect* 1999; 31: 272–9. doi: 10.2307/2991537
18 Weller SC, Davis KR. Condom effectiveness in reducing heterosexual HIV transmission. *Cochrane Database Syst Rev* 2002; CD003255.
19 Pinkerton SD, Abtramson PR. Effectiveness of condoms in preventing HIV transmission. *Soc Sci Med* 1997; 44: 1303–12. doi: 10.1016/S0277-9536(96)00258-4
20 Weller SC. A meta-analysis of condom effectiveness in reducing sexually transmitted HIV. *Soc Sci Med* 1993; 36: 1635–44. doi: 10.1016/0277-9536(93)90352-5
21 Fitch TJ, *et al*. Condom Effectiveness: Factors that influence risk reduction. *Sex Transm Dis* 2002; 29: 811–7. doi: 10.1097/00007435-200212000-00013
22 Rangsin R, *et al*. The natural history of HIV-1 infection in young Thai men after seroconversion. *J Acquir Immune Defic Syndr* 2004; 36: 622–9. doi: 10.1097/00126334-200405010-00011
23 Richardson BA, *et al*. Comparison of Human Immunodeficiency Virus Type 1 Viral Loads in Kenyan Women, Men, and Infants during Primary and Early Infection. *J Virol* 2003; 77: 7120–3. doi: 10.1128/JVI.77.12.7120-7123.2003
24 Simon V, Ho DD, Abdool Karim Q, HIV/AIDS epidemiology, pathogenesis, prevention, and treatment. *Lancet* 2006; 368: 489–504. doi: 10.1016/S0140-6736(06)69157-5
25 Sarr AD, *et al*. Viral dynamics of primary HIV-1 infection in Senegal, West Africa. *J Infect Dis* 2005; 191: 1460–7. doi: 10.1086/429409
26 Rodriguez RJ, *et al*. Comparison of serum and plasma viral RNA measurements in primary and chronic human immunodeficiency virus type 1 infection. *J Acquir Immune Defic Syndr Hum Retrovirol* 1997; 15: 49–53.
27 Lavreys L, *et al. Viral load during primary HIV-1 infection in a cohort of female commercial sex workers in Mombasa, Kenya.* Int Conf AIDS, 2000. **13**: p. MoPeB2247.
28 Sabin CA, *et al*. Course of viral load throughout HIV-1 infection. *J Acquir Immune Defic Syndr* 2000; 23: 172–7.
29 Swindells S, *et al*. Predictive value of HIV-1 viral load on risk for opportunistic infection. *J Acquir Immune Defic Syndr* 2002; 30: 154–8.
30 Anekthananon T, *et al*. Safety and efficacy of a simplified fixed-dose combination of stavudine, lamivudine and nevirapine (GPO-VIR) for the treatment of advanced HIV-infected patients: a 24-week study. *J Med Assoc Thai* 2004; 87: 760–7.
31 Bonjoch A, *et al*. Long-term safety and efficacy of nevirapine-based approaches in HIV type 1-infected patients. *AIDS Res Hum Retroviruses* 2006; 22: 321–9. doi: 10.1089/aid.2006.22.321
32 Yozviak JL, Doerfler RE, Woodward WC. Effectiveness and tolerability of nevirapine, stavudine, and lamivudine in clinical practice. *HIV Clin Trials* 2001; 2: 474–6. doi: 10.1310/T0RR-TGY0-8QWB-8YT2
33 Blower S, *et al*. The antiretroviral rollout and drug-resistant HIV in Africa: insights from empirical data and theoretical models. *AIDS* 2005; 19: 1–14. doi: 10.1097/00002030-200501030-00001

34 Zhang H, *et al*. Human immunodeficiency virus type 1 in the semen of men receiving highly active antiretroviral therapy. *N Engl J Med* 1998; 339: 1803–9. doi: 10.1056/NEJM199812173392502
35 Vittinghoff E, *et al*. Per-contact risk of human immunodeficiency virus transmission between male sexual partners. *Am J Epidemiol* 1999; 150: 306–11.
