Mathematical models to investigate recent trends in HIV notifications among men who have sex with men in Australia

National Centre in
HIV Epidemiology and
Clinical Research

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THE UNIVERSITY OF NEW SOUTH WALES

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Contents

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Executive Summary

Background

In recent years there has been a noticeable increase in the number of HIV diagnoses in Australia, predominantly amongst men who have sex with men (MSM). Similar trends have also been observed in the USA, UK, The Netherlands, and other developed countries (1-6). This increasing trend in HIV notifications has been most pronounced in Victoria and Queensland, with little or no increase seen in New South Wales. We investigate the HIV epidemic amongst Australian MSM in an attempt to explain why the increase in HIV notifications has occurred, assess differences between Australian States and Territories, and to identify the most effective targets for potential public health intervention strategies.

Methods

We investigated the epidemic through statistical back-projection analyses and through the development and analysis of a mathematical transmission model. The transmission model uses a mechanistic framework to combine epidemiological, behavioural, biological, and clinical data, and assess how factors interact and together contribute to the HIV incidence in Australian MSM. The data include

- the average number of sexual partners (from the National Centre in HIV Social Research),
- testing rates, condom usage, and disclosure of known serostatus and subsequent risk behaviour (from the States' Gay Periodic Surveys),
- trends in treatment rates and effectiveness of treatment regimes (from the Australian HIV Observational Database),
- other biological and clinical data from the literature, such as rates of disease progression and death, and transmission probabilities based on viral loads for each disease stage.

In addition, based on published data we assumed a 2-5-fold increase in HIV transmission in the presence of another sexually transmitted infection.

Results

The transmission model suggests that the major factors that have contributed to increases in HIV notifications in MSM since 1999 were:

- Increased rates of unprotected anal intercourse (reduced rates of condom use) and
- Increased rates of other sexually transmissible infections (STIs).

The number of HIV notifications could have been significantly higher had it not been for increased effectiveness of antiretroviral treatment in decreasing HIV viral load in treated individuals. The model suggests that changes in numbers of sexual partners, disclosure of HIV status, HIV testing rates and rates of early antiretroviral treatment among MSM since 1999 have had a modest impact on HIV incidence.

An important finding from the transmission model is that the increased HIV notifications seen among MSM in Australia could only be reproduced with a large increase in a 'transmission-increasing factor' since 1999. We cannot directly infer that STIs are responsible for the trends, however, increasing other STIs is the only factor that makes sense biologically. That is, without such an increase in STIs the HIV notifications data cannot be accounted for purely by changes in unprotected anal intercourse, testing rates, or early treatment patterns. It therefore appears that **STIs have played an important role as cofactors in contributing to increased HIV incidence**. Differences in HIV notification trends among MSM between New South Wales, Victoria and Queensland could be reproduced by differences in increases in rates of STIs. In order to reproduce notifications data our transmission model predicts that there has to have been a:

- Very large increase in the prevalence of other STIs in VIC;
- Moderately large increase in the prevalence of other STIs in QLD;
- Relatively small increase in the prevalence of other STIs in NSW.

These model predictions are not inconsistent with differential State incidence data for other STIs.

STATISTICAL BACK-PROJECTION ANALYSES

Statistical back-projection analyses confirmed that the different trends in HIV notifications among MSM seen in New South Wales, Victoria and Queensland appeared to reflect divergent trends in underlying HIV incidence in these three States. These analyses estimated that to the end of 2006 a total of 19,500 men have been infected with HIV through male homosexual sex, of whom 13% were estimated to have not been diagnosed with their HIV infection.

DISPROPORTIONATE TRANSMISSION

The transmission model estimated that HIV prevalence among MSM in Australia at the end of 2006 is 10.5%. Of all new HIV infections, the model estimated that

- 19% were transmitted from the estimated 3% of MSM who were close to their own HIV-seroconversion during primary HIV infection.
- 31% of new HIV infections were estimated to be transmitted from the 9-13% of MSM with undiagnosed HIV.

EPIDEMIC PROJECTIONS

The transmission model was used to project trends in HIV notifications to 2015. Assuming all parameters remained at their 2006 values, the model predicts

- a decrease in New South Wales from 303 HIV notifications in 2006 to ~266 in 2015,
- an increase in Victoria from 234 HIV notifications in 2006 to ~406 in 2015,
- an increase in Queensland from 122 HIV notifications in 2006 to ~146 in 2015.

Various interventions could change these epidemic trajectories. Projections of HIV notifications to 2015 were most sensitive to changes in assumptions regarding rates of STIs and rates of condom use. Projections also suggested that increasing HIV testing and antiretroviral treatment during primary HIV infection would have some effect, albeit more modest, on decreasing future HIV incidence.

Interpretation and implications

DIRECT AND INDIRECT EFFECTS OF REDUCED CONDOM USAGE

Reduction in condom usage increases the risk of HIV transmission in serodiscordant sexual relationships and can therefore be expected to result directly in increased HIV notifications. However, reduced condom usage will also lead to an increase in the transmission of other STIs, and consequently to an increase in the prevalence of STIs in the MSM population. STIs are known to increase the risk of HIV transmission and therefore reduced condom usage can also be expected to indirectly result in increased HIV notifications through the increased prevalence of other STIs. Because the association between condom use and the increase in other STIs is decoupled in our modelling analyses, we cannot ascribe with any certainty the relative independent contributions of increased unprotected anal intercourse and STIs on HIV incidence. However, these analyses strongly suggest that decreased condom usage has had significant but modest direct effects on HIV incidence and it is likely that the indirect effects, through increases in other STIs, have been considerably more substantial.

CONCLUSIONS

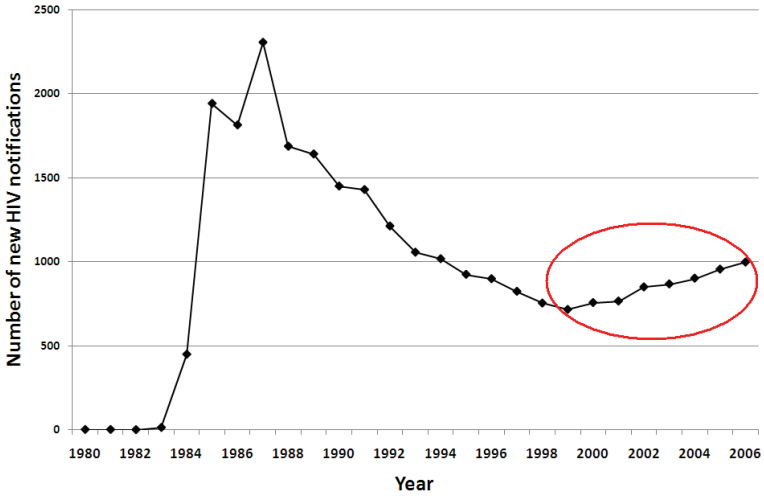
This suggests that promoting condom use and targeting other STIs are the most effective interventions for interrupting HIV in MSM. Increasing testing rates and treatment in primary infection are also important for reducing transmission. This study also highlights gaps in data. Given the significance of other STIs as an outcome from this work, the implementation of broader STI surveillance systems are required as well as strategies for STI testing and treatment. Improved modelling of HIV transmission in MSM requires expanding data sources in all Australian States and Territories, principally regarding detailed sexual behaviour and better surveillance of STIs.

Chapter 1: Summary of epidemiology, behaviour, and treatment

1.1 HIV notifications

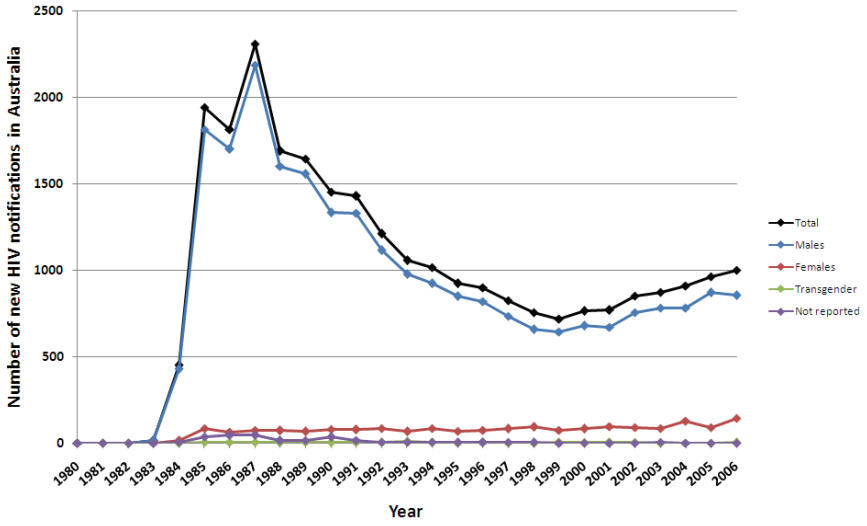
The total number of HIV notifications in Australia peaked in 1988, and gradually declined to a low of 720 new HIV diagnoses in 1999 (Figure 1.1). Since 1999, total new HIV notifications have steadily increased in Australia, to almost 1,000 new diagnoses in 2006.

Figure 1.1: The total number of new notifications across Australia by year, since 1980. The data since 1999 is circled.



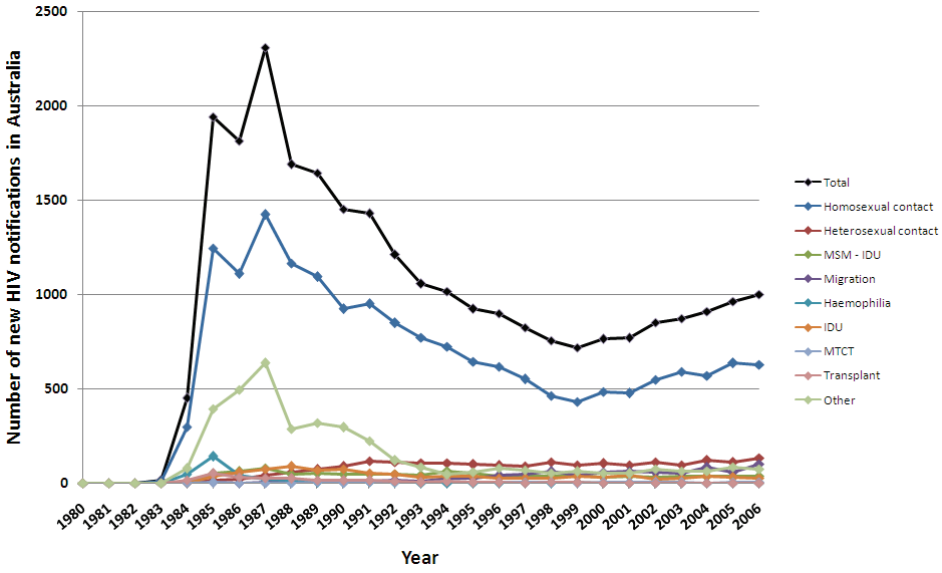
The overwhelming majority of new HIV notifications in Australia have been in men rather than women (Figure 1. 2). There is evidence of a strong increasing trend in HIV notifications in men since 1999, with no statistically significant increase in women. Furthermore, the increasing slope in men seems parallel to the slope in total HIV notifications.

Figure 1.2: The total number of new notifications across Australia by year, since 1980, according to gender: all notifications (black), notifications in males (blue), females (red), transgender (green), not reported (purple).



The majority of new HIV notifications in Australia have been reported to have been transmitted through male homosexual contact (Figure 1.3). Male homosexual contact is the only exposure route that has a significantly increasing trend in HIV notifications since 1999, although there was some evidence of increasing HIV notifications ascribed to other or unknown transmission routes. The increasing trend in HIV diagnoses through male homosexual contact again appears to mirror the increasing trend seen in total HIV notifications.

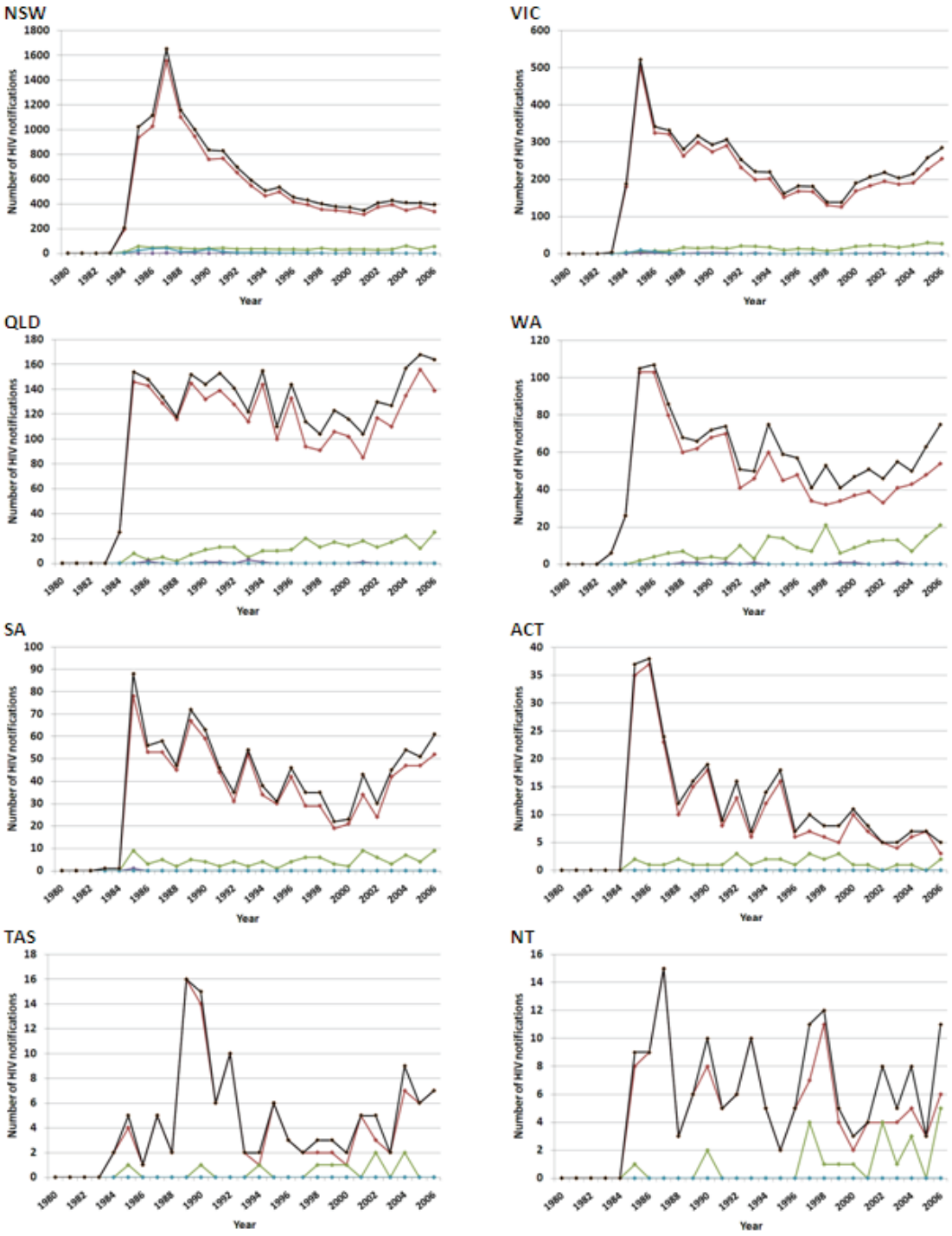
Figure 1.3: The total number of new notifications across Australia by year, since 1980, according to reported route of exposure: all notifications (black), male homosexual contact (brown), heterosexual contact (green), homosexual contact and injecting drug use (orange), migration from high-prevalence country (blue), haemophilia (red), injecting drug use (purple), mother-to-child transmission (light blue), transplant (light green), and undetermined (pink).



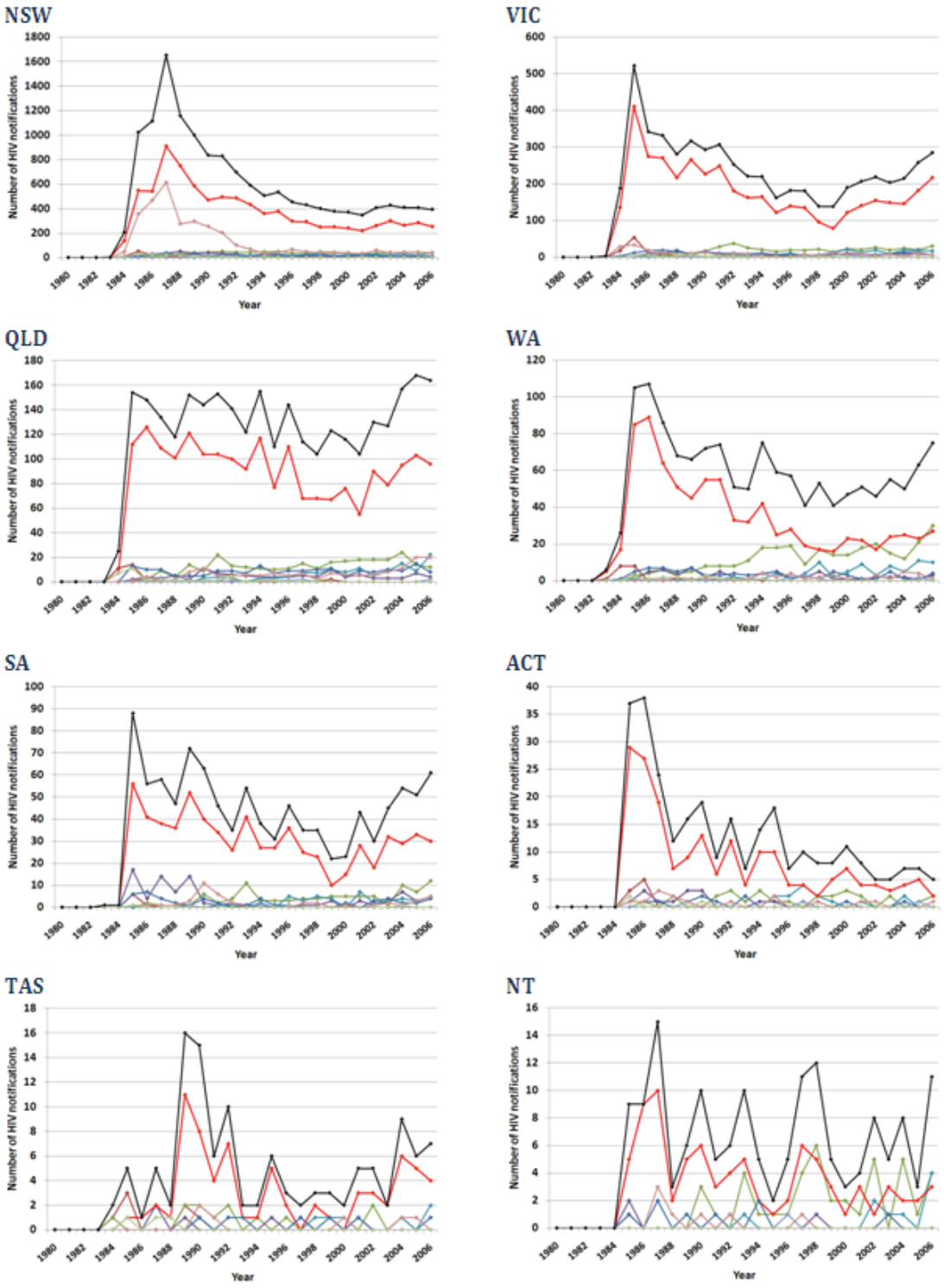
HIV notifications are presented by sex and exposure category and by State in Figure 1.4. Across all States and Territories, similar to national patterns, the majority of HIV notifications are in men, and ascribed to male homosexual contact.

Figure 1.4: The number of new notifications across Australia and by each State/Territory by year, since 1980, according to (a) gender (total: black; males: red; females: green; transgender: purple; not reported: blue), (b) exposure (total: black; male homosexual contact: red; migration: indigo; heterosexual contact: dark green ; MSM – IDU: blue; IDU: purple; transplant: light green; haemophilia: dark red ; other: pink).

(a)

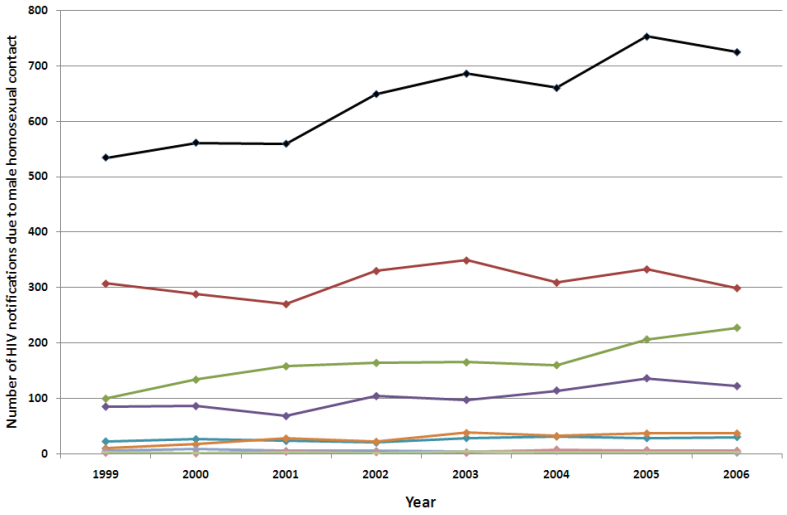


(b)



Patterns in HIV notifications differ across States and Territories in one important respect. The increasing trend is apparent predominantly in Victoria and then Queensland, South Australia and Western Australia. But the total number of notifications is broadly stable since 1999 in New South Wales, Australian Capital Territory, Tasmania, and the Northern Territory (Figure 1.4). This trend is further confirmed if analyses are limited to HIV notifications ascribed to male homosexual contact (Figure 1.5); in the three largest Australian States: HIV notifications are generally flat in NSW, and increasing trends seen in Victoria and Queensland.

Figure 1.5: The number of new notifications due to male homosexual contact across Australia by each State from 1999-2005 (Total: black; NSW: red; VIC: green; QLD: purple; SA: orange; WA: indigo; ACT: light blue; TAS: pink; NT: light green).



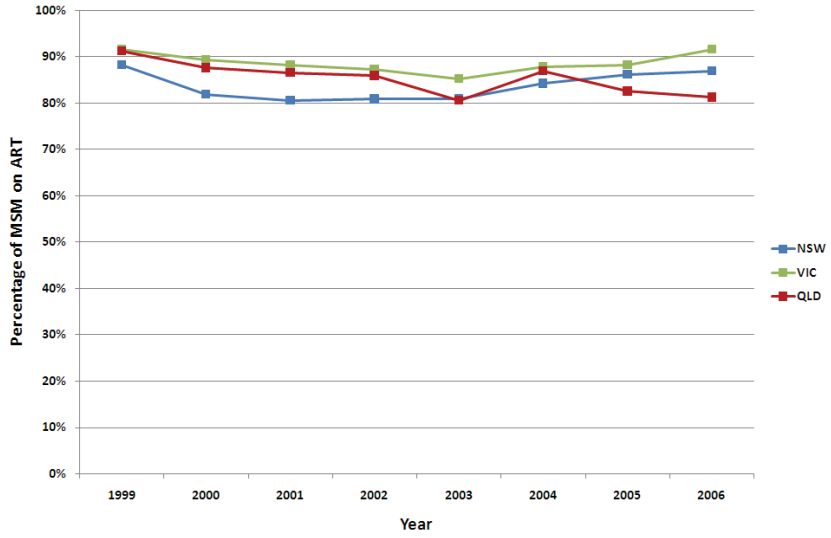
1.2 Behaviour and treatment

Over the same time period that these trends in HIV notifications in homosexual men have been observed, other important changes in HIV treatment and behavioural data have been seen.