36 DeGruttola V, *et al*. Infectiousness of HIV between male homosexual partners. *J Clin Epidemiol* 1989; 42: 849–56. doi: 10.1016/0895-4356(89)90098-X
37 Varghese B, *et al*. Reducing the risk of sexual HIV transmission: quantifying the per-act risk for HIV on the basis of choice of partner, sex act, and condom use. *Sex Transm Dis* 2002; 29: 38–43. doi: 10.1097/00007435-200201000-00007
38 Chesson HW, *et al*. HIV infections and associated costs attributable to syphilis coinfection among African Americans. *Am J Public Health* 2003; 93: 943–8.
39 Royce RA, *et al*. Sexual transmission of HIV. *N Engl J Med* 1997; 336: 1072–8. doi: 10.1056/NEJM199704103361507
40 Johnson AM, *et al*. Transmission of HIV to heterosexual partners of infected men and women. *AIDS* 1989; 3: 367–72. doi: 10.1097/00002030-198906000-00005
41 McCormick AW, *et al*. The effect of antiretroviral therapy on secondary transmission of HIV among men who have sex with men. *Clin Infect Dis* 2007; 44: 1115–22. doi: 10.1086/512816
42 Grulich AE, *et al*. Sexual behaviour and human herpesvirus 8 infection in homosexual men in Australia. *Sex Health* 2005; 2: 13–8. doi: 10.1071/SH04029
43 Jin F, *et al*. Epidemic syphilis among homosexually active men in Sydney. *Med J Aust* 2005; 183: 179–83.
44 Bautista CT, *et al*. Seroprevalence of and risk factors for HIV-1 infection among South American men who have sex with men. *Sex Transm Infect* 2004; 80: 498–504. doi: 10.1136/sti.2004.013094
45 Fleming DT, Wasserheit JN. From epidemiological synergy to public health policy and practice: the contribution of other sexually transmitted diseases to sexual transmission of HIV infection. *Sex Transm Infect* 1999; 75: 3–17.
46 Galvin SR, Cohen MS. The role of sexually transmitted diseases in HIV transmission. *Nat Rev Microbiol* 2004; 2: 33–42. doi: 10.1038/nrmicro794
47 Piot P, Laga M. Genital ulcers, other sexually transmitted diseases, and the sexual transmission of HIV. *BMJ* 1989; 298: 623–4.
48 Rottingen JA, Cameron DW, Garnett GP. A systematic review of the epidemiologic interactions between classic sexually transmitted diseases and HIV: how much really is known? *Sex Transm Dis* 2001; 28: 579–97. doi: 10.1097/00007435-200110000-00005
49 Simonsen JN, *et al*. Human immunodeficiency virus infection among men with sexually transmitted diseases. Experience from a center in Africa. *N Engl J Med* 1988; 319: 274–8.
50 Read TRH, *et al*. Rick factors for incident HIV infection in men having sex with men: a case-control study. *Sex Health* 2007; 4: 35–9. doi: 10.1071/SH06043
51 Crawford JM, *et al*. Number of risk acts by relationship status and partner serostatus: Findings from the HIM cohort of homosexually active men in Sydney, Australia. *AIDS Behav* 2006; 10: 325–31. doi: 10.1007/s10461-005-9057-3
52 Kaufmann GR, *et al*. Patterns of viral dynamics during primary human immunodeficiency virus type 1 infection. The Sydney Primary HIV Infection Study Group. *J Infect Dis* 1998; 178: 1812–5. doi: 10.1086/314480
53 Schacker TW, *et al*. Biological and Virologic Characteristics of Primary HIV Infection. *Ann Intern Med* 1998; 128: 613–20.