ANTIRETROVIRAL TREATMENT

Very effective combination antiretroviral treatment for HIV first became widely available in Australia during 1996, and was rapidly and widely taken up among HIV-infected patients (7). This treatment was accompanied with a rapid improvement in morbidity and mortality, but by decreasing HIV viral load in treated individuals, could also have reduced infectiousness of those individuals and served to reduce HIV transmission. Data from the Australian HIV Observational Database show that up to 90% of HIV-infected homosexual men in that study were receiving antiretroviral treatment, with little difference between NSW, Victoria and Queensland (Figure 1.6).

Figure 1.6: Proportion of MSM patients under follow up in AHOD on ART, by year and state.

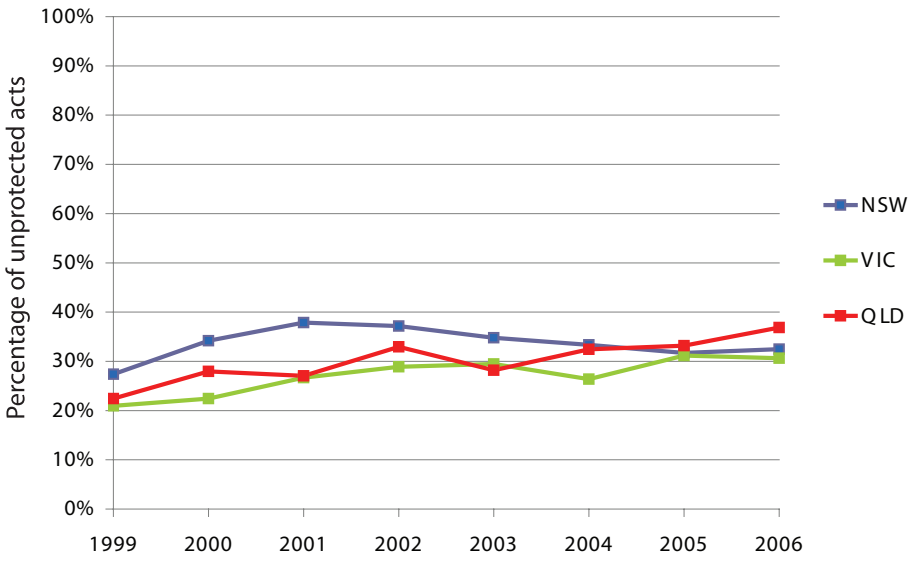


Data from the HIV Futures Surveys and the Gay Periodic Surveys show lower rates of antiretroviral treatment in HIV-infected homosexual men, with rates around 70-80%, but confirm that there is little difference between NSW, Victoria and Queensland in terms of treatment rates (8).

SEXUAL BEHAVIOUR

A key marker of sexual behaviour in homosexual men is the rate of unprotected anal intercourse with casual partners (UAIC) (9, 10). Data on UAIC reported in the NSW, Victoria and Queensland Periodic Surveys (Figure 1.7) indicate UAIC increased in all three States between 1998 and 2001, but since 2001 there has been a reported plateau of UAIC in NSW, with continuing increases in Victoria and Queensland.

Figure 1.7: Proportion of anal intercourse acts with casual partners that are unprotected (Gay Periodic Surveys)

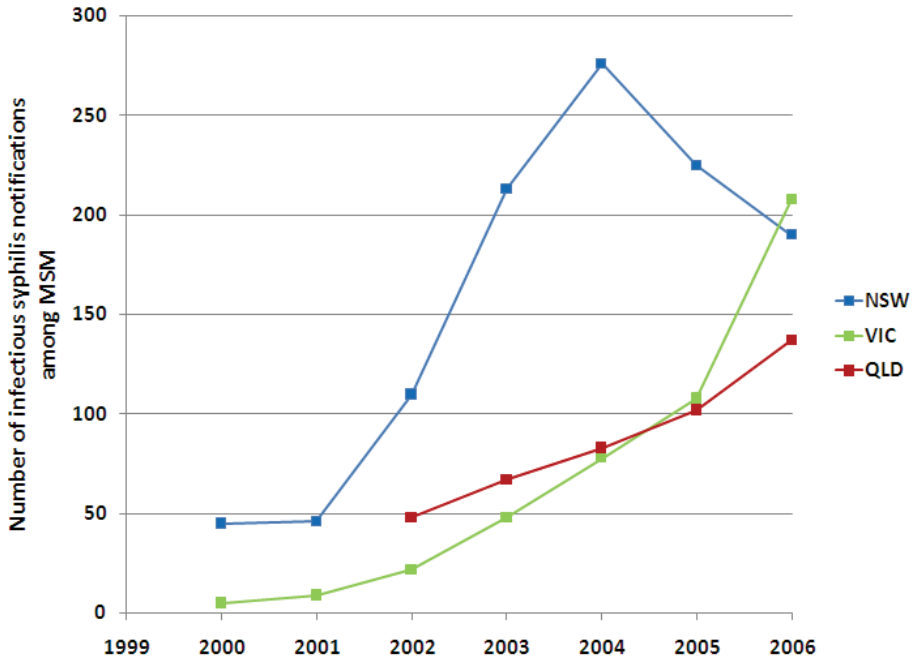


The effect of these differing trends in UAIC is difficult to judge as they have been accompanied by increased rates of serosorting, whereby homosexual men engage in UAIC only with men they believe to be the same HIV-status as themselves (11, 12). Furthermore, data also suggest HIV-negative men tend to engage in insertive rather than receptive UAIC, which is known to carry a lower risk of HIV-transmission. There has also been little difference between the three largest Australian States in rates of unprotected anal Intercourse with regular partners (UAIR).

RATES OF SEXUALLY TRANSMISSIBLE INFECTIONS

Rates of sexually transmissible infections (STIs) are interesting to monitor in two respects. First, since they are transmitted sexually, they act as an indirect measure of the use of condoms. Second, STIs are known to act as a co-factor, increasing the risk of sexual transmission of HIV (13-18). National notifications of STIs in Australia have seen increases in rates of syphilis in men between 2000 and 2006 (Figure 1.8). Increases in rates of gonorrhoea and Chlamydia in men were also observed (19). Direct data on rates of STIs in homosexual men are not available, but reported rates of anal gonorrhoea also increased in NSW, Victoria and Queensland.

Figure 1.8: Infectious syphilis in men by year and State



1.3 Summary and objectives

HIV notifications have increased in Australia since 1999, with substantial increases observed in Victoria and Queensland but not in New South Wales. The majority of HIV notifications remain among homosexual men. These increases in HIV notifications have been accompanied by widespread effective antiretroviral treatment, increasing rates of UAIC in homosexual men, and increasing rates of STIs.

The purpose of this report is to use mathematical transmission modelling and statistical back-projection modelling to assess the extent to which observed increases in HIV notifications reflect increases in underlying HIV incidence. Analyses will be limited to male homosexual contact (including male homosexuals who also report injecting drug use, and men who report unknown HIV exposure routes) since this remains the large majority of the HIV epidemic in Australia, and also largely captures the changing trends in HIV notifications. The focus will also be limited to the three largest States of NSW, Victoria, and Queensland, the States that form the majority of the HIV epidemic in Australia, and also for which the most comprehensive supporting data are available.

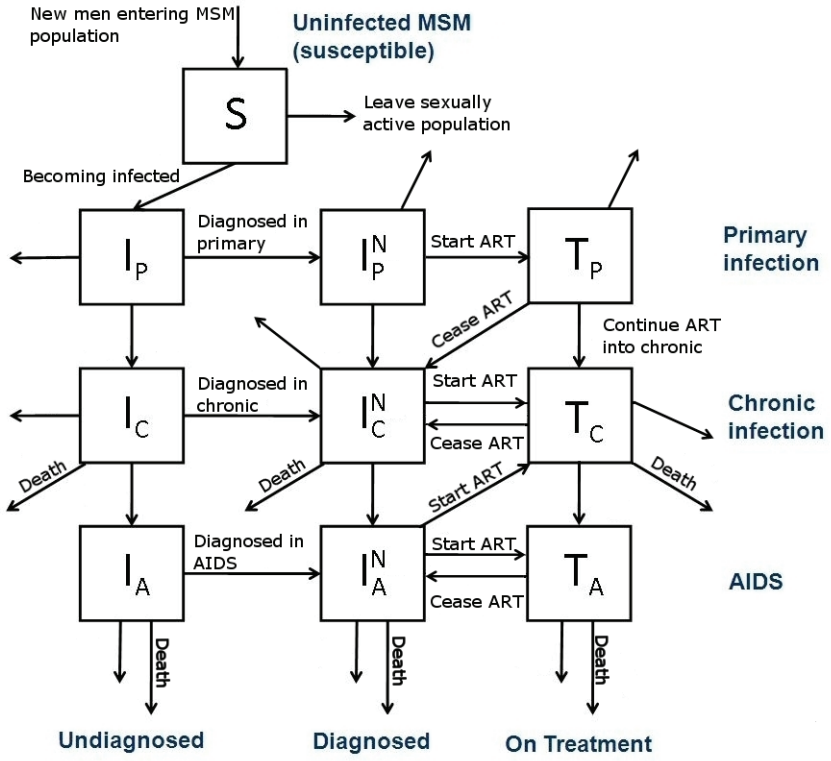
A transmission model will be used to explore and attempt to explain the difference between these States, and assess the role of antiretroviral treatment, sexual behaviour, STIs and other factors such as primary HIV infection and rates of HIV diagnosis. It will also be used to make projections over the next ten years of the number of new HIV infections according to various scenarios. The back-projection model will be used as an independent statistical analysis to assess whether the observed increases in HIV notifications truly reflect increases in underlying HIV incidence.

Chapter 2: Brief description of the transmission model and key parameters

A mathematical model was developed to simulate HIV transmission in the male homosexual population in Australia and was used to assist in identifying the major contributing factors in the number of reported new HIV diagnoses. A detailed description of the model is given in the Appendix including a complete listing of the parameters and explanation of their estimated values. The following is a brief description of the model and key parameters, in particular those that were identified in sensitivity analyses as being the most important contributors to HIV incidence.

The model is population-based, that is it does not track individuals but rather the flow of the population between the various disease compartments or "states" as illustrated in Figure 2.1. Males enter the MSM population in the susceptible (S) state and then may become infected (I). Diagnosed infection (corresponding to HIV notifications) is denoted by a superscript 'N' (e.g., I^N) and the stage of infection is denoted by subscripts 'P' for primary, 'C' for chronic and 'A' for AIDS. Diagnosis, progression from primary to chronic infection and AIDS, and uptake of treatment (denoted by 'T') occur at defined rates (see Appendix Table A.1). The model was calibrated such that total diagnoses matched 1999 notifications at the steady state (see Appendix). Viral loads were assumed to be a function of the stage of infection (higher in primary infection and AIDS than in chronic infection) and treatment (higher for untreated than for treated). The probability of HIV transmission was in turn a function of the viral load (i.e., the higher the viral load the higher the probability of transmission). Partnerships were defined as either regular or casual and within these partnerships the frequency of sexual acts (anal intercourse), level of condom usage and disclosure of serostatus was considered. The impact of other STIs, effectiveness of treatment (proportion of those on treatment with undetectable viral load), AIDS-related death and exit from the sexually active population were accommodated in the model.

Figure 2.1: Schematic diagram of our HIV compartmental model for MSM in Australia. The transition from one compartment to another is of a probabilistic nature based on rates defined in Table A.1 and methods (in Appendix). Individuals represented in the model do not necessarily transition between all compartments. It is thus important to note that the majority of the MSM population will remain in the uninfected (susceptible) compartment because the overall probability of transmission is low.



2.1 Key baseline parameters

The following is a brief description of the parameters that were most important in determining HIV incidence at the 1999 baseline level (see Appendix: Uncertainty and Sensitivity Analyses and Fig. A.3).

Change in behaviour post-diagnosis (f in Table A.1): refers to the change in the number of sexual partnerships formed by men once they have been diagnosed with HIV. It is assumed that the rate of partnership formation changes by a factor of between 0.4 and 1.1 (20-28).

Rate of progression from untreated primary to chronic infection (ω_p): refers to the rate at which, on average, an untreated individual progresses from the primary to the chronic stage of infection. The average time an individual spends in the primary infection state (1/ ω_p in Table A.1) is assumed to range between 3 and 9 months (29-31).

Viral load: refers to the average number of virus particles (copies) per ml of blood for HIV-infected individuals. In primary infection (V_{PI} in Table A.1) this is taken to range between $10^{6.5}$ and 10^8 copies/ml (30, 32-35), in chronic infection (W in Table A.1) this ranges between 10^4 and 10^5 copies/ml (30, 32-34, 36), and in the AIDS stage (V_A in Table A.1) of infection is assumed to range between $10^{5.5}$ and $10^{6.5}$ copies/ml (32, 37, 38).

Rate of progression from chronic infection to AIDS (τ_c in Table A.1): refers to the rate at which, on average, a treated individual in the chronic stage of infection will progress to AIDS. The average time an individual remains in the treated chronic infection stage (1/ τ_c in Table A.1) is assumed to range between the rate for untreated individuals (1/ ω_c; (34, 37, 39-42)) and 20 years.

Condom usage in sero-discordant regular partnerships ($p^{\text{reg}}_{\text{condom}}$ in Table A.1, footnote *c*): refers to the proportion of acts in regular partnerships in which condoms are used. We assume condoms are used in 75-85% of anal intercourse acts between discordant MSM (9, 11).

2.2 Key time-dependent parameters

The following is a brief description of parameters that the model has identified as being important in contributing to the observed increases in HIV notifications since 1999 or mitigating against them (see Section 3.5 Sensitivity Analyses and Tables 3.2 & 3.3).

Prevalence of other STIs (P_{STI} in Table A.1): refers to the proportion of HIV-negative MSM having other STIs and is assumed to range between 5% and 15% (15, 43). Increases in the prevalence of other STIs contribute to increases in HIV notifications.

Condom usage (p_{condom} in Table A.1): refers to the proportion of sexual acts in which condoms are used and depends on both the nature of the partnership and whether serostatus is disclosed (9, 11). Decreases in condom usage (i.e. increases in unprotected anal intercourse) in sero-discordant sexual partnerships contribute to increases in HIV notifications.

Treatment rate for primary infection (p_p in Table A.1): refers to the proportion of MSM diagnosed in the primary infection stage that will commence treatment. Decreases in this proportion contribute to increases in HIV notifications.

Rate of testing amongst MSM (p_{test} in Table A.1): refers to the proportion of MSM that were tested for HIV in the previous 12 months (9). Increases in testing rates tend to mitigate against increases in HIV incidence.

Effectiveness of ART (p_s in Table A.1): refers to the proportion of MSM on treatment that have undetectable viral load (20, 44-46). Increases in the effectiveness of ART mitigate against increases in HIV notifications.

Number of sexual partners (*c* in Table A.1): refers to the average number of sexual partnerships per year for MSM who have not been diagnosed with HIV (21, 46, 47). Decreases in the average number of sexual partnerships mitigate against increases in HIV notifications.

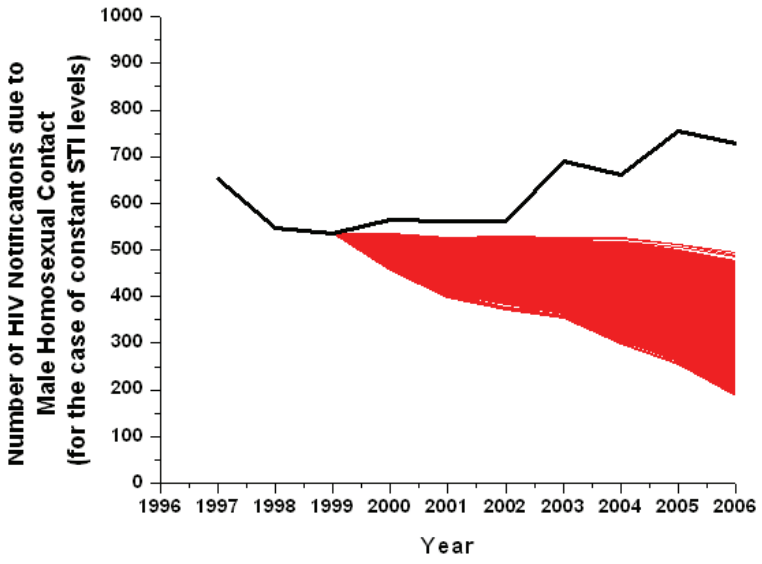
Disclosure of serostatus (p_{disclose} in Table A.1): refers to the proportion of sexual partnerships in which serostatus is disclosed in negotiating condom use. Increases in disclosure mitigate against increases in HIV notifications.

Chapter 3: Trends in HIV incidence – possible reasons for increased National notifications

3.1 Uncertainty analysis based on reported data

Due to the heterogeneity and uncertainty in some parameter estimates we defined a uniform probability density function over a range of values for each parameter in the model (see Table A.1). Latin Hypercube sampling was employed to sample the parameter space, generating 10,000 parameter sets. The parameter for the rate of diagnosis of MSM in primary infection, γ_P, was used to calibrate the transmission model to the data for the number of HIV notifications in 1999 (Monte Carlo filtering removed parameter sets that did not provide a valid solution; see Appendix) when there is a local minimum in the data. For our modelling we impose a stricter condition by setting initial conditions for our model system at 1999 to be at steady state equilibrium for the numbers of men in each compartment. Then, we simulated the HIV epidemic in the Australian homosexual population using the time-dependent data (and variability in all other constant parameters; see Table A.1) as input parameters for our model. The resultant simulated number of HIV notifications in this population due to the full variability placed on the input parameter values is shown in Figure 3.1. Clearly there is large variability in the simulated outcome. This is not surprising given the nature of the time-dependent data in Table A.1. Furthermore, the data available does not explain the extent of increase in notifications. Indeed, these simulations result in a decrease in notifications (Fig. 3.1). However, other factors (such as increases in other STIs have not been factored into these simulations; see below). Data reporting changes over time in some parameters suggest that the HIV incidence would decrease whereas changes in other parameters contribute to increased HIV incidence. Factors contributing to a decrease in notifications include an increase in the level of disclosing serostatus (assuming MSM diagnosed with HIV truthfully indicate their serostatus and that testing rates are adequate), slight decreases in the number of casual partners, increase in the effectiveness of treatment (as measured by the percentage of men on ART with undetectable viral load). Factors contributing to an increase in notifications include an increase in unprotected anal intercourse, decrease in commencement of early treatment, and slight increases in HIV testing.

Figure 3.1: The number of HIV notifications in MSM in Australia since 1999: black curve (surveillance data), red curves (all simulated time courses from our uncertainty analysis)



3.2 Changes contributing to decreased notifications

THE INFLUENCE OF SEROSORTING AND DISCLOSING SEROSTATUS

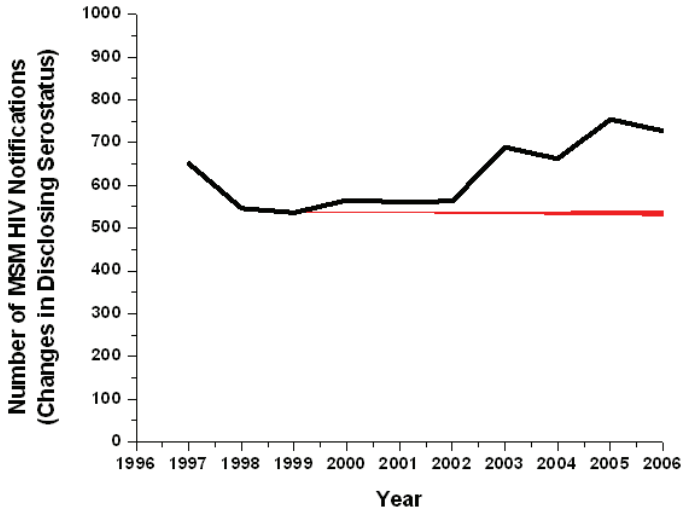
Serosorting refers to the practice of seeking sex with partners of the same HIV serostatus, usually in order to negotiate unprotected anal sex with that partner. Among men believed to be in HIV-negative seroconcordant relationships there is a presumed lower risk of HIV transmission; or in the case of HIV-infected men serosorting for seroconcordant HIV positive men, no risk of HIV transmission. Most partnerships are formed regardless of HIV serology but then serostatus is disclosed within some partnerships (serostatus is disclosed in the majority of regular partnerships and in a certain proportion of casual partnerships; Table A.1) and condom usage is negotiated based on serological disclosure. Based on our model and assumptions of protection for different types of relationships and disclosure, we estimated the average incidence probability of HIV transmission per partner (per year) if serostatus is or is not disclosed. To determine the influence of serological disclosure we compared these probabilities at the dynamic equilibrium levels (initial conditions) for our system over all parameter sets (see Table 3.1). We found that in 77% of our simulations disclosing serostatus in regular relationships, given the average likely behaviour in such relationships (Table A.1), would actually result in a greater chance of acquiring HIV than not disclosing serostatus (see Table 3.1). In contrast, in casual partnerships we found that in only 34% of our simulations disclosing serostatus would result in greater HIV acquisition rates than not disclosing. The differences lie in the levels of condom usage given the assumed concordance or discordance and the type of relationship (reflecting that there is more trust in a regular partner and less likelihood of condom use). The extent of the risk associated with negotiating condom usage based on disclosure is highly dependent on the rates of diagnoses of new infections (that is, the testing rate). Although MSM are likely to have many more casual partners than regular partners (Table A.1) we found that there is considerably greater risk of acquiring HIV infection from regular partners than from casual partners (Table 3.1). Disclosure

within these partnerships could have complex effects on risk. To quantify how much serological disclosure offsets changes due to other behavioural changes, we simulated the HIV epidemic in the Australian homosexual population using the time-dependent data for disclosure only and kept every other parameter as constant over time, at the 1999 level. The resultant simulated number of HIV notifications due to changes in serological disclosure is shown in Figure 3.2. It appears that changes in serological disclosure contribute negligibly to the HIV incidence.

Table 3.1: The probability of HIV transmission per casual partnership and per regular partnership per year if serological status is or is not disclosed

Probability of HIV transmission (median, Q1-Q3)		
	Disclose serostatus	**Do not disclose serostatus**
Per regular partner per year	0.00977 (0.00900-0.01066)	0.00885 (0.00808-0.00970)
Per casual partnership	0.00013 (0.00010-0.00016)	0.00014 (0.00012-0.00017)

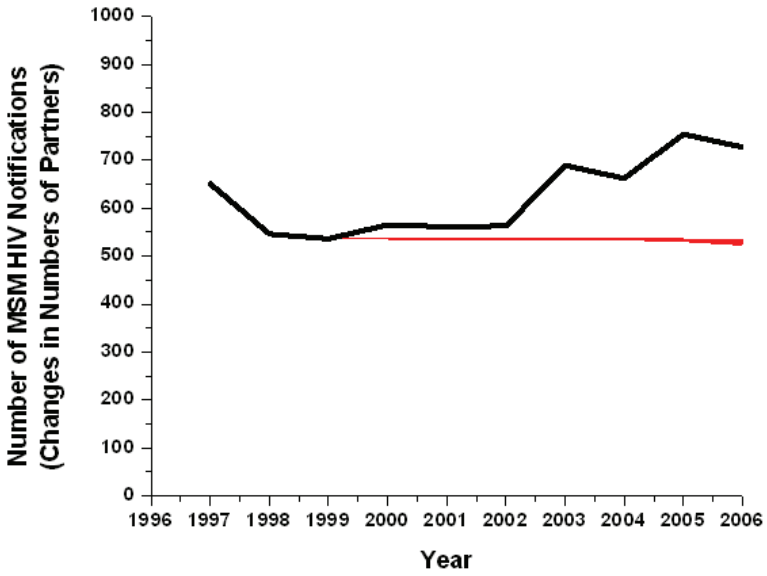
Figure 3.2: The number of HIV notifications in MSM in Australia since 1999: black curve (surveillance data), red curves (simulated time courses from our uncertainty analysis by keeping all parameters independent of time except for serological disclosure)



THE INFLUENCE OF CHANGES IN THE NUMBER OF SEXUAL PARTNERS

There is some data to suggest that the average number of sexual partners of men in the Australian homosexual population has changed slightly over time (overall a slight decrease; Table A.1). Generally, the number of sexual partners is one of the strongest attributors of risk of HIV acquisition. Therefore, we quantified how much this behaviour change would have influenced the number of HIV notifications by simulating the HIV epidemic in the Australian homosexual population using the time-dependent data for the number of sexual partners only and kept every other parameter as constant over time (but variable across simulations based on the uncertainty outlined in Table A.1). The resultant simulated number of HIV notifications due to changes in numbers of partners is shown in Figure 3.3. Because the change in number of partners has not been large, it has had negligible influence on the number of HIV infections.

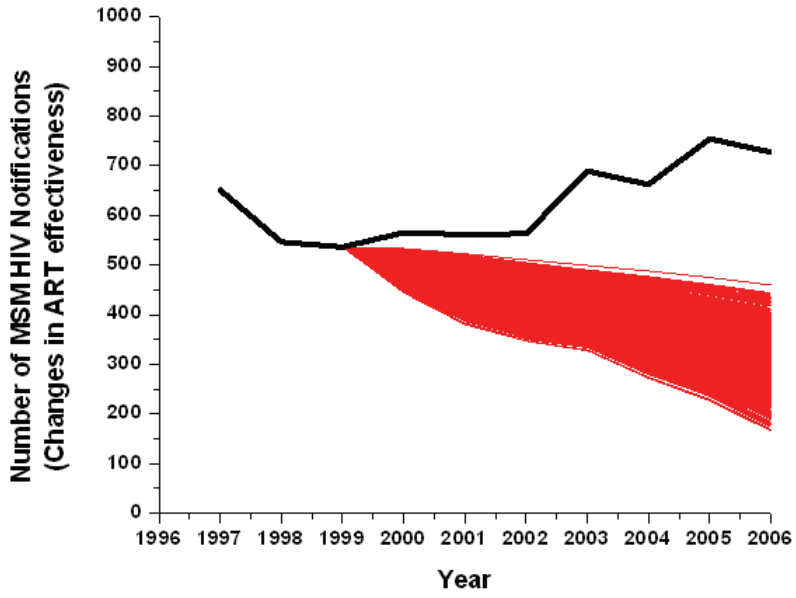
Figure 3.3: The number of HIV notifications in MSM in Australia since 1999: black curve (surveillance data), red curves (simulated time courses from our uncertainty analysis by keeping all parameters independent of time except for the number of sexual partners)



THE INFLUENCE OF THE EFFECTIVENESS OF ART

Clinical surveillance data has indicated a marked increase in the proportion of patients treated with combination antiretroviral therapy (ART) that have undetectable viral loads (Table A.1). That is, treatment has become more effective. This could be due to more effective antiretroviral drugs, better management of treatment, or behavioural attributes such as better adherence to the prescribed treatment schedule. The simulated number of HIV notifications due to changes in the effectiveness of ART is shown in Figure 3.4. Clearly, the increased effectiveness of ART amongst treated patients greatly decreases HIV incidence, even more than the effect of serological disclosure (compare Fig. 3.2). Consequently, if the effectiveness of ART remained at its 1999 levels the number of HIV infections would likely have been substantially greater than what was observed.

Figure 3.4: The number of HIV notifications in MSM in Australia since 1999: black curve (surveillance data), red curves (simulated time courses from our uncertainty analysis by keeping all parameters independent of time except for the proportion of patients on ART who achieve viral suppression)

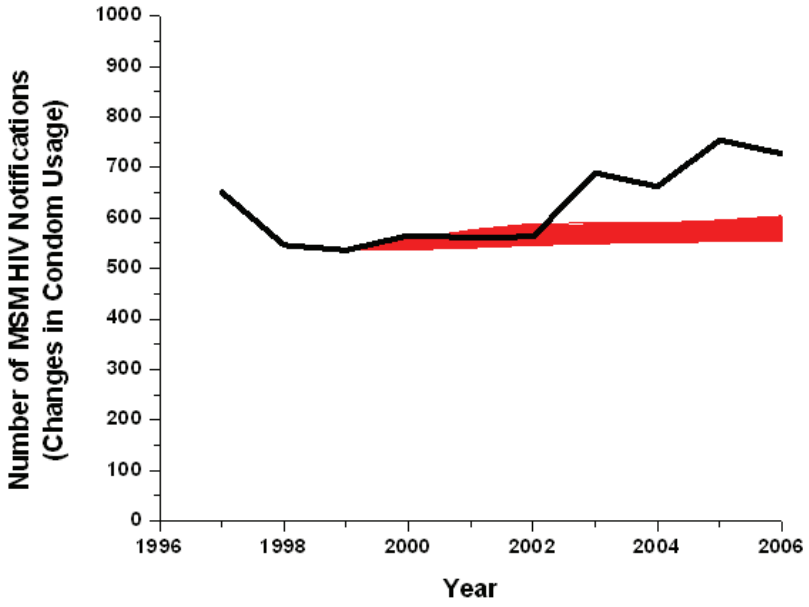


3.3 Changes contributing to increased notifications

THE INFLUENCE OF CHANGES IN CONDOM USAGE

Although there are differences between Australian States in the reported usage of condoms, overall the trend in the data is towards an increase in levels of unprotected anal intercourse (9) (Table A.1). The simulated number of HIV notifications due to changes in unprotected anal intercourse is shown in Figure 3.5. Risky sex, by decreasing the use of condoms, contributes towards the observed number of HIV notifications. However, it is not adequate to explain the entire increase in HIV incidence.

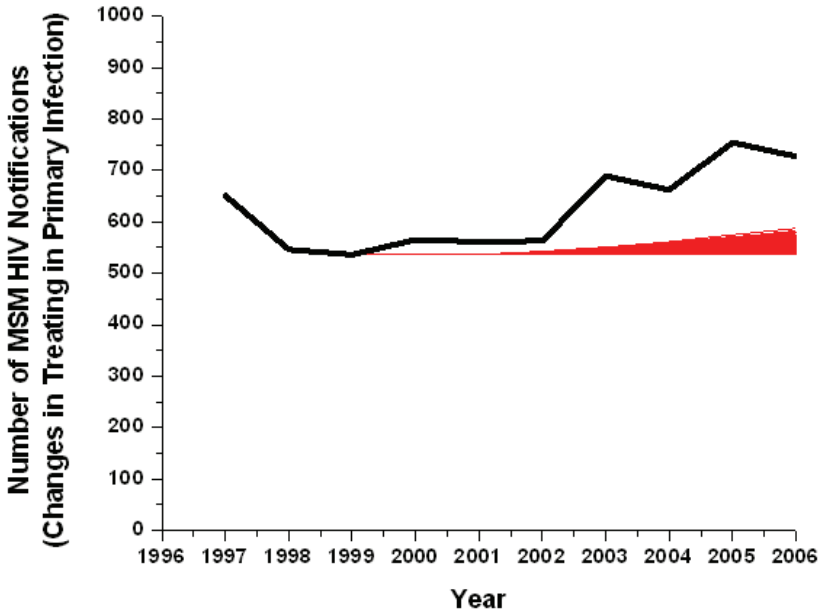
Figure 3.5: The number of HIV notifications in MSM in Australia since 1999: black curve (surveillance data), red curves (simulated time courses from our uncertainty analysis by keeping all parameters independent of time except for the change in unprotected anal intercourse).



THE INFLUENCE OF PATTERNS IN EARLY TREATMENT

During the late 1990s the changing trend in clinical settings for treating HIV was to hit the disease hard and hit it early. Consequently, clinicians in Australia tended to highly recommend that newly HIV-infected patients commence ART. Within a few years the trend shied away from such an aggressive approach to early treatment, although it has still been pursued. Recently, especially since the SMART study results (48-52), treatment trends have changed. For the time of our simulations, the proportion of patients diagnosed with HIV infection in primary infection to commence ART remained steady for a few years before decreasing steadily (see Table A.1). Decreasing treatment of HIV-infected individuals who have the highest viral load levels could potentially lead to substantial increases in HIV transmission. However, our simulations reveal that significant change in early treatment patterns has had a modest but not substantial effect on HIV notifications (Figure 3.6).

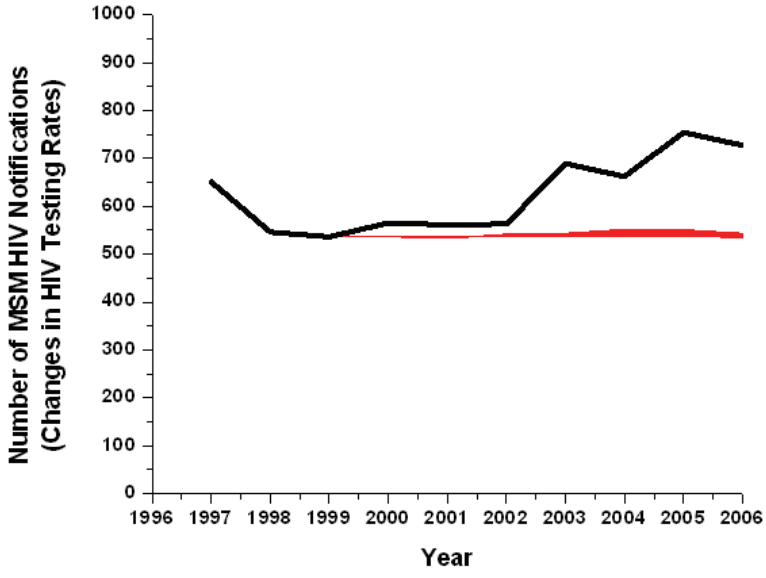
Figure 3.6: The number of HIV notifications in MSM in Australia since 1999: black curve (surveillance data), red curves (simulated time courses from our uncertainty analysis by keeping all parameters independent of time except for changes in treatment patterns for patients in primary infection)



THE INFLUENCE OF TESTING PATTERNS

There have been slight increases in the rate of testing for HIV. Increases in testing could account for greater numbers of diagnoses purely by detecting otherwise undiagnosed seroconverters. Our simulations reveal that increased testing for HIV has had a small effect on the number of HIV notifications (Figure 3.7).

Figure 3.7: The number of HIV notifications in MSM in Australia since 1999: black curve (surveillance data), red curves (simulated time courses from our uncertainty analysis by keeping all parameters independent of time except for changes in rates of testing for HIV)



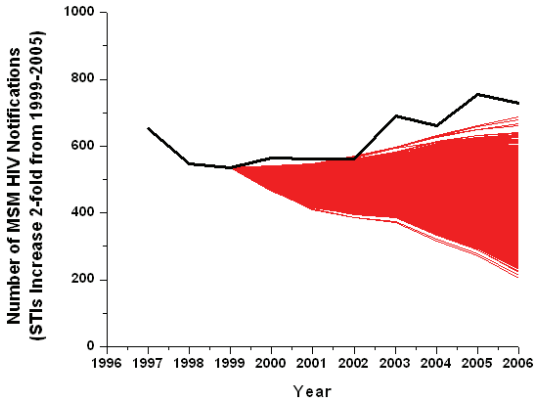
3.4 The balance between contrasting factors and the influence of other STIs

Some factors have contributed to decreasing the number of notifications (most notably, increases in serosorting and increased effectiveness of ART). However, this has been offset significantly by decreased condom usage. The overall outcome has been a rise in the number of HIV notifications. If the factors that decrease incidence had remained unchanged and only condom use changed with time then this variable would come close to explaining all of the increase in HIV diagnoses (Fig. 3.5). However, it does not fully explain the number of notifications, especially when the factors that decrease incidence are considered (Fig. 3.1).

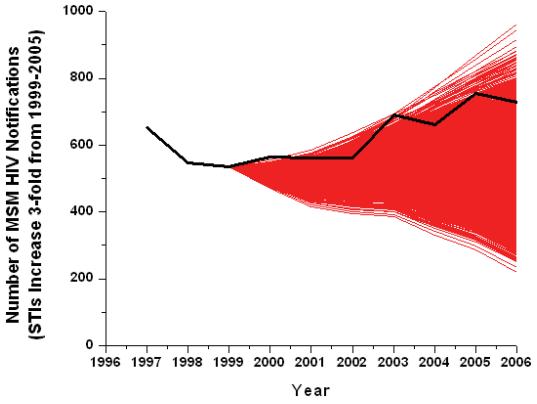
Comprehensive and consistent data has not been available for the number of MSM who have other sexually transmitted infections (STIs). However, the dominant opinion among sexual health experts in Australia is that the prevalence of other STIs has been increasing in recent years. Therefore, we simulated a number of scenarios related to a rise in STIs. Our simulations commenced with an uncertainty range of 5-15% of men with other STIs. We investigated, in 10% increments, increases up to 500% in the prevalence of other STIs among MSM over the duration of our simulations and other time-dependent parameters varied according to the data and uncertainty bounds (Table A.1). In Figure 3.8 we present the cases of 2-fold, 3-fold, 4-fold, and 5-fold increases of STI prevalence over the period of 1999-2002. These results suggest that a 5-fold increase in the prevalence of other STIs, in conjunction with changes in all other parameter values, would explain the national increase in HIV notifications (Fig. 3.8d).

Figure 3.8: The number of HIV notifications in MSM in Australia since 1999: black curve (surveillance data), red curves (simulated time courses for the cases of increases in other STIs of (a) 2-fold, (b) 3-fold, (c) 4-fold, (d) 5-fold)

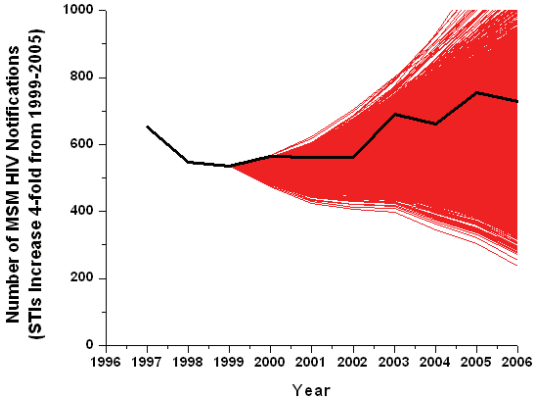
(a) 2-fold Increase in STIs



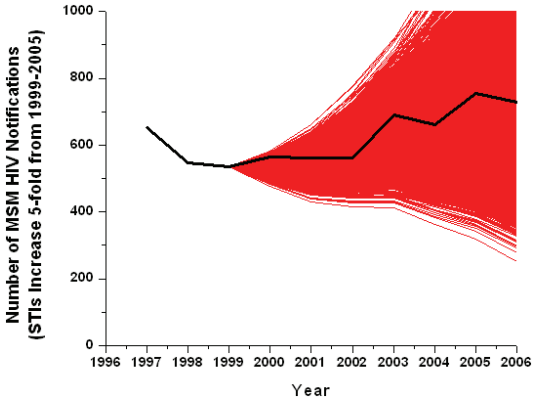
(b) 3-fold Increase in STIs



(c) 4-fold Increase in STIs



(d) 5-fold Increase in STIs

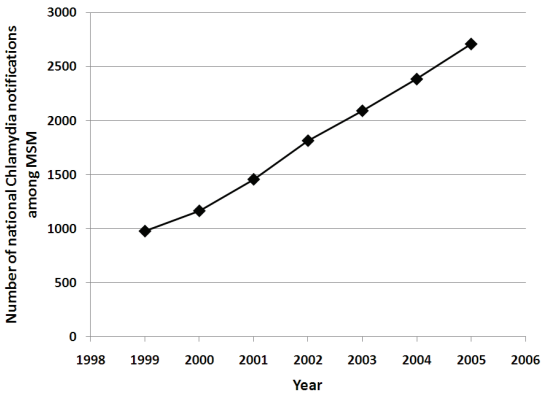


These simulations demonstrated that in order to reproduce the observed data for the number of notifications our model would require an increase in overall STIs of approximately 5-fold over 1999-2006. Therefore, we obtained data for the number of notifications in Australian MSM for various STIs to determine whether a 500% increase is realistic. In Figure 3.9 we present the number of notifications in MSM for Chlamydia, Gonorrhoea, and Syphilis. There has been a close to linear increase in National Chlamydia and Gonorrhoea notifications since 1999 (Fig. 3.9a,b) of ~3-fold and ~1.6 fold, respectively. Syphilis is thought to be much more important to the increased transmissibility of HIV than Chlamydia and Gonorrhoea. There have been much more marked increases in notifications of infectious Syphilis (Fig. 3.9c). There has been an ~5-fold increase in NSW and ~20-fold increase in Victoria for infectious Syphilis. Taken together, a National increase in the prevalence of STIs that contribute to increasing HIV transmission of 5-fold over the time period of our investigation is realistic. But it is important to note that we are not implying that syphilis is solely responsible for the increased transmission. Given the importance of other STIs, particularly those that cause genital ulcerative conditions, in increasing the transmission risks of HIV it is important to invest in heightened and ongoing data collection, surveillance mechanisms and interventions for all 'key' STIs, including Chlamydia, gonorrhoea, herpes,

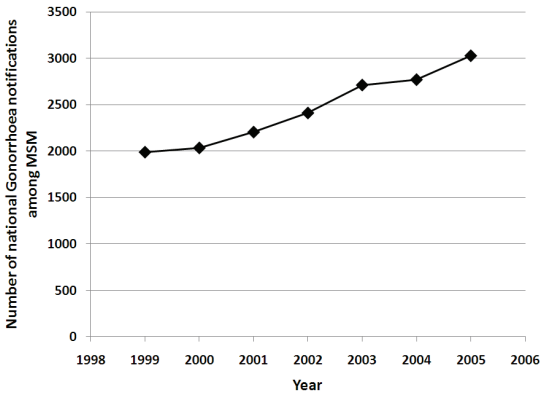
and syphilis. In our model we do not distinguish between different STIs and their respective impacts in contributing to HIV transmission. We subsequently investigated an uncertainty range of 4-6-fold increase in other STIs Nationally over 1999-2006. Accordingly, the resultant simulated number of HIV notifications in the National MSM population due to the full variability placed on all input parameter values is shown in Figure 3.10.

Figure 3.9: The number of notifications of (a) Chlamydia, (b) Gonorrhoea, (c) infectious Syphilis, in MSM in Australia

(a)



(b)



(c)

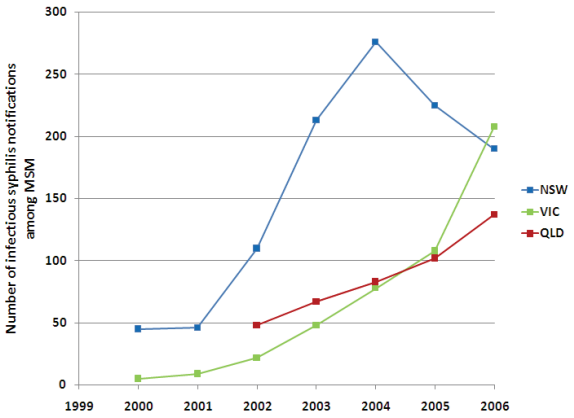
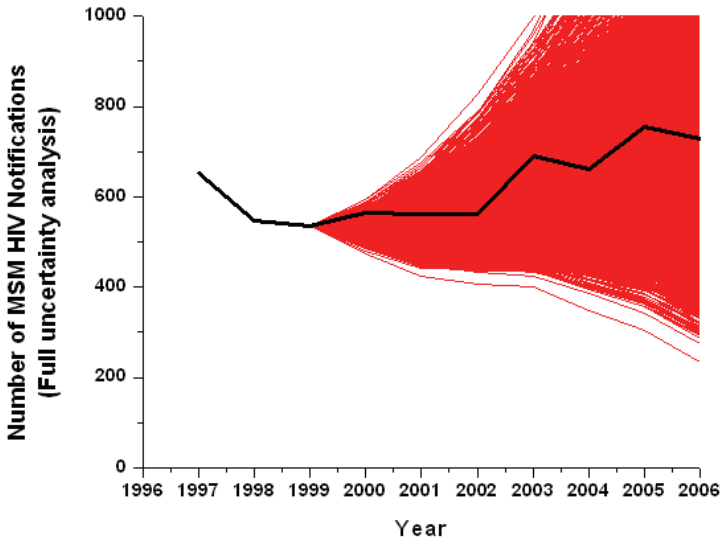


Figure 3.10: The number of HIV notifications in MSM in Australia since 1999: black curve (surveillance data), red curves (all simulated time courses from our full uncertainty analysis)



3.5 Sensitivity Analyses

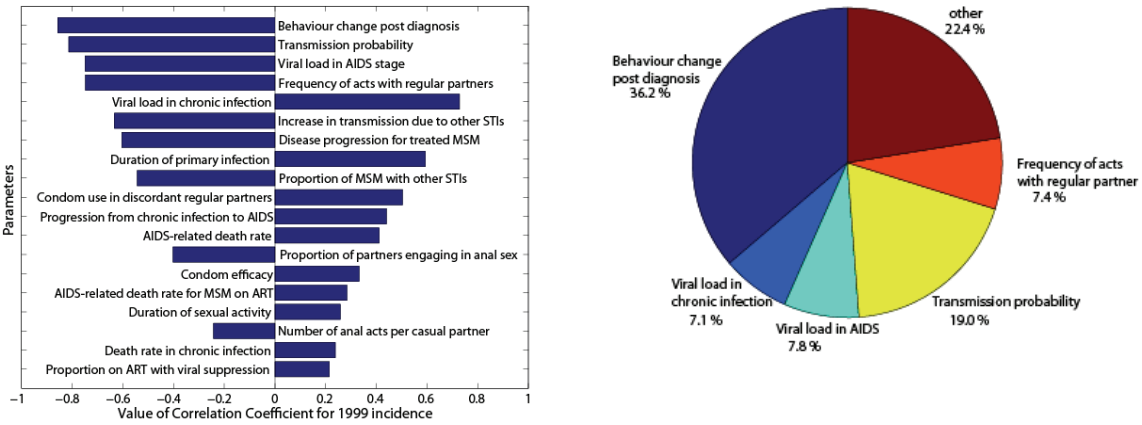
We carried out sensitivity analyses on the model outcomes to determine the relationship and importance of each of the model input parameters in influencing outcome variables, most notably the HIV incidence (see Appendix for sensitivity analysis methods used). We investigated how the variability in the input parameters contributed to the variability in the number of simulated notifications. Firstly, we determined which factors were most important in producing the baseline level of HIV incidence. Secondly, we determined which factors were most important in producing the rise in HIV incidence.

SENSITIVITY ANALYSES ON BASELINE HIV INCIDENCE

We calculated partial rank correlation coefficients and performed reduction of variance sensitivity analyses to ascertain the effect of model input parameters on the number of new HIV infections at baseline (in 1999). The steady state solutions of our model system (see Appendix) were used in calculating the outcome variable. We determined that the parameters most influential in contributing to the variability in the baseline number of HIV notifications were the frequency of anal intercourse acts with regular partners, change in risky behaviour post-diagnosis, viral load, condom usage, and presence of other STIs (see Fig. 3.11). This suggests that at the time of diagnosis, counselling of seroconverters is highly important for preventing subsequent transmissions.

Figure 3.11: (a) Tornado plot of partial rank correlation coefficients of all input parameters on the baseline level of HIV infections in 1999 (parameters with PRCCs < 0.2 were excluded from the plot), (b) Pie-chart of the percentage of variation in the baseline level of HIV infections in 1999 attributable to the variation in the input parameters (as calculated by factor prioritization by reduction of variance)(parameters that individually contributed less than 5% to the variation were lumped as 'Other').

(a) (b)



SENSITIVITY ANALYSES ON RISE IN HIV INCIDENCE

Next, we investigated the influence of changes in input parameters, and uncertainty in these parameters, on the rise in HIV notifications. Specifically, we calculated the percentage of the number of HIV notifications directly attributable to changes in the input parameters. We refer to this as the notification attributable percentage (NAP). We calculated the NAP for every simulation over our uncertainty analysis and for each parameter for which its change contributed to an increase in notifications (see Table 3.2). Some other parameters changed in ways that decreased HIV incidence. Therefore, we also calculated the percentage of extra notifications that could have been expected had these parameters not changed (see Table 3.3). We determined that the rise in other STIs directly attributed to ~169% of the total notifications and the rise in unprotected anal intercourse (UAIC) directly attributed to ~22% of the total notifications. That is, since greater than 100% of notifications are attributable to other STIs, had there not been a rise in other STIs there would have actually been a decrease in HIV notifications (due to changes in other behavioural parameters). Indeed, there would have been a considerable decrease in notifications. There was a rise in the data of new notifications from the baseline level of ~31% by 2006, and had condom usage remained unchanged over this period then the rise in HIV notifications would have only been approximately one-fifth of the actual increase. Therefore, other STIs contributed almost entirely to the rise in HIV infections, followed by UAIC. Of course, these factors are not mutually exclusive. It is highly likely that increases in UAIC have been causal for the increase in incidence of other STIs, and together these factors interacted to cause increased incidence of HIV. The increased prevalence of HIV and other STIs have then most likely also fed off each other to further magnify incidence of HIV and other STIs. It is also important to recall that the simulations are based on an increase in UAIC by a multiplicative factor of ~1.3-1.6 (data) and an increase in other STIs of 4-6-fold. Although there have been significant increases in HIV notifications, it should be noted that it could have been a lot worse. Various factors contributed to decreasing HIV incidence. We investigated the likely effect if these factors had remained at their 1999 levels (Table 3.2) and determined that the number of notifications would have risen by an additional 72% if ART effectiveness had not changed. Other factors were not highly influential.

Table 3.2: The percentage of the increase in notifications at 2006 attributable to the model factors that influence the rise in HIV infections; this is calculated for each simulation by the following and summary statistics (median and inter-quartile-range) are reported: (simulated number of notifications with full time-dependent uncertainty MINUS simulated number of notifications with factor constant at 1999 level) ÷ (simulated increase in the number of notifications with full time-dependent uncertainty)

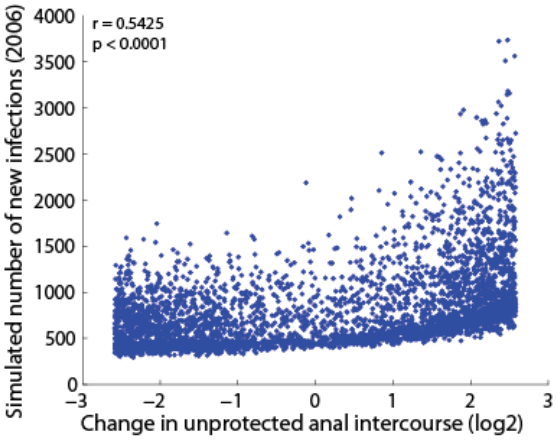
Factor contributing to the rise in HIV incidence	Percentage of the increase in notifications directly attributable to factor (NAP)
Rise in other sexually transmitted infections	169% (median, IQR (120-271%))
Rise in unprotected anal intercourse	22% (median, IQR (12-40%))
Decline in early treatment	6% (median, IQR (1-17%))
Rise in testing rates	-2% (median, IQR (-7-1%))

Table 3.3: Percentage of extra notifications that would have occurred at 2006 had it not been for model factors that influence a decrease in HIV infections; this is calculated for each simulation by the following and summary statistics (median and inter-quartile-range) are reported: (simulated number of notifications with factor constant at 1999 level MINUS simulated number of notifications with full time-dependent uncertainty) ÷ (simulated number of notifications with full time-dependent uncertainty)

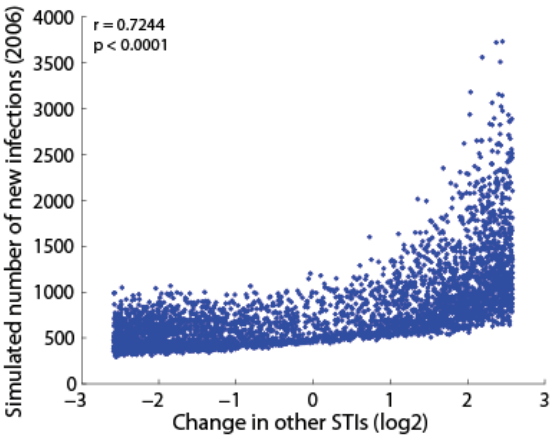
Factor contributing to decrease in HIV incidence	Percentage of extra notifications expected had it not been for the change in factor
Rise in effectiveness of ART	72% (median, IQR (54-97%))
Slight decline in number of sexual partners	0.9% (median, IQR (0.6-1.3%))
Rise in disclosing serostatus	0.4% (median, IQR (-0.2-0.3%))
All of the above	74% (median, IQR (55-100%))

Figure 3.12: Scatter plots of the simulated number of new HIV infections in 2006 versus (a) change in unprotected anal intercourse, (b) change in other STIs. For each case, the x-axis is on a $\log_2$ scale; e.g., 0 refers to no change (multiplicative increase of 2^0=1), 1 refers to doubling of the factor (2^1=2), and -1 refers to halving of the factor (2^{-1}=0.5). Spearman correlation calculations are also shown.

(a)



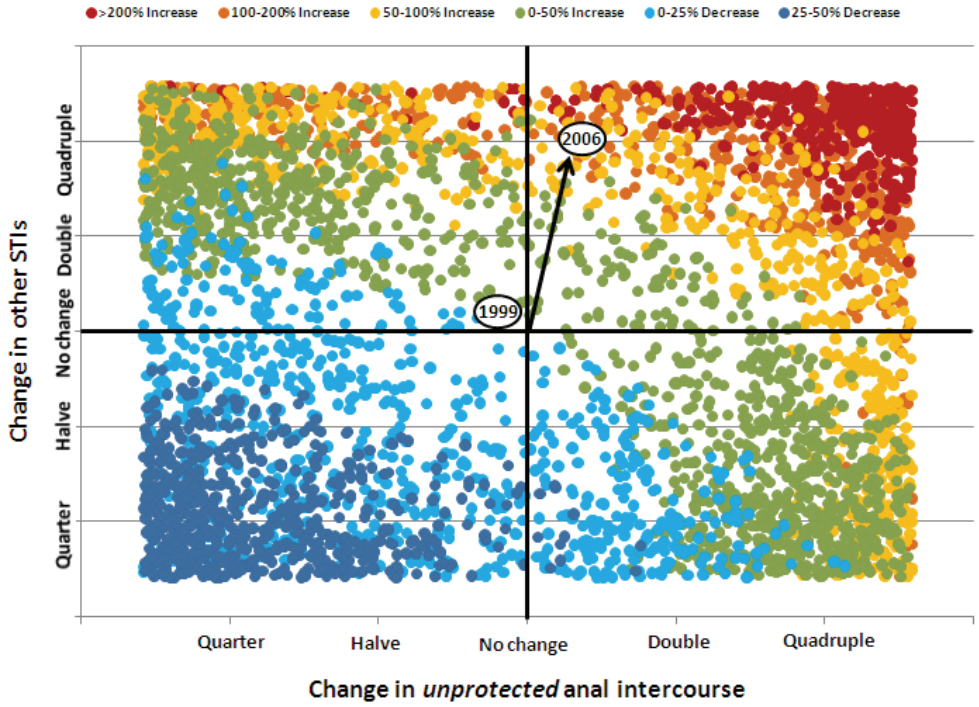
(b)



Condom usage and the presence of other STIs appear to be the main drivers of the increase in new HIV notifications. Therefore, we simulated a range of increases in STIs and condom usage to ascertain the influence of these factors. We simulated epidemic trajectories over the range from a 6-fold decrease to a 6-fold increase over both variables simultaneously (Fig. 3.12). Interestingly, there was greater correlation between the number of new notifications and the increase in unprotected anal intercourse than with the increased in prevalence of other STIs (Fig. 3.12). To further explore the interaction between these factors and the HIV incidence we generated a two-dimensional scatterplot (see Figure 3.13); for ease of interpretation we kept other parameters constant. The plot is divided into four quadrants where the intersection of the two dark axes represents the 1999 levels of STI prevalence and condom usage. The lower left quadrant refers to an increase in UAIC and decrease in STI prevalence, the lower right quadrant refers to a decrease in both UAIC and STI prevalence, the upper right quadrant refers to a decrease in UAIC and an increase in STI prevalence, and the upper right quadrant refers to increases in both UAIC and STI prevalence. It can be seen that relative changes in UAIC are more important in contributing to the number of infections than the same changes in the prevalence of other STIs. This is observed by the curvature in the colour bands; for example, if there was a 2-fold increase in UAIC but no change in STIs from the 1999 levels then we would end up in the green region of the plot where there is a 0-50% increase in HIV infections, but in contrast we would end up in the yellow region where there is a 50-100% increase in HIV infections if there was no change in UAIC but a 4-fold increase in the prevalence of STIs. The upper right quadrant of the response surface plot is the region where both UAIC and STI prevalence increase; this is the region of parameter space that the HIV epidemic in Australian MSM has progressed (as shown by the black directed arrow). Because UAIC and STIs have increased, the HIV incidence has increased. The large concern for the future is further increase in UAIC. If the recent trends continue and the prevalence of other STIs continues to increase then it can be expected that HIV incidence will increase substantially further.

Intervention strategies that would be most effective in reducing HIV incidence in Australia would aim to treat other STIs to reduce their prevalence and to promote the increased use of condoms. With respect to the two-dimensional scatterplot of Figure 3.13 the aim would be to move the incidence trajectory from the green-yellow border through the green region and into the blue region. It could take considerable efforts to achieve this, but it could be achieved in multiple ways by increasing condom usage and decreasing the prevalence of other STIs. Targeting only STIs will lead to the incidence trajectory of Figure 3.13 moving vertically down the graph and targeting only condom usage will lead to horizontal changes. Of course they are not independent factors. Decreasing UAIC would also decrease the incidence (and subsequent prevalence) of other STIs. It should also be noted that HIV disease is increasingly viewed as a manageable infection, with HIV-infected people able to live relatively normal lives and lifespan, and this may increase risk behaviour. Conversely, ongoing research may highlight that despite the sustained life-expectancy there are other serious liabilities associated with long-term HIV infection (e.g., heightened risk of cancer, cardiovascular disease, neurological disease, mental health disease, osteoporosis, etc.) and this may result in reduced risk-taking. It is thus important to monitor perceptions of HIV risk and associated behaviour change as it continues to evolve.

Figure 3.13: Two-dimensional scatterplot of the effect of increased prevalence of STIs and increased unprotected anal intercourse on the degree of change in the number of new HIV infections.



Chapter 4: Trends in HIV incidence – differences between Australian States

4.1 Rise in notifications expected in each State based on change in parameters

The trends in HIV notifications have differed between the Australian States (see Figures in Chapter 1). We applied our transmission model to the three largest States in Australia, namely, NSW, VIC, and QLD to ascertain the important factors giving rise to these differences. We used State-specific data where available, including parameters that change over time. We simulated the HIV epidemic in each State under the conditions of various factors changing. Specifically, we let each parameter be fixed (at its 1999 level) except for one parameter which we set to change with time according to the data available. We then compared the number of HIV notifications expected under conditions of change in the one factor relative to the number of notifications expected if it had not changed from its 1999 level. We did this calculation over all parameter sets (that is, we conducted a full uncertainty analysis). In Table 4.1 we present the expected percent change (increase or decrease) in HIV notifications due solely to changes in various factors. This is calculated nationally and for NSW, VIC, and QLD and is compared with the actual percent rise in HIV notifications based on regression trends fitting the actual notifications data.

Overall there has been a ~44% rise in HIV notifications in Australia since 1999. But this is not consistent across the States. There has only been a ~7% rise in NSW compared with ~68% in QLD and almost doubling (~96%) in VIC. Condom usage has differed substantially between the States (see Table 2.1). UAIC has increased only marginally in NSW overall but has recently been declining. The overall rise in UAIC accounts for a rise of ~5.2% in HIV notifications compared with an actual increase of 7.2%. That is, the majority of HIV notifications in NSW are due solely to changes in UAIC and then also by changes in treatment patterns for early infection. This is offset by a significant decrease in notifications prevented due to effectiveness of ART. ART has improved with respect to the proportion of patients that achieve viral suppression and if that treatment improvement had not occurred then a significant number of extra notifications could have been expected in NSW. To balance these factors and match the data for the number of notifications our model suggests that a doubling of the prevalence of other STIs is required in MSM in NSW.

There have been greater (and consistent) increases in UAIC in QLD and VIC compared with NSW. Not surprisingly, our model indicates that greater increases in HIV notifications could be expected in both VIC and QLD (Table 4.1). However, unlike NSW these increases do not come close to directly explaining the increase in HIV notifications. For example, in VIC the change in UAIC would have been expected to directly give rise to ~8% increase in HIV notifications; but the actual increase in VIC has been ~96%. Additionally, there have been large improvements in ART effectiveness in VIC over this time period, suggesting that many of the notifications are unexplained. In order to reproduce the data our model suggests that the prevalence of STIs would have to have increased in VIC by ~11-fold. Similarly, in QLD the prevalence of other STIs would have to have increased markedly, by ~9-fold in

order to explain the data. Whether the increase in UAIC can account for the epidemic outbreaks of other STIs and thus UAIC is indirectly responsible for the majority of the entire HIV notifications is an interesting hypothesis that merits considerable attention. It is beyond the scope of this report and will be addressed in future work.

Table 4.1: Percent change in HIV notifications (from 1999 to 2006) attributable to various factors (each model parameter was kept constant except for the factor of interest and the calculation is based on the Median and Inter-Quartile Range of simulations)

Factor	National	NSW	VIC	QLD
Number of HIV notifications among MSM in 1999	536	313	102	85
Percent increase in notifications data from 1999 to 2006 (linear regression)	44.49%	7.25%	96.43%	67.69%
	Percent increase in HIV notifications due to factor			
Change in condom usage in casual partnerships	7.11% (6.12,8.15)	5.23% (4.48,6.03)	7.89% (6.78,9.13)	9.45% (8.04,10.97)
Change in number of casual partners	-0.72% (-0.47,-1.07)	-0.45% (-2.20,-0.74)	-1.23% (-0.86,-1.62)	-0.57% (-0.39,-0.75)
Change in disclosure of serostatus	-0.09% (-0.28,0.06)	-0.11% (-0.33,0.07)	-0.14% (-0.42,0.12)	0.01% (0.01,0.03)
Change in testing rates	0.28% (0.12,0.52)	-0.31% (-0.18,-0.46)	0.17% (0.03,0.41)	1.73% (1.04,2.52)
Change in treatment during primary infection	0.81% (0.36,1.63)	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	-42.98% (-50.15,-36.29)	-25.81% (-32.56,-20.26)	-56.13% (-62.2,-49.3)	-47.01% (-54.45,-39.97)
Change in other STIs required to explain data	~5-fold increase	~2-fold increase	~11-fold increase	~9-fold increase

4.2 Magnitude of STI prevalence and differential increase between Australian States

In our model, to avoid undue complexity, we have not modelled STIs individually. Rather we have assumed that the relative susceptibility of HIV-negative MSM to HIV infection is increased by a factor of between 2 and 5 when infected with an STI. The weakness of this assumption is that it does not account for the differential impact of different STIs on HIV transmission. In particular, it is thought that ulcerative STIs such as herpes and infectious syphilis are likely to be more important than non-ulcerative STIs in modifying the risk of HIV transmission, and STIs differ in the length and timing of their infectious periods.

Our model suggests that the proportion of HIV-negative MSM with STIs has to have increased by ~5-fold nationally, ~2-fold in NSW, ~11-fold in Victoria, and ~9-fold in Queensland, between 1999 and 2006 to explain the respective increases in notifications. While comprehensive and robust data on STI prevalence in MSM in each of the States is not available, notifications for Chlamydia, gonorrhoea, and

syphilis have increased sharply since 1999 (see Fig. 3.9), particularly for syphilis which is thought to be the most important of these in increasing HIV transmissibility. Syphilis notifications have increased ~5-fold in NSW and ~20-fold in Victoria since 1999. Syphilis notifications have increased by ~3-fold in Queensland since 2002 and possibly by a considerably higher factor since 1999 but data is not available (53). This apparent epidemic of syphilis in Australia mirrors similar ones in the United Kingdom and the United States (54-56). It has been hypothesized that other STIs have largely contributed to the increase in HIV infections in Australia (19). In San Francisco, for example, syphilis notifications increased from 44 to 522 per year between 1999 and 2004, a ~12-fold increase. Grassly ***et al.*** (57) have analysed syphilis data from US cities over the last 50 years. They suggest that epidemics have occurred periodically in these cities on an 8-11 year cycle and that the increasing connectedness of sexual networks over time has led to increased synchronicity in these. The magnitudes of these epidemics vary but are certainly on the same scale as the increases observed in Australia in recent years.

It cannot be construed from this that syphilis is entirely responsible for the increases in notifications that have been observed in Australia, particularly in Victoria and Queensland, since 1999. However, the data suggest that syphilis may be in an epidemic phase in Australia and there may be some synchronicity between States. Together with increases in other STIs and considerable uncertainty surrounding STI notification data for MSM, the increases in STIs our model suggests are required do not seem unreasonable. It should also be noted that although increases in STIs may be in part due to increases in UAIC, oral sex is known to be a common route of transmission for syphilis (55).

One factor that we have not attempted to model separately by State is serosorting, whereby MSM engage in unprotected anal intercourse (UAI) 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 UAI. It is possible that differential success in serosorting between States 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 New South Wales than the other States, then it is likely that less marked differences in trends in rates of STIs would be required to reproduce the observed trends in HIV notifications by State.

4.3 Impact of other STIs and unprotected anal intercourse

We conducted simulations according to various scenarios of changes in UAIC and prevalence of STIs (UAIC ranging from 1, 2, 3 or 4-fold increase relative to 1999 and STI prevalence varying incrementally 1-10-fold increase relative to 1999). For each set of simulations we determined the percentage difference between the median simulation values at 2006 compared with the actual number of HIV notifications. We then produced colour-shaded tables representing the percent difference (see Tables 4.2-4.5). This is a visual representation for indicating the region of UAIC-STI space in which the notifications data is matched appropriately.

Table 4.2: Representation of the UAIC-STI space for National notification data. Colour gradient represents where the median from our results is within a certain percentage of the data: red – within 10%, orange – within 20%, yellow – within 30%, green – within 40%, blue – within 50%, and white – greater than 50%.

UAIC 4-fold increase										
UAIC 3-fold increase										
UAIC 2-fold increase										
UAIC 1-fold increase										
	1xSTI	2xSTI	3xSTI	4xSTI	5xSTI	6xSTI	7xSTI	8xSTI	9xSTI	10xSTI

Table 4.3: Representation of the UAIC-STI space for New South Wales notification data. Colour gradient represents where the median from our results is within a certain percentage of the data: red – within 10%, orange – within 20%, yellow – within 30%, green – within 40%, blue – within 50%, and white – greater than 50%.

UAIC 4-fold increase										
UAIC 3-fold increase										
UAIC 2-fold increase										
UAIC 1-fold increase										
	1xSTI	2xSTI	3xSTI	4xSTI	5xSTI	6xSTI	7xSTI	8xSTI	9xSTI	10xSTI

Table 4.4: Representation of the UAIC-STI space for Victoria notification data. Colour gradient represents where the median from our results is within a certain percentage of the data: red – within 10%, orange – within 20%, yellow – within 30%, green – within 40%, blue – within 50%, and white – greater than 50%.

UAIC 4-fold increase										
UAIC 3-fold increase										
UAIC 2-fold increase										
UAIC 1-fold increase										
	1xSTI	2xSTI	3xSTI	4xSTI	5xSTI	6xSTI	7xSTI	8xSTI	9xSTI	10xSTI

Table 4.5: Representation of the UAIC-STI space for Queensland notification data. Colour gradient represents where the median from our results is within a certain percentage of the data: red – within 10%, orange – within 20%, yellow – within 30%, green – within 40%, blue – within 50%, and white – greater than 50%.

UAIC 4-fold increase										
UAIC 3-fold increase										
UAIC 2-fold increase										
UAIC 1-fold increase										
	1xSTI	2xSTI	3xSTI	4xSTI	5xSTI	6xSTI	7xSTI	8xSTI	9xSTI	10xSTI

Chapter 5: Number of transmissions during primary infection and before diagnosis

5.1 Magnitude of incidence caused by primary infection and undiagnosed cases

We used our transmission model steady state values (see Appendix) to estimate the proportion of all MSM in each of the respective compartments of our model system and the proportion of all new infections that are caused by the number of people in each infected compartment. Our simulations had an overall HIV prevalence in the MSM population of 10.5% (median, IQR (9.5-11.5%)). Of the infected MSM, we estimated the percentage in each disease stage and designation of undiagnosed, diagnosed and untreated, or treated (see Table 5.1). Our simulations revealed that 9.1% (median, IQR (5.6-12.4%)) of infected MSM were undiagnosed and ~3.0% (median, IQR (2.5-3.8%)) of infected MSM are in the primary stage of infection. Next, we estimated the proportion of all new infections that were transmitted from MSM in each of these compartments (see Table 5.2). Although ~9% of HIV-infected MSM were undiagnosed, they are responsible for ~31% (median, IQR (19-42%)) of the new infections and although only ~3% of MSM are in primary infection they are responsible for ~18.6% (median, IQR (13.5-24.5%)) of all new infections. The disproportionate nature of the cause of infections is shown graphically in Figures 5.1 and 5.2. It is not surprising that treated individuals contribute lower proportions of new infections because viral load is suppressed in a large number of treated patients. So we compared untreated MSM who are undiagnosed with those who are diagnosed but untreated; although there are almost three times as many diagnosed (untreated) MSM as undiagnosed MSM, the undiagnosed MSM contributed greater numbers of new infections.

Table 5.1: Breakdown of the percentage of HIV-infected MSM in each model compartment (stage of disease and diagnosis/treatment status)

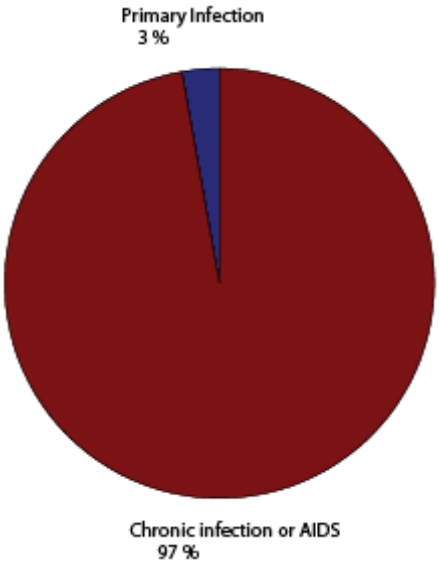
Disease Stage	Undiagnosed	Diagnosed & Untreated	Treated
Primary	1.9% (1.2 – 2.7%)	0.46% (0.23 – 0.84%)	0.53% (0.28 – 0.81%)
Chronic	6.8% (4.2 – 9.3%)	29.0% (24.9 – 34.8%)	58.1% (52.6 – 63.1%)
AIDS	0.12% (0.07–0.17%)	0.44% (0.35 – 0.57%)	3.6% (2.6 – 5.5%)

Table 5.2: Breakdown of the percentage of new HIV infections caused by HIV-infected MSM in each model compartment (stage of disease and diagnosis/treatment status)

Disease Stage	Undiagnosed	Diagnosed & Untreated	Treated
Primary Infection	16.2% (9.9 – 22.7%)	1.48% (0.67 – 2.81%)	0.46% (0.22 – 0.79%)
Chronic Infection	13.5% (8.5 – 18.2%)	16.0% (12.8 – 20.0%)	48.5% (39.8 – 57.5%)
AIDS	0.14% (0.09 – 0.23%)	0.18% (0.13 – 0.26%)	0.8% (0.5 – 1.2%)

Figure 5.1: Pie chart of (a) the proportion of all HIV-infected MSM according to their stage of disease progression (primary or progressed beyond primary to chronic or AIDS), and (b) the corresponding proportion of all infections caused by each category of HIV-infected man.

(a) Breakdown of HIV-infected MSM population



(b) Breakdown of cause of new HIV infections

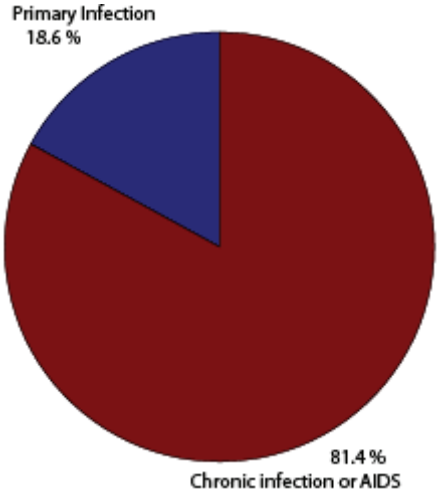
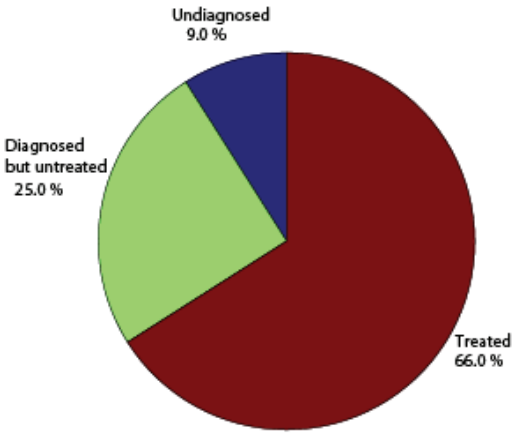
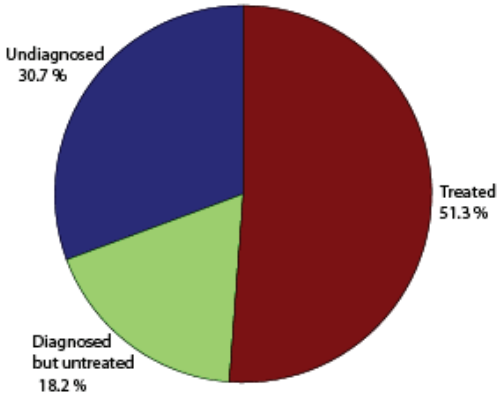


Figure 5.2: Pie chart of (a) the proportion of all HIV-infected MSM as undiagnosed, diagnosed but untreated, or treated, and (b) the corresponding proportion of all infections caused by each category of HIV-infected men.

(a) Breakdown of HIV-infected MSM population



(b) Breakdown of cause of new HIV infections



5.2 Sensitivity Analyses

We determined the parameters which had greatest influence on the percentage of new infections caused in primary infection and by undiagnosed MSM by calculating partial rank correlation coefficients and performing factor prioritisation by reduction of variance (see Appendix). According to each of these methods we determined that the same parameters (in order) were dominant in influencing the variability in the proportion of infections caused by MSM in primary infection and by

undiagnosed MSM. Therefore, we present just one example of this sensitivity analysis (see Fig. 5.3 for a tornado plot of PRCCs for the importance of parameters contributing to infections caused by undiagnosed MSM). Note that the dominant parameters do not appear to consist of factors that relate directly to men who have primary or undiagnosed infection status. The most important parameter is the number of sexual partners, followed by the viral load in AIDS stage, baseline transmission probability of MSM with chronic infection, and viral load in chronic infection. This is because these parameters are the most influential in causing new infections overall; that is, in contributing to the number of MSM in primary infection and the number of MSM that have undiagnosed HIV infection. This suggests that the cause of the magnitude of new infections from MSM in primary infection or undiagnosed infection is not greatly related to the viral load in primary infection, rate of progression of disease, or other parameters directly related to these compartments but to the sheer number of infected MSM who have entered these compartments. However, if we scale the number of infections caused by people in each compartment by the number of people in each compartment, we obtain a measure of a type of reproductive ratio (58) per compartment. We calculated two reproductive ratios: the average number of new HIV infections caused per MSM per year whilst (i) in primary infection, (ii) undiagnosed. These ratios were calculated to be 0.54 (median, IQR (0.44-0.64)) and 0.31 (median, IQR (0.28-0.35)), respectively. Note that we standardised these ratios to the rate per year for comparative purposes. We then carried out sensitivity analyses based on these ratios. In this case, the transmission probability in primary infection (based on viral load levels and the presence of other STIs), duration in primary infection, and frequency of sexual acts with regular partners were the most important parameters. Of these, the transmission probability (with presence of other STIs and primary infection viral load) was the most influential in contributing to the reproductive ratio for both primary infection (Fig. 5.4a) and those with undiagnosed infection (Fig. 5.4b). It is substantially more important in influencing infections caused by MSM in primary infection than in undiagnosed MSM. Since transmission in primary infection contributes greatly to new infections, it is not surprising that for undiagnosed men, the next most important parameter is the duration of time in primary infection. The association between the average number of infections caused per MSM whilst undiagnosed and the three dominant parameters is shown in Figure 5.5.

Figure 5.3: Tornado plot of partial rank correlation coefficients of all input parameters on the proportion of all new infections caused by undiagnosed MSM (parameters for which |PRCC|<0.2 were excluded).

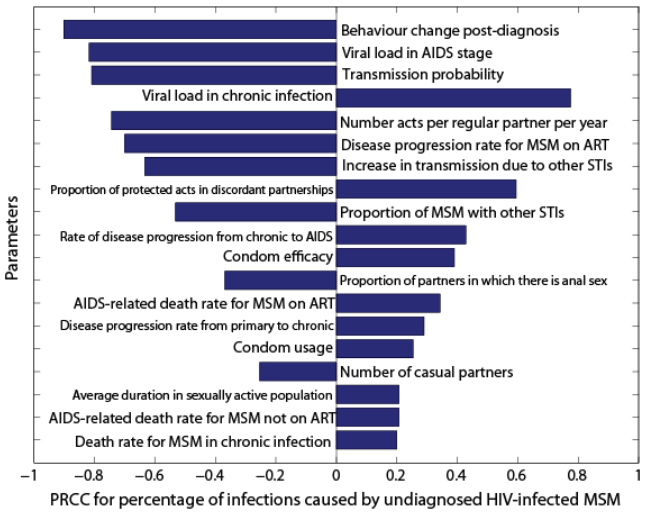
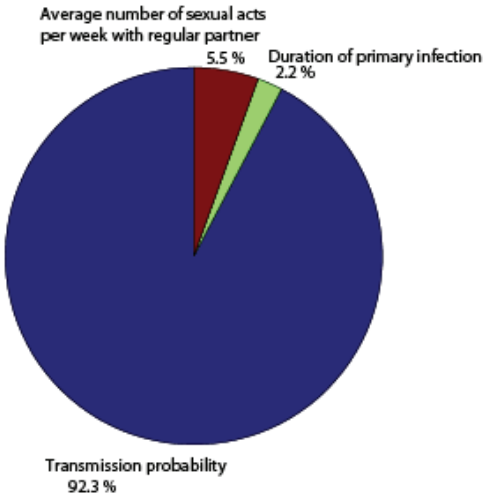


Figure 5.4: Pie chart of results of factor prioritization by reduction of variance methods: proportion of the variation in reproductive ratio for (a) primary infection and (b) undiagnosed infection.

(a)



(b)

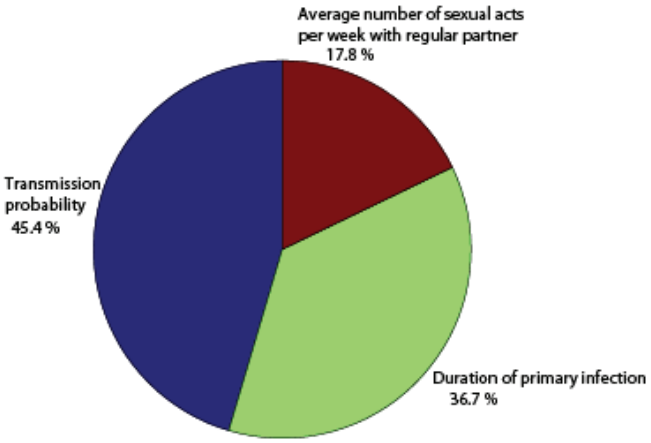
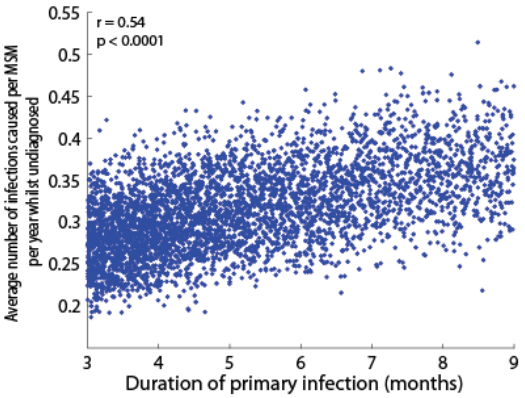
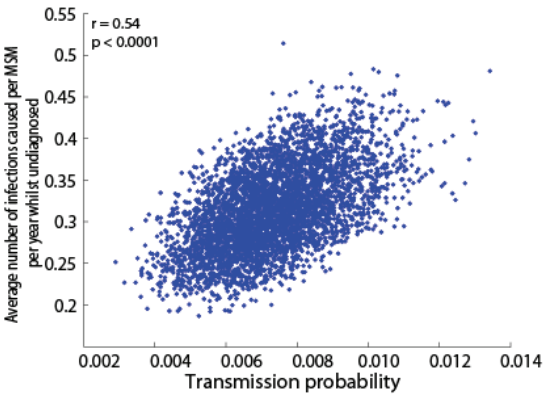


Figure 5.5: Scatter plots of the association between the average numbers of infections caused per MSM whilst undiagnosed and (a) duration of primary infection, (b) the transmission probability in primary infection, and (c) frequency of sexual acts (anal intercourse). Spearman correlation coefficients were calculated for each association.

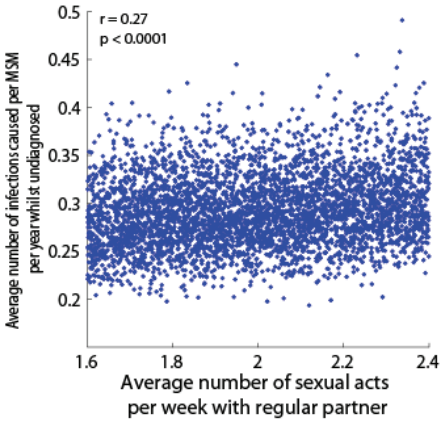
(a)



(b)



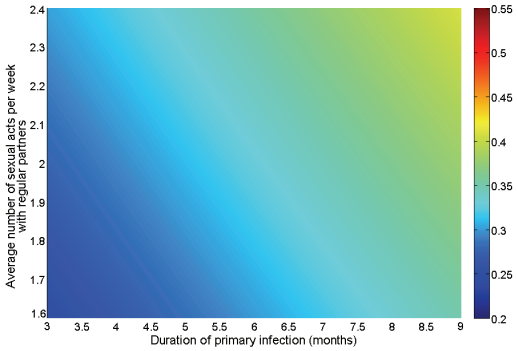
(c)



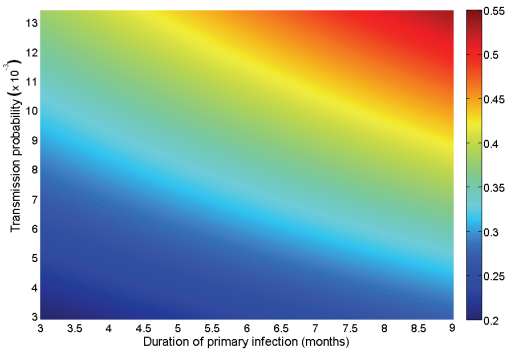
Although the duration of primary infection and the transmission probability in primary infection are biological parameters that cannot be altered directly, possible interventions could effectively target these parameters (e.g., by (i) increased testing and progression to treatment for newly diagnosed individuals or by (ii) increasing condom usage or reduction of other STIs). The frequency of sexual acts is clearly a behavioural parameter that is unlikely to be altered significantly, but awareness of its importance by men engaging in anal intercourse could have a significant epidemiological impact. To explore the interactive effect of combinations of parameters (and effect of changes in these parameters through interventions for example), we extended the sensitivity analyses by calculating standardised regression coefficients and producing response hypersurfaces based on regression techniques (Fig. 5.6). The standardized regression coefficients were 0.69 (0.67-0.70, 95%CI) for the transmission probability, 0.63 (0.62-0.64, 95%CI) for the duration of primary infection, and 0.43 (0.42-0.44, 95%CI) for the frequency of sexual acts. Clearly, the combination of the duration of primary infection and transmission probability in primary infection influenced the greatest change in the response variable (the greatest change in the colour gradient in Fig. 5.6); this is also emphasised by the relatively large regression coefficient for the interaction term between duration of primary infection and the transmission probability (0.07 (0.06-0.08, 95%CI)), compared with small interaction coefficients for the other pairs of parameters. The standardized regression coefficients provide an estimate of the comparative effects of different factors; for example, a 25% change in the transmission probability will produce a result equivalent to a 40% (0.25×0.69/0.43) change in the number of sexual acts.

Figure 5.6: Response surface plots of the reproductive ratio of the average number of new HIV infections caused per MSM per year whilst undiagnosed as dependent on (a) duration of primary infection and the frequency of sexual acts, (b) duration of primary infection and transmission probability in primary infection, and (c) frequency of sexual acts and the transmission probability in primary infection.

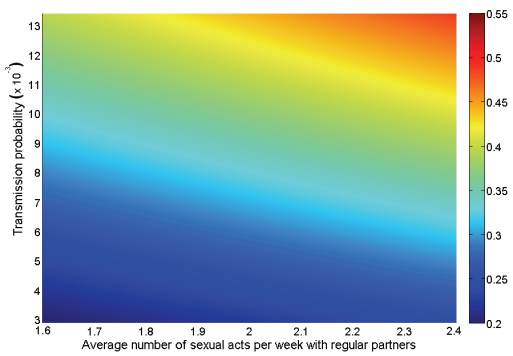
(a)



(b)



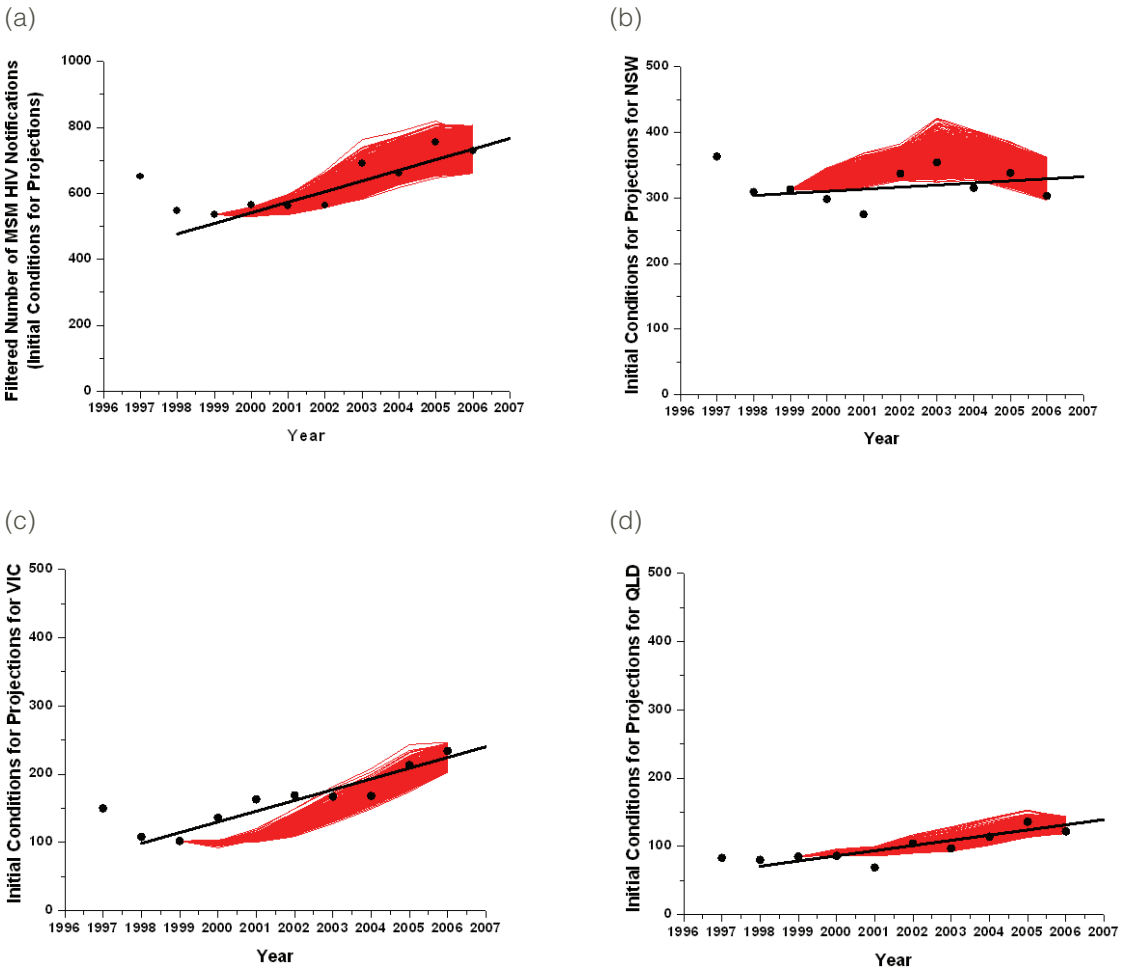
(c)



Chapter 6: Projections to 2015

We use our model to predict the course of the HIV epidemic among MSM in Australia (and for NSW, VIC, QLD) into the future according to a number of scenarios. Each of the scenarios we consider for projecting the number of notifications up to 2015 are outlined by the headings below and shown in the form of Figures of all simulations. Summaries of the projected results are presented in Table 6.1. Because of the large uncertainty in our outcome variables from the full uncertainty analysis, we filtered the simulations to a smaller subset to extrapolate to 2006. We calculated the best-fitting linear regression line through the notification data from 1999 to 2006 and then we restricted our parameter sets to those that produce a time-course for the number of notifications that are within ±10% of the regression line at 2006; the resulting (990) parameter sets for National simulations are illustrated in Figure 6.1a, and the remaining 1482, 443, and 799 simulations for NSW, VIC, and QLD are shown in Figures 6.1b, c, and d respectively.

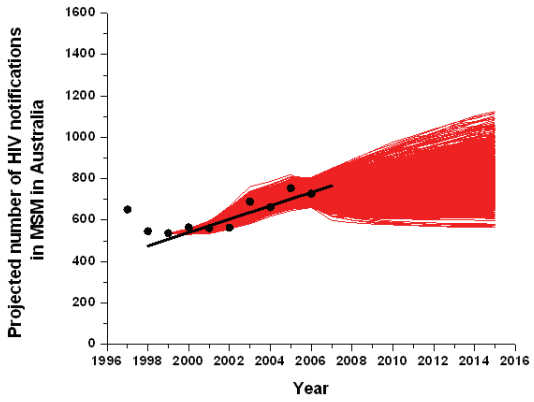
Figure 6.1: The subset of parameter sets to be used after filtering used for future projections for (a) Australia, (b), NSW, (c) VIC, and (d) QLD.



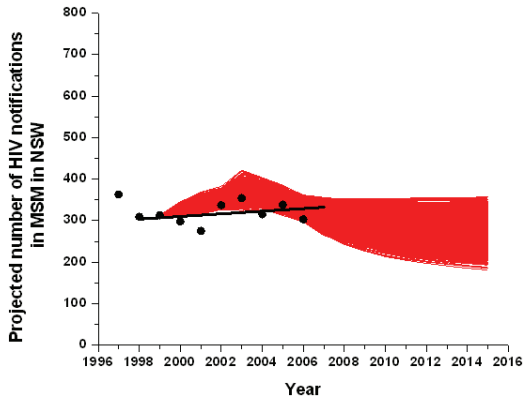
6.1 All parameters remain at their 2006 levels

Figure 6.2: Projections to 2015 for the number of HIV notifications in (a) Australia (b) NSW (c) VIC (d) QLD, if all parameters remain at their 2006 levels.

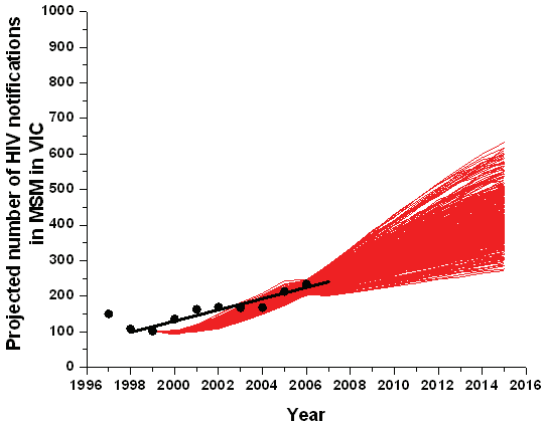
(a)



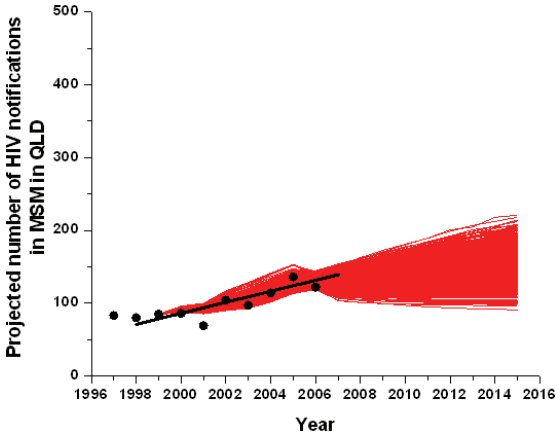
(b)



(c)

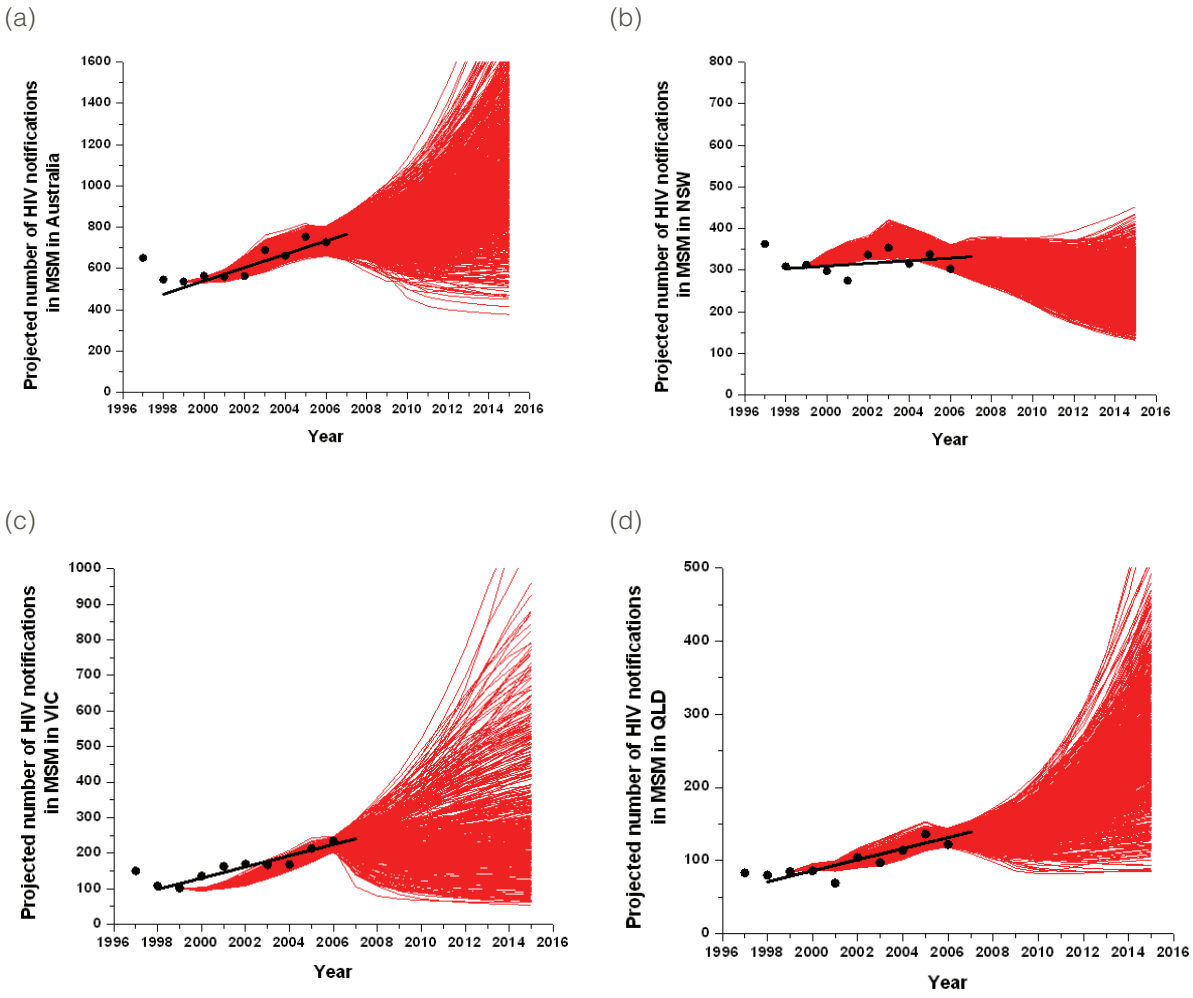


(d)



6.2 All time-dependent parameters continue to change on their current trends

Figure 6.3: Projections to 2015 for the number of HIV notifications in (a) Australia (b) NSW (c) VIC (d) QLD, if all parameters continue to change according to their trends from 1999 to 2006.



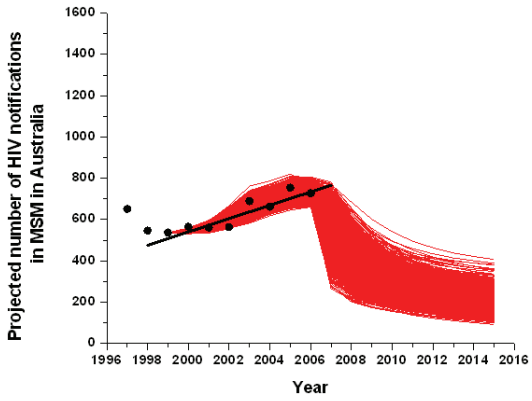
6.3 Changes in prevalence of other STIs

For our baseline estimates, at 1999, we assumed that each State had an STI prevalence of between 5% and 15% (15, 43) (see Table A.1). In this section we investigate the influence of changes in STI prevalence between 2006 and 2015 in each State and also Nationally.

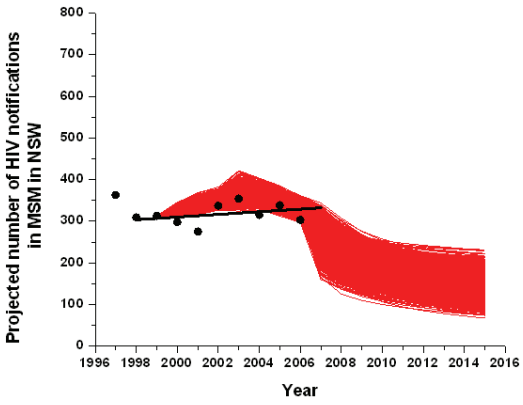
PREVALENCE OF OTHER STIs: 5%

Figure 6.4: Projections to 2015 for the number of HIV notifications in (a) Australia (b) NSW (c) VIC (d) QLD, if the prevalence of other STIs was brought to 5% and remained at 5%. All other parameter values remained at 2006 levels.

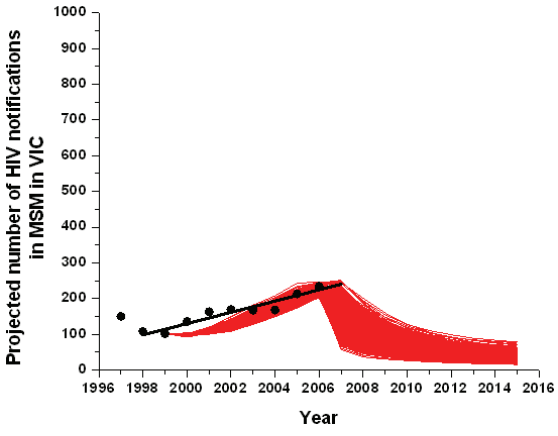
(a)



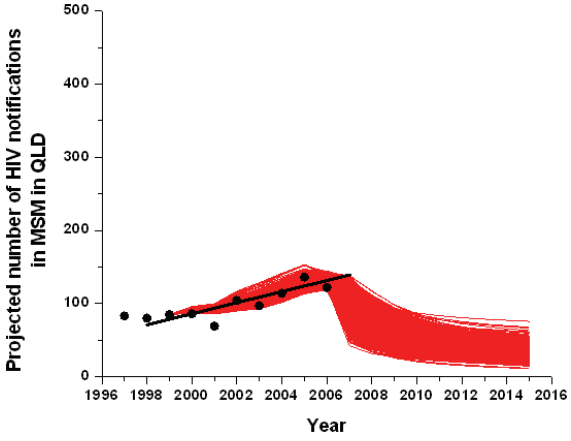
(b)



(c)



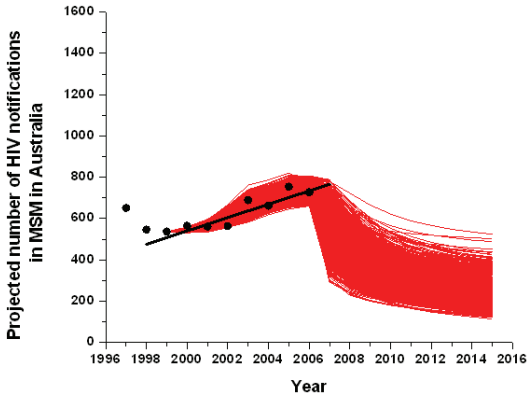
(d)



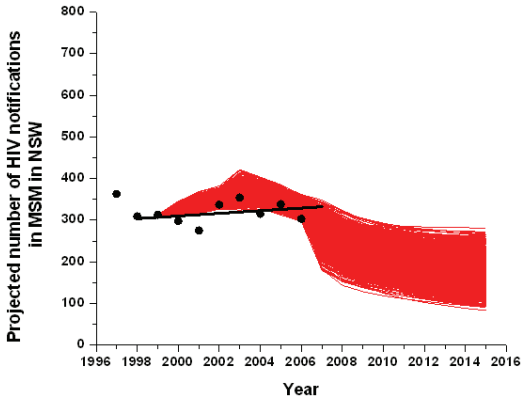
PREVALENCE OF OTHER STIs: 10%

Figure 6.5: Projections to 2015 for the number of HIV notifications in (a) Australia (b) NSW (c) VIC (d) QLD, if the prevalence of other STIs was brought to 10% and remained at 10%. All other parameter values remained at 2006 levels.

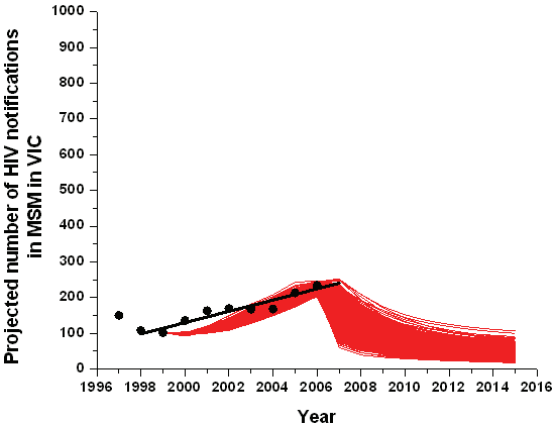
(a)



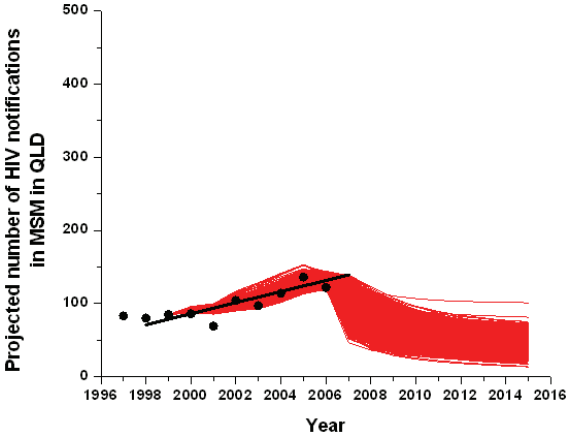
(b)



(c)



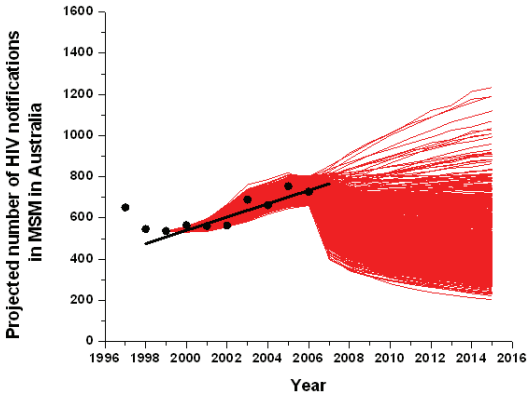
(d)



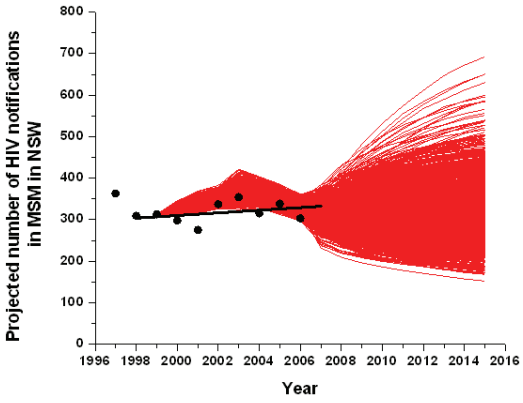
PREVALENCE OF OTHER STIs: 30%

Figure 6.6: Projections to 2015 for the number of HIV notifications in (a) Australia (b) NSW (c) VIC (d) QLD, if the prevalence of other STIs was brought to 30% and remained at 30%. All other parameter values remained at 2006 levels.

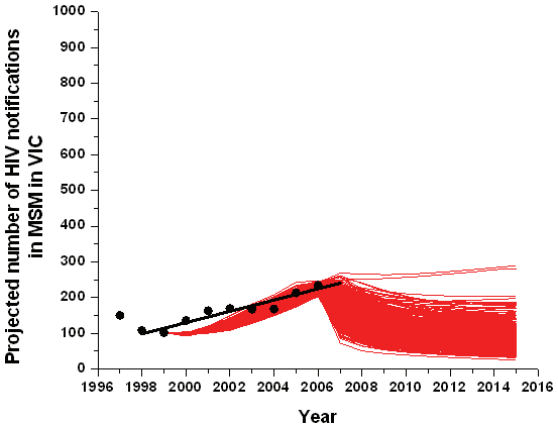
(a)



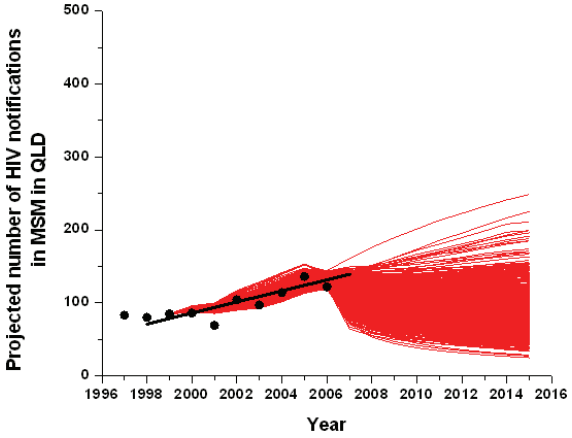
(b)



(c)



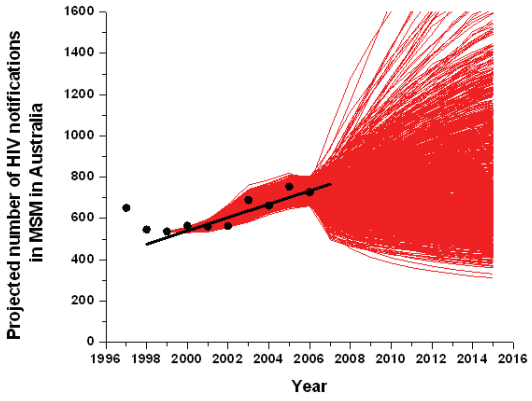
(d)



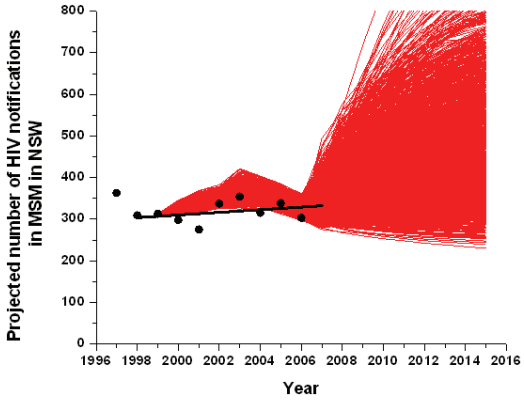
PREVALENCE OF OTHER STIs: 50%

Figure 6.7: Projections to 2015 for the number of HIV notifications in (a) Australia (b) NSW (c) VIC (d) QLD, if the prevalence of other STIs was brought to 50% and remained at 50%. All other parameter values remained at 2006 levels.

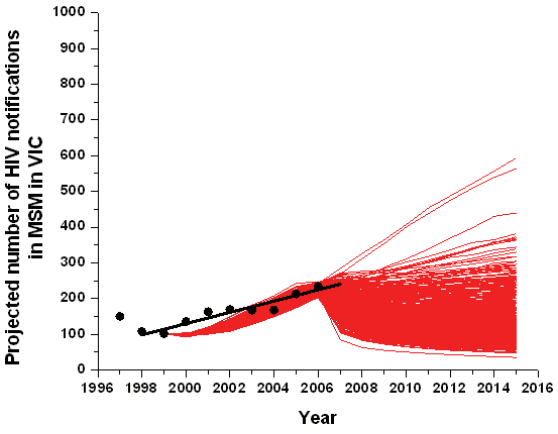
(a)



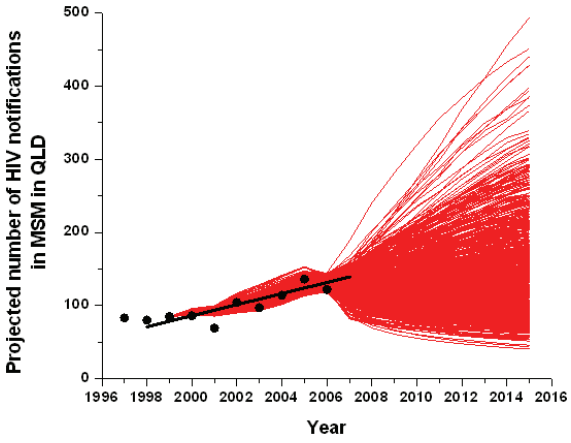
(b)



(c)



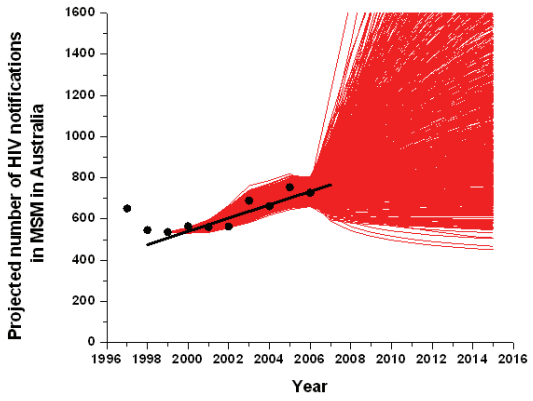
(d)



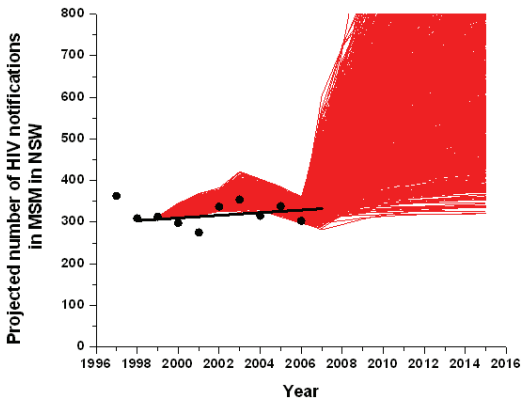
PREVALENCE OF OTHER STIs: 70%

Figure 6.8: Projections to 2015 for the number of HIV notifications in (a) Australia (b) NSW (c) VIC (d) QLD, if the prevalence of other STIs was brought to 70% and remained at 70%. All other parameter values remained at 2006 levels.

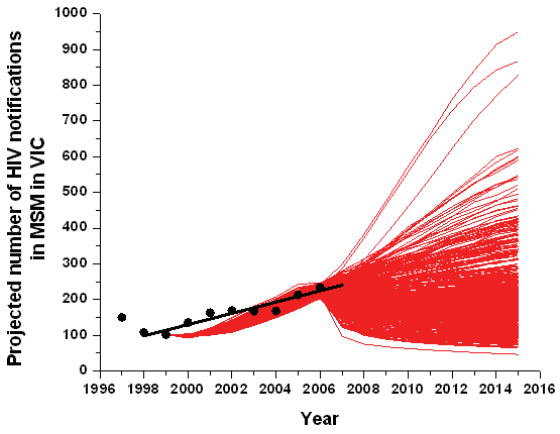
(a)



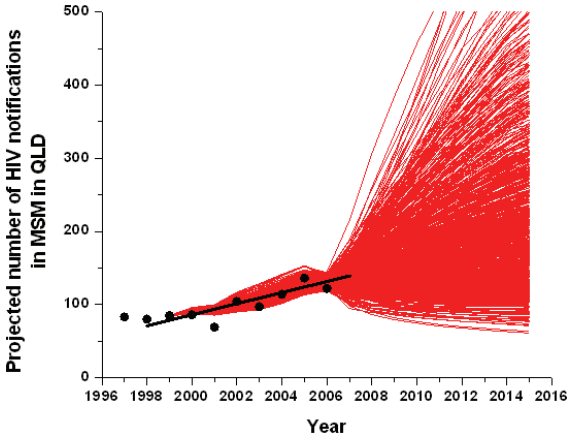
(b)



(c)



(d)

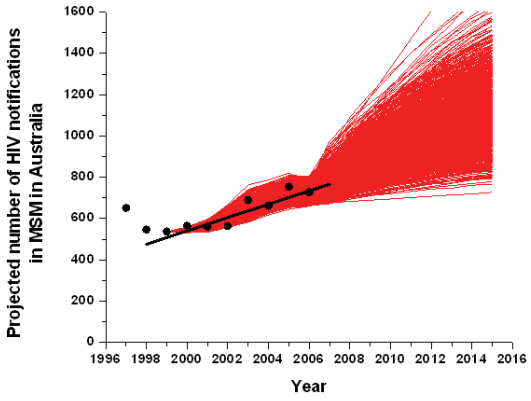


6.4 Changes in Unprotected Anal Intercourse

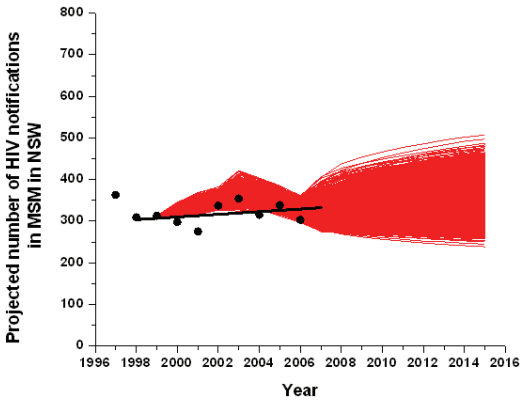
CONDOMS USED IN AN AVERAGE OF 30% OF ANAL INTERCOURSE ACTS

Figure 6.9: Projections to 2015 for the number of HIV notifications in (a) Australia (b) NSW (c) VIC (d) QLD, if condoms are used in 30% of acts. All other parameter values remained at 2006 levels.

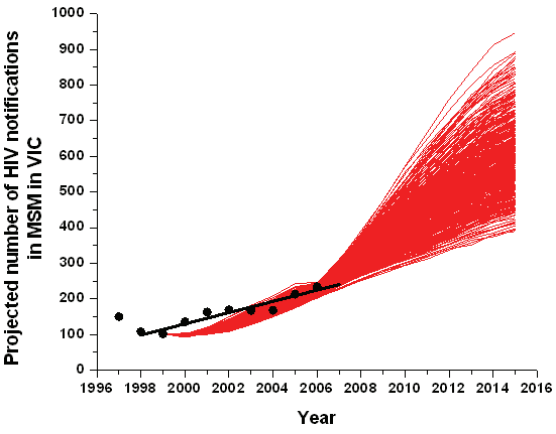
(a)



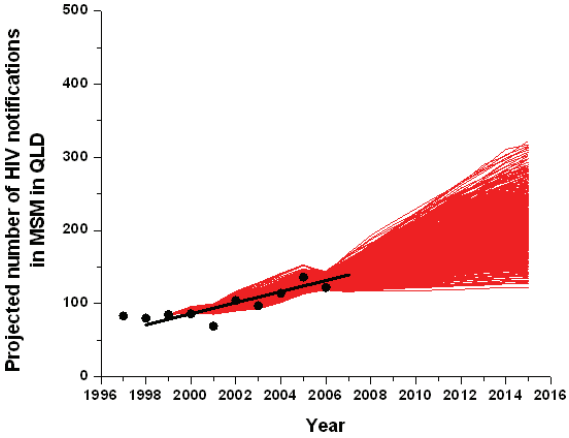
(b)



(c)



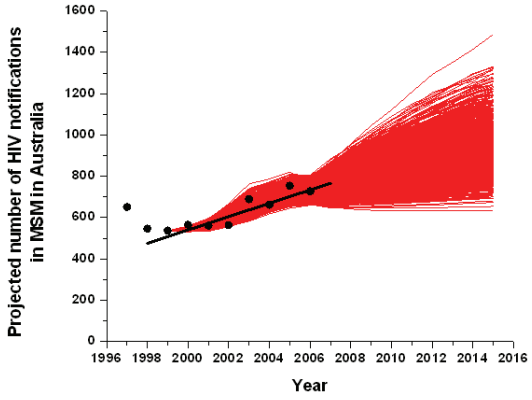
(d)



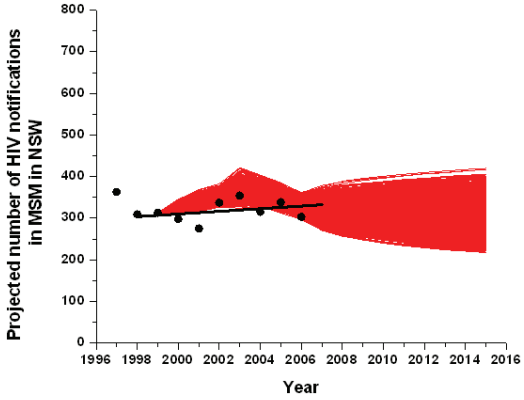
CONDOMS USED IN AN AVERAGE OF 50% OF ANAL INTERCOURSE ACTS

Figure 6.10: Projections to 2015 for the number of HIV notifications in (a) Australia (b) NSW (c) VIC (d) QLD, if condoms are used in 50% of acts. All other parameter values remained at 2006 levels.

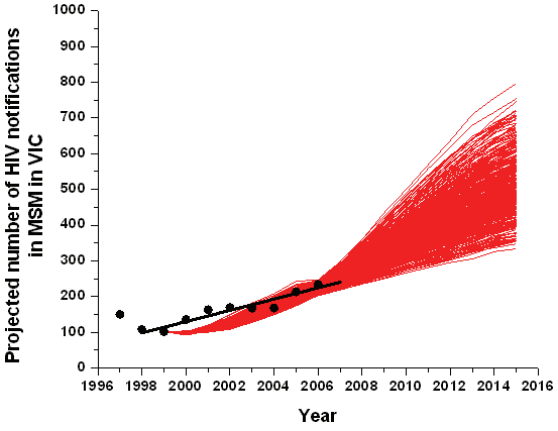
(a)



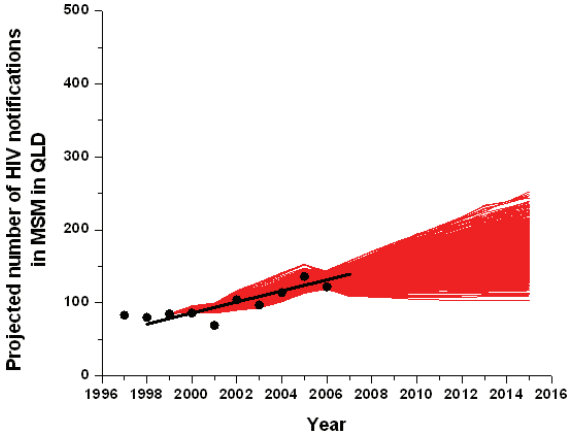
(b)



(c)



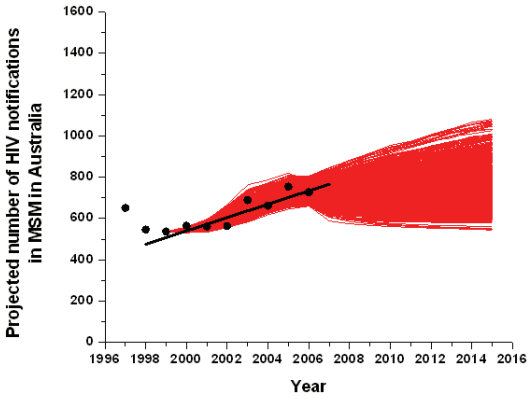
(d)



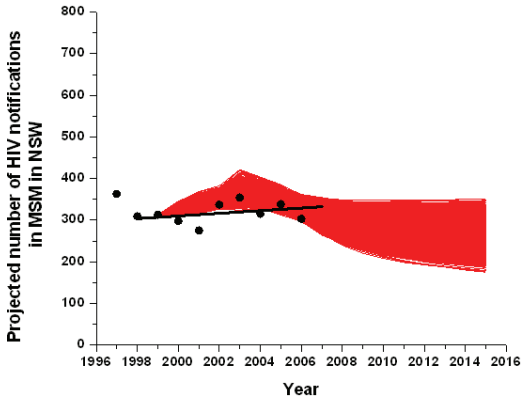
CONDOMS USED IN AN AVERAGE OF 70% OF ANAL INTERCOURSE ACTS

Figure 6.11: Projections to 2015 for the number of HIV notifications in (a) Australia (b) NSW (c) VIC (d) QLD, if condoms are used in 70% of acts. All other parameter values remained at 2006 levels.

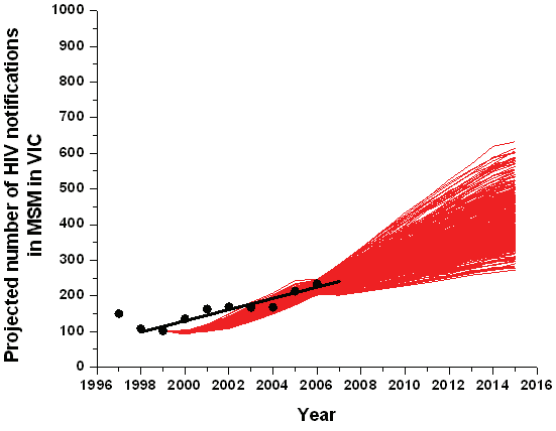
(a)



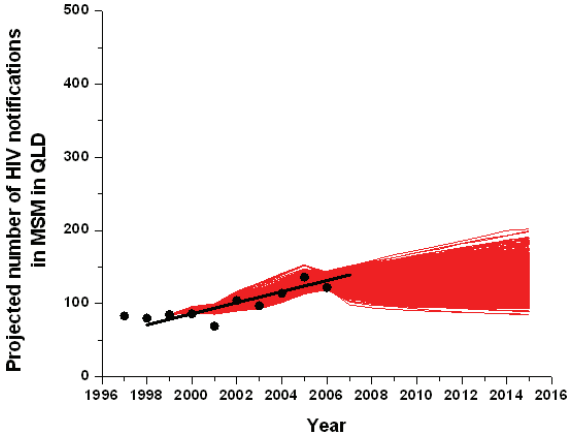
(b)



(c)

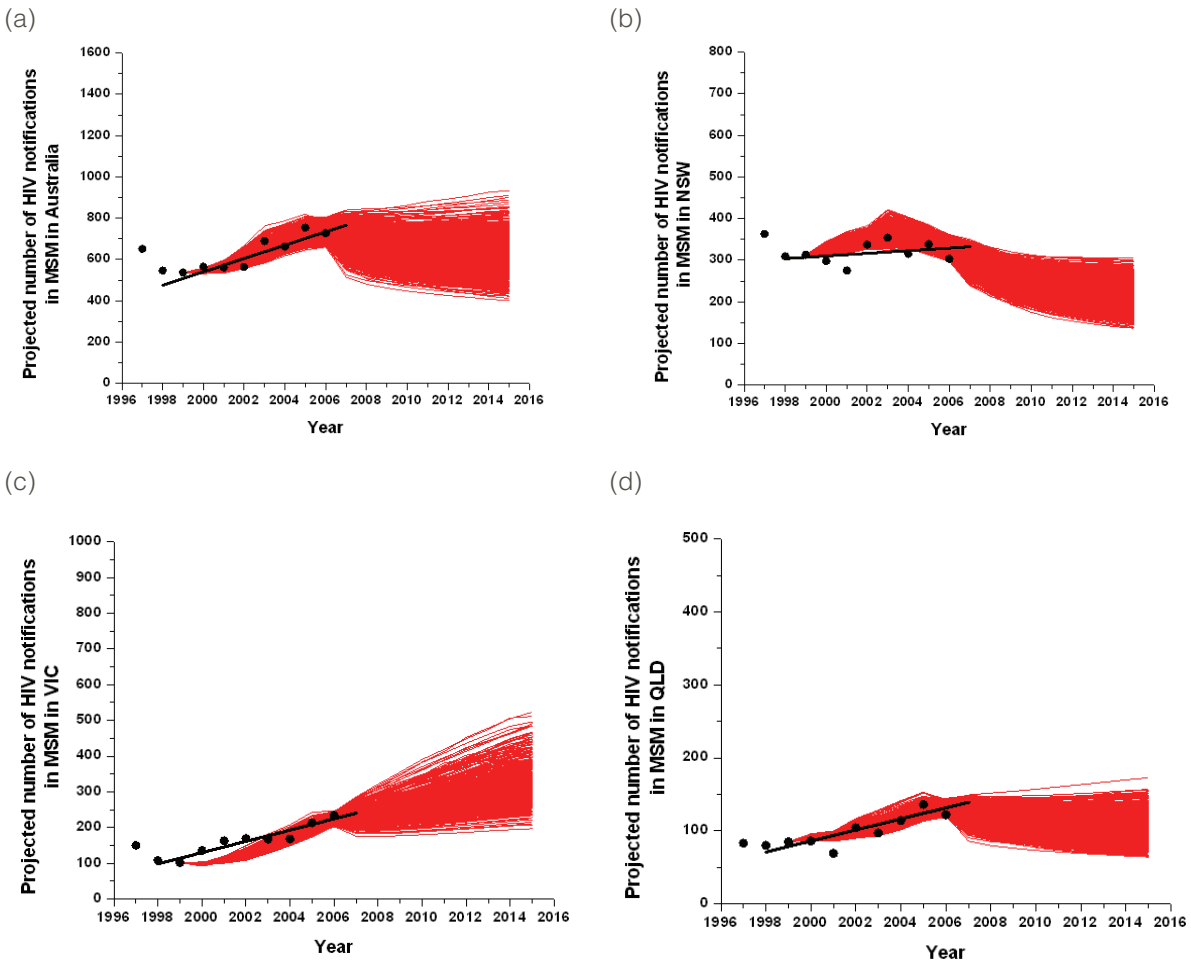


(d)



CONDOMS USED IN AN AVERAGE OF 90% OF ANAL INTERCOURSE ACTS

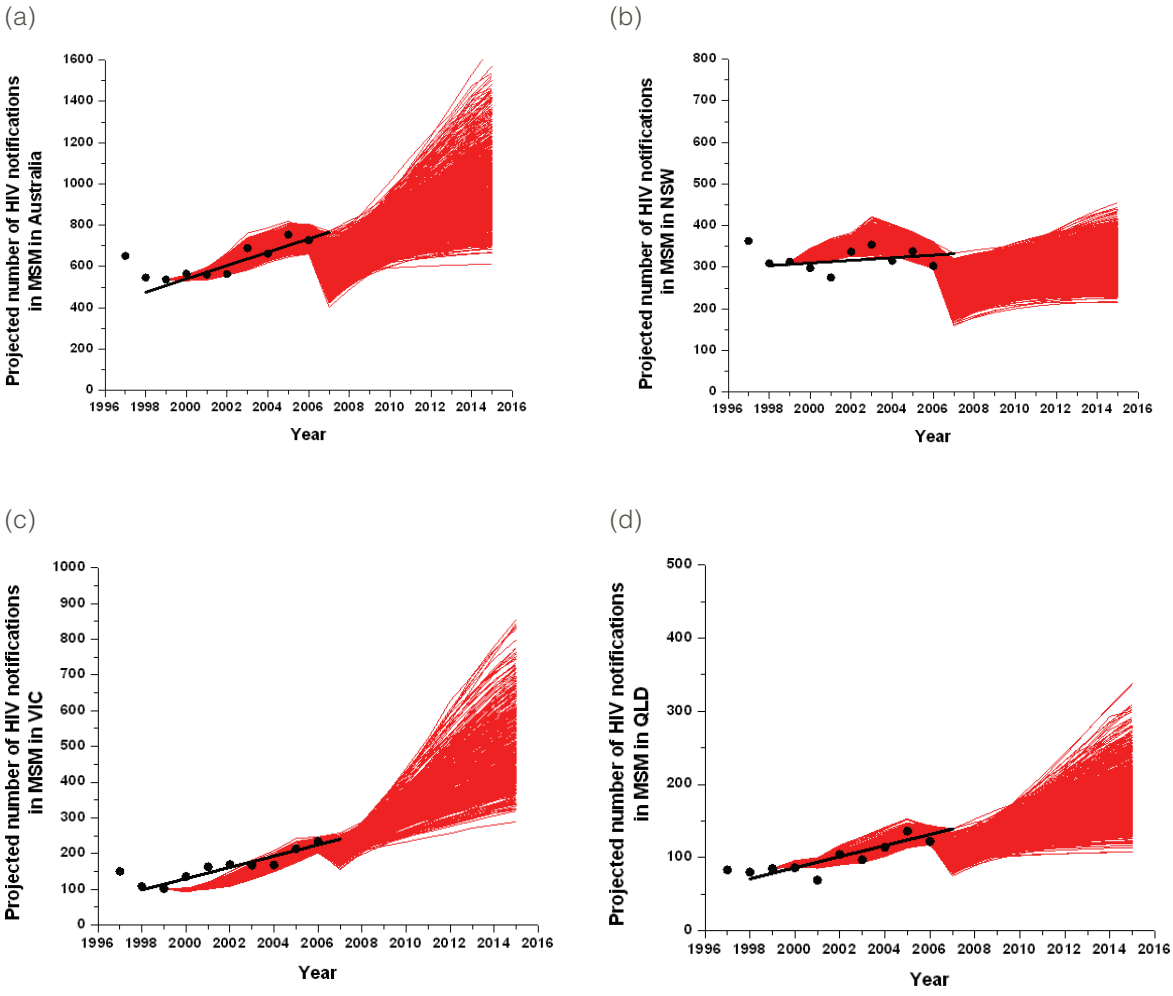
Figure 6.12: Projections to 2015 for the number of HIV notifications in (a) Australia (b) NSW (c) VIC (d) QLD, if condoms are used in 90% of acts. All other parameter values remained at 2006 levels.



6.5 Changes in testing rates

30% OF MSM TEST FOR HIV EACH YEAR

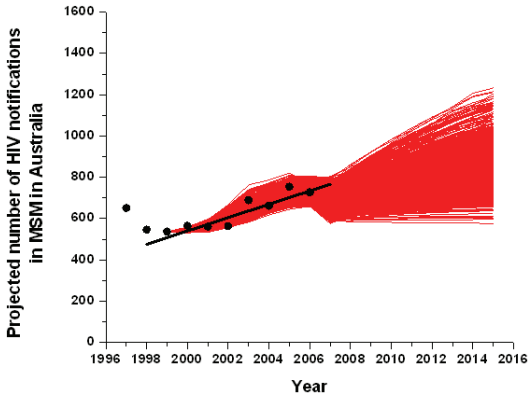
Figure 6.13: Projections to 2015 for the number of HIV notifications in (a) Australia (b) NSW (c) VIC (d) QLD, if MSM testing rates are 30% per year. All other parameter values remained at 2006 levels.



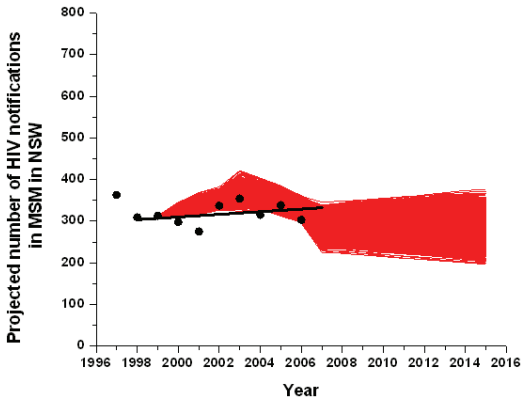
50% OF MSM TEST FOR HIV EACH YEAR

Figure 6.14: Projections to 2015 for the number of HIV notifications in (a) Australia (b) NSW (c) VIC (d) QLD, if MSM testing rates are 50% per year. All other parameter values remained at 2006 levels.

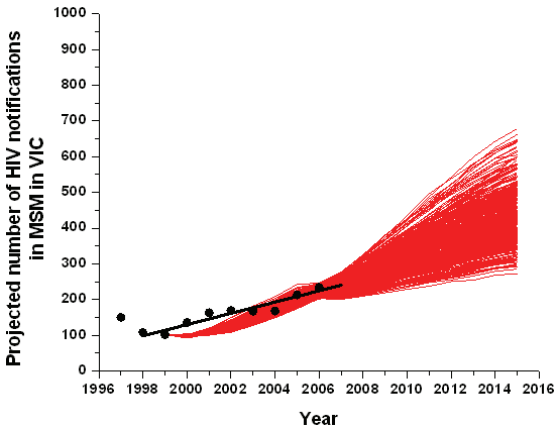
(a)



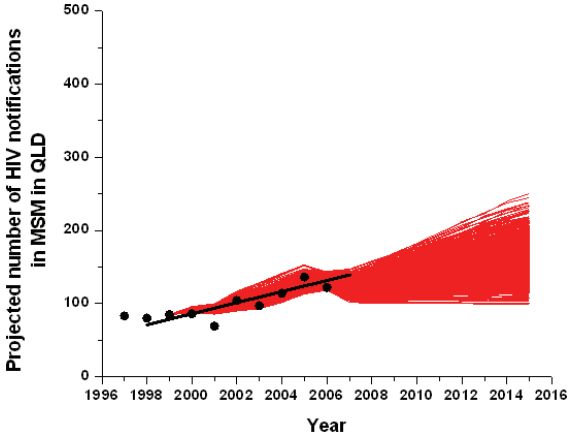
(b)



(c)



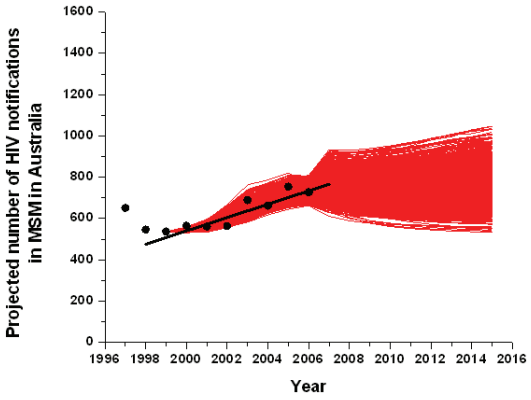
(d)



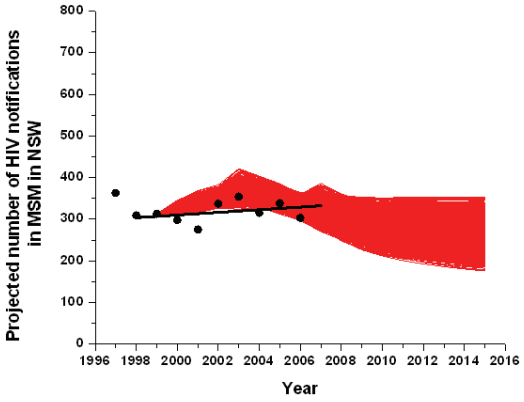
70% OF MSM TEST FOR HIV EACH YEAR

Figure 6.15: Projections to 2015 for the number of HIV notifications in (a) Australia (b) NSW (c) VIC (d) QLD, if MSM testing rates are 70% per year. All other parameter values remained at 2006 levels.

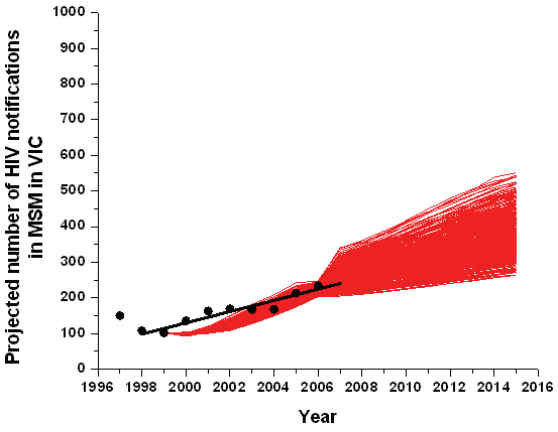
(a)



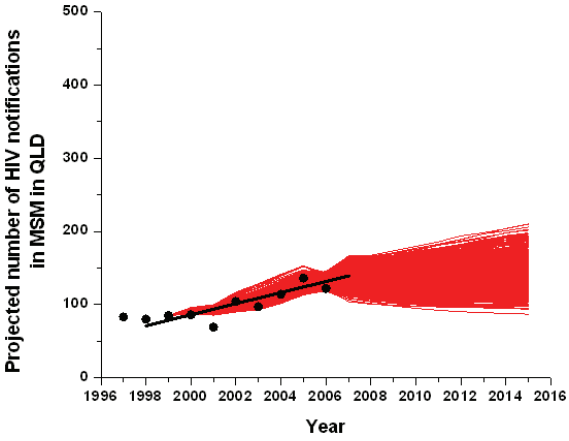
(b)



(c)

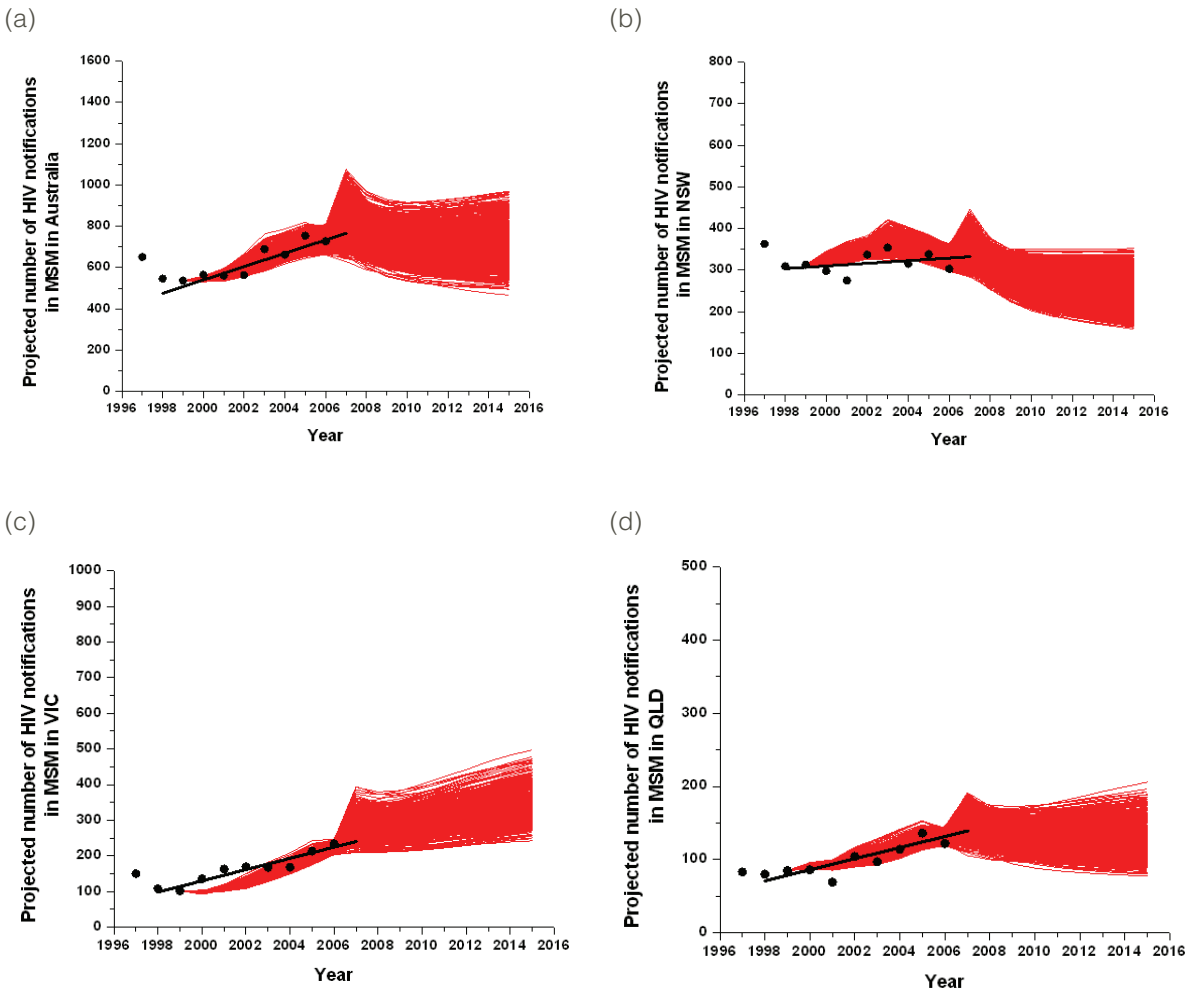


(d)



90% OF MSM TEST FOR HIV EACH YEAR

Figure 6.16: Projections to 2015 for the number of HIV notifications in (a) Australia (b) NSW (c) VIC (d) QLD, if MSM testing rates are 90% per year. All other parameter values remained at 2006 levels.



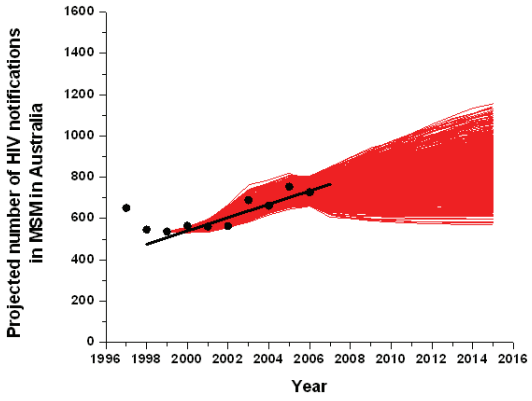
6.6 Treating primary infection

We conducted simulations for the scenarios of immediately treating 30%-90%, in 10% increments, of MSM diagnosed in primary infection (see Table 6.1). But since the results do not vary substantially for these cases we only present figures for the low (30% (Fig. 6.26)) and high (90% (Fig. 6.27)) treatment. These results suggest that public health interventions aimed at encouraging early treatment during primary infection may be effective at reducing transmission. However, the extent to which targeting primary infection is viable is currently uncertain and the potential detrimental consequences to infected individuals commencing treatment from primary infection stage are not well established. Additionally, some individuals diagnosed during primary infection will be manifesting symptoms of seroconversion illness and thus may be less likely to pose a transmission threat. It may therefore be more appropriate to focus attention on interventions which strengthen early HIV diagnosis, primarily through increased rates of testing (see section 6.5).

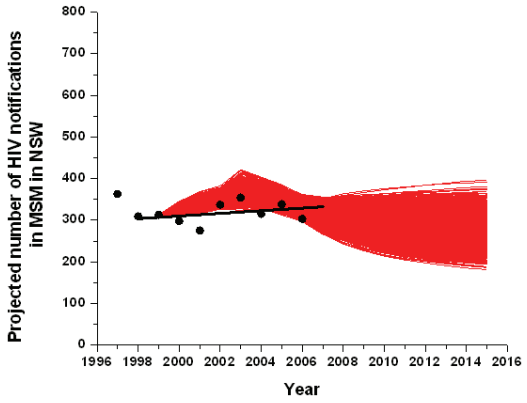
TREATING 30% OF MSM DIAGNOSED IN PRIMARY INFECTION

Figure 6.17: Projections to 2015 for the number of HIV notifications in (a) Australia (b) NSW (c) VIC (d) QLD, if 30% of MSM diagnosed in primary infection commence therapy. All other parameter values remained at 2006 levels.

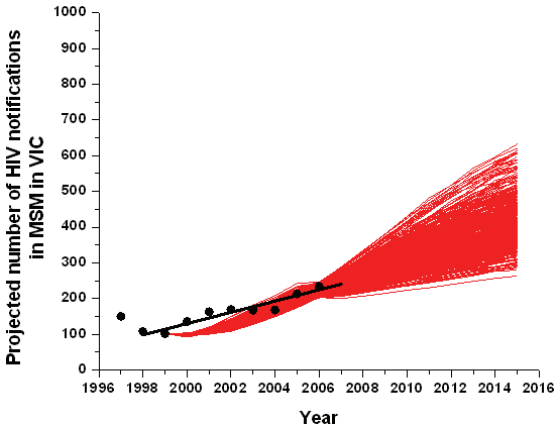
(a)



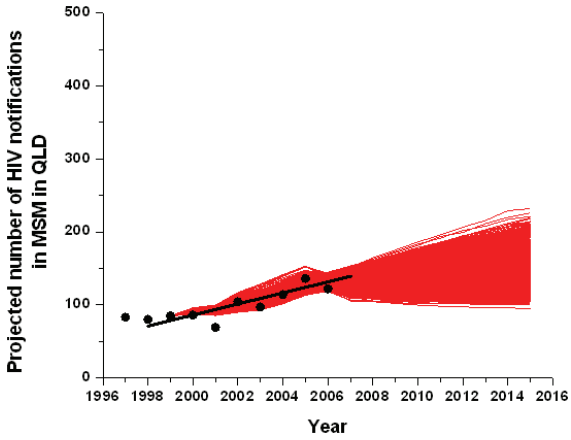
(b)



(c)



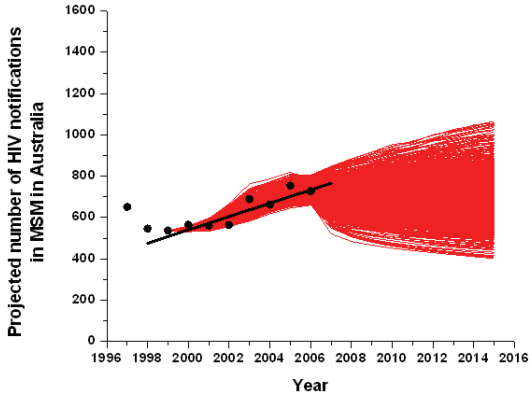
(d)



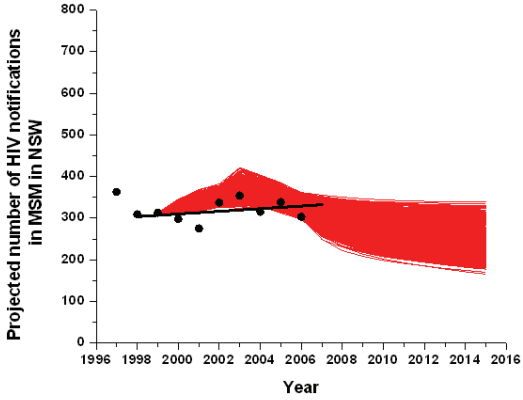
TREATING 90% OF MSM DIAGNOSED IN PRIMARY INFECTION

Figure 6.18: Projections to 2015 for the number of HIV notifications in (a) Australia (b) NSW (c) VIC (d) QLD, if 90% of MSM diagnosed in primary infection commence therapy. All other parameter values remained at 2006 levels.

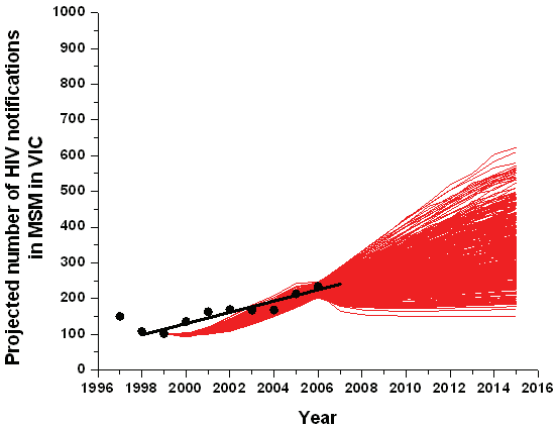
(a)



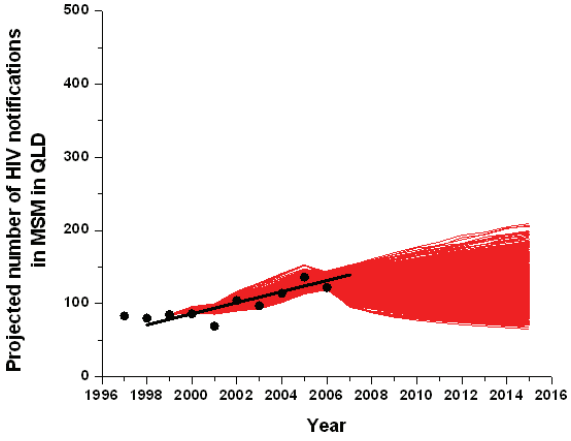
(b)



(c)



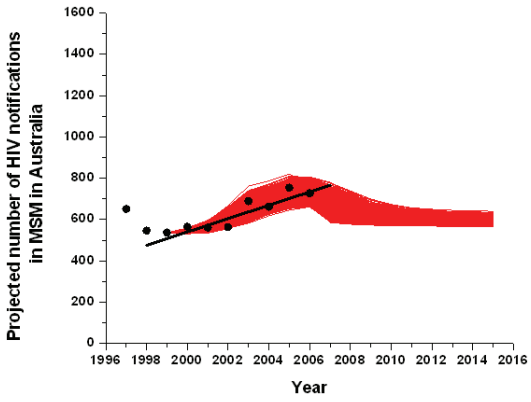
(d)



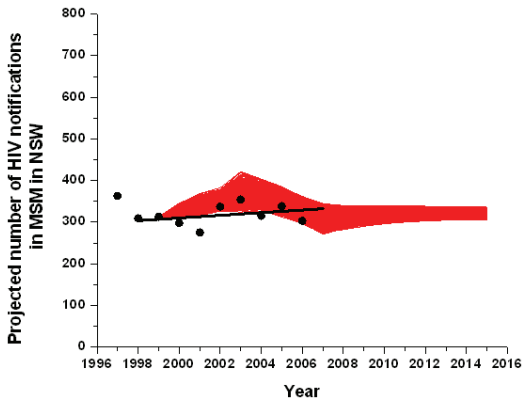
6.7 All parameters return to 1999 levels

Figure 6.19: Projections to 2015 for the number of HIV notifications in (a) Australia (b) NSW (c) VIC (d) QLD, if all parameters return to 1999 levels.

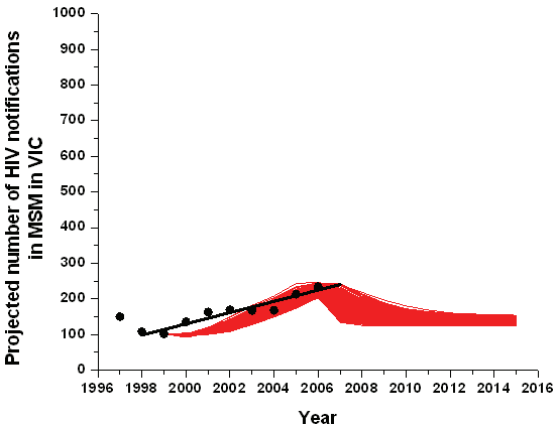
(a)



(b)



(c)



(d)

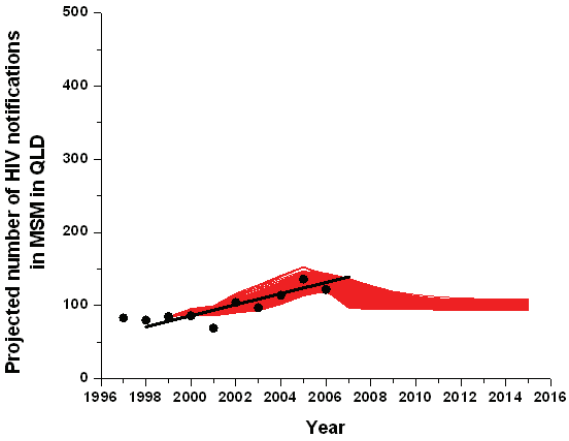


Table 6.1: Summary of the projected number of HIV notifications in MSM per year at 2006: Nationally and in NSW, VIC, QLD according to various scenarios (Interquartile range)

Scenario		National	NSW	VIC	QLD
HIV notifications in 2006		725	303	234	122
All factors remain at their 2006 levels		786 (720,871)	266 (241,292)	406 (363,460)	146 (132,165)
All factors continue on their current trends		1063 (889, 1275)	243 (206, 286)	250 (174, 389)	254 (202, 312)
Prevalence of other STIs	5%	200 (169, 232)	138 (121, 159)	37 (30, 45)	33 (28, 40)
	10%	240 (204, 284)	165 (146, 189)	44 (36, 54)	40 (34, 50)
	20%	335 (283, 406)	228 (198, 263)	59 (48, 73)	57 (46, 72)
	30%	447 (372, 564)	297 (256, 359)	78 (63, 97)	76 (62, 101)
	40%	583 (476, 756)	379 (318, 468)	100 (79, 129)	100 (81, 134)
	50%	742 (587, 984)	472 (383, 588)	126 (97, 168)	130 (100, 176)
	60%	923 (713,1252)	573 (455, 713)	154 (117, 213)	163 (123, 226)
	70%	1127 (853, 1555)	680 (533, 838)	186 (140, 265)	204 (150, 287)
Condom usage	30%	1108 (1000, 1236)	353 (323, 390)	592 (533, 666)	201 (178, 228)
	40%	1017 (918, 1127)	329 (300, 363)	544 (489, 612)	182 (162, 208)
	50%	932 (842, 1028)	306 (277, 336)	495 (448, 561)	165 (148, 186)
	60%	843 (766, 929)	282 (256, 311)	451 (405, 511)	148 (133, 167)
	70%	757 (694, 838)	259 (235, 286)	404 (362, 458)	132 (120, 149)
	80%	678 (620, 752)	236 (213, 260)	361 (319, 406)	117 (106, 133)
	90%	601 (550, 670)	213 (192, 236)	318 (277, 357)	103 (92, 116)
Testing rates (MSM tested per year)	30%	962 (853, 1083)	306 (280, 337)	496 (423, 583)	182 (160, 208)
	40%	894 (802, 994)	291 (266, 321)	456 (396, 531)	167 (149, 191)
	50%	834 (757, 927)	278 (253, 306)	423 (372, 482)	156 (140, 177)
	60%	788 (721, 873)	269 (243, 294)	394 (356, 444)	147 (132, 166)
	70%	753 (688, 830)	260 (235, 286)	374 (341, 415)	140 (126, 158)
	80%	727 (663, 802)	252 (228, 278)	357 (328, 396)	135 (121, 151)
	90%	706 (641, 779)	246 (222, 272)	345 (317, 380)	130 (116, 146)
Treating in primary infection	30%	808 (735, 894)	271 (245, 299)	409 (364, 462)	149 (135, 170)
	40%	783 (715, 869)	267 (242, 294)	393 (346, 450)	144 (130, 164)
	50%	760 (693, 841)	262 (238, 288)	379 (331, 438)	139 (125, 159)
	60%	739 (672, 817)	258 (235, 283)	361 (313, 430)	134 (120, 155)
	70%	722 (651, 797)	253 (230, 278)	345 (294, 421)	129 (115, 150)
	80%	702 (630, 781)	248 (227, 273)	333 (279, 412)	126 (111, 146)
	90%	686 (608, 766)	243 (223, 269)	322 (264, 403)	122 (106, 143)
Parameters return to 1999 levels		593 (583, 604)	316 (320, 324)	136 (132, 140)	99 (97, 101)

6.8 Comparison of scenarios

Here, we compare these projection scenarios graphically for Australia and for each State in the form of bar graphs in order to clearly understand which scenarios could lead to large or small numbers of future HIV infections. Because testing rates will determine the number of notifications (as well as indirectly influencing the number of new infections) we do not present the diagnoses but the simulated number of new infections in 2006 compared with the simulated number of new infections in 2015 according to each scenario.

Figure 6.20: Bar graph of the simulated number of infections in 2006 in Australia compared with the projected number in 2015 according to various scenarios. Median values are shown. For comparative purposes the dashed red line is the estimated level of new HIV infections in 2006 and the dashed orange line is the projected number of HIV infections in 2015 if all factors remain constant at their 2006 levels.

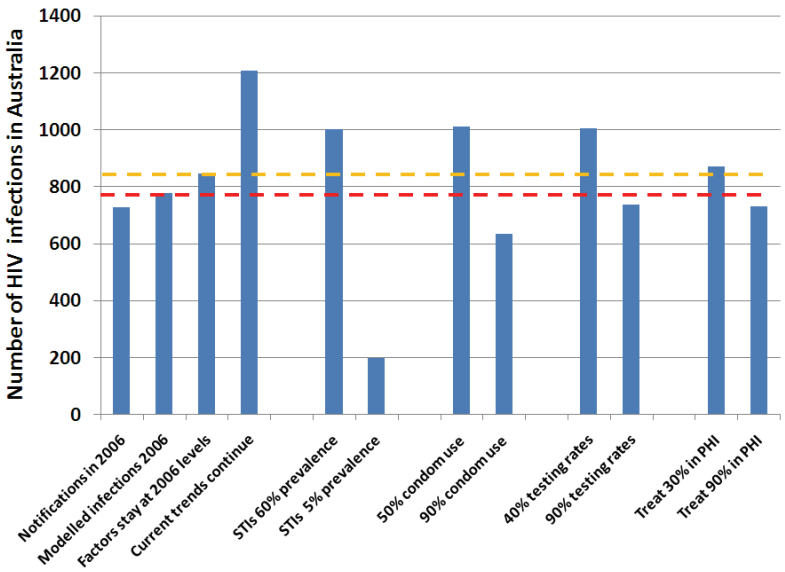


Figure 6.21: Bar graph of the simulated number of infections in 2006 in NSW compared with the projected number in 2015 according to various scenarios. Median values are shown. For comparative purposes the dashed red line is the estimated level of new HIV infections in 2006 and the dashed orange line is the projected number of HIV infections in 2015 if all factors remain constant at their 2006 levels.

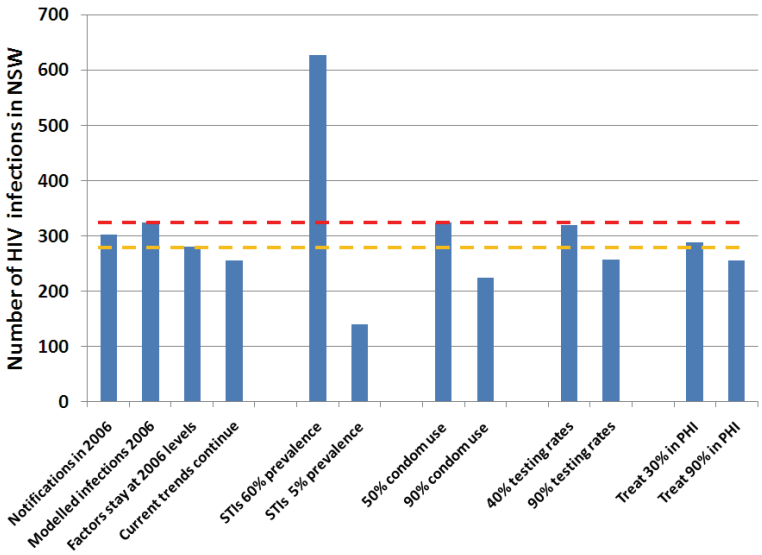


Figure 6.22: Bar graph of the simulated number of infections in 2006 in VIC compared with the projected number in 2015 according to various scenarios. Median values are shown. For comparative purposes the dashed red line is the estimated level of new HIV infections in 2006 and the dashed orange line is the projected number of HIV infections in 2015 if all factors remain constant at their 2006 levels.

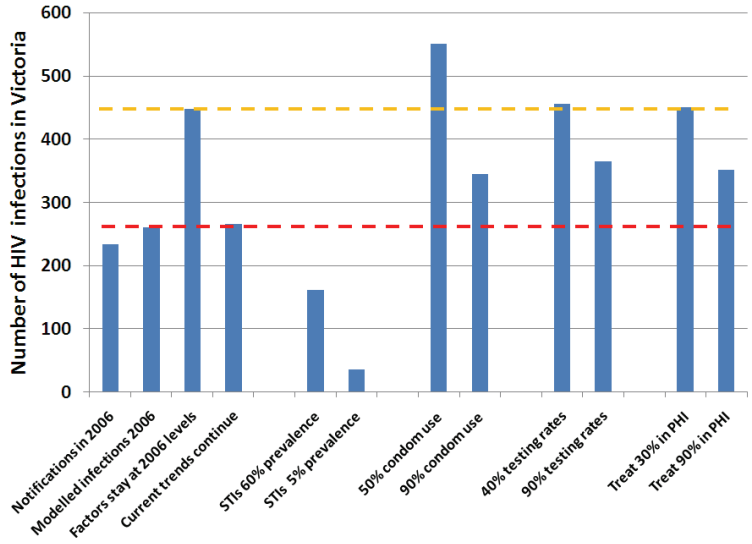