54 MAP Workshop. Extending public health surveillance of HIV infection: information from a five cohort workshop. (Multi-cohort Analysis Project). *Stat Med* 1993; 12: 2065–85. doi: 10.1002/sim.4780122203
55 MAP Workshop. Marker paths. (Multi-cohort Analysis Project). *Stat Med* 1993; 12: 2099–126. doi: 10.1002/sim.4780122205
56 Law MG, *et al*. Modelling the effect of combination antiretroviral treatments on HIV incidence. *AIDS* 2001; 15: 1287–94. doi: 10.1097/00002030-200107060-00011
57 Kilmarx PH, *et al*. Disease progression and survival with human immunodeficiency virus type 1 subtype E infection among female sex workers in Thailand. *J Infect Dis* 2000; 181: 1598–606. doi: 10.1086/315469
58 Glenday K, *et al. HIV antiretroviral treatment differences by state in Australia.* In Preparation, 2007.
59 Bonnet F, *et al*. Causes of death among HIV-infected patients in the era of highly active antiretroviral therapy, Bordeaux, France, 1998–1999. *HIV Med* 2002; 3: 195–9. doi: 10.1046/j.1468-1293.2002.00117.x
60 Keiser O, *et al*. All cause mortality in the Swiss HIV Cohort Study from 1990 to 2001 in comparison with the Swiss population. *AIDS* 2004; 18: 1835–43. doi: 10.1097/00002030-200409030-00013
61 Lewden C, *et al*. Factors associated with mortality in human immunodeficiency virus type 1-infected adults initiating protease inhibitor-containing therapy: role of education level and of early transaminase level elevation (APROCO-ANRS EP11 study). The Antiproteases Cohorte Agence Nationale de Recherches sur le SIDA EP 11 study. *J Infect Dis* 2002; 186: 710–4. doi: 10.1086/342047
62 Petoumenos K, Law MG. Risk factors and causes of death in the Australian HIV Observational Database. *Sex Health* 2006; 3: 103–12. doi: 10.1071/SH05045
63 Krentz HB, Kliewer G, Gill MJ. Changing mortality rates and causes of death for HIV-infected individuals living in Southern Alberta, Canada from 1984 to 2003. *HIV Med* 2005; 6: 99–106. doi: 10.1111/j.1468-1293.2005.00271.x
64 Luo K, *et al*. The role of initial AIDS-defining illness in survival following AIDS. *AIDS* 1995; 9: 57–64. doi: 10.1097/00002030-199501000-00008
65 Costello C, *et al*. HIV-1 subtype E progression among northern Thai couples: traditional and non-traditional predictors of survival. *Int J Epidemiol* 2005; 34: 577–84. doi: 10.1093/ije/dyi023
66 Li Y, *et al*. Improving survival following AIDS in Australia, 1991–1996. National HIV Surveillance Committee. *AIDS* 2000; 14: 2349–54. doi: 10.1097/00002030-200010200-00016
67 Wilson DP, Kahn J, Blower SM. Predicting the epidemiological impact of antiretroviral allocation strategies in KwaZulu-Natal: the effect of the urban-rural divide. *Proc Natl Acad Sci USA* 2006; 103: 14228–33. doi: 10.1073/pnas.0509689103
68 Barbour JD, *et al*. Higher CD4+ T cell counts associated with low viral pol replication capacity among treatment-naive adults in early HIV-1 infection. *J Infect Dis* 2004; 190: 251–6. doi: 10.1086/422036
69 Egger M, *et al*. Impact of new antiretroviral combination therapies in HIV infected patients in Switzerland: prospective multicentre study. Swiss HIV Cohort Study. *BMJ* 1997; 315: 1194–9.
70 Egger M, *et al*. Prognosis of HIV-1-infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospective studies. *Lancet* 2002; 360: 119–29. doi: 10.1016/S0140-6736(02)09411-4

71 Hogg RS, *et al*. Improved survival among HIV-infected individuals following initiation of antiretroviral therapy. *JAMA* 1998; 279: 450–4. doi: 10.1001/jama.279.6.450

72 Mocroft A, *et al*. Changing patterns of mortality across Europe in patients infected with HIV-1. EuroSIDA Study Group. *Lancet* 1998; 352: 1725–30. doi: 10.1016/S0140-6736(98)03201-2

73 Palella FJJr, *et al*. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. *N Engl J Med* 1998; 338: 853–60. doi: 10.1056/NEJM199803263381301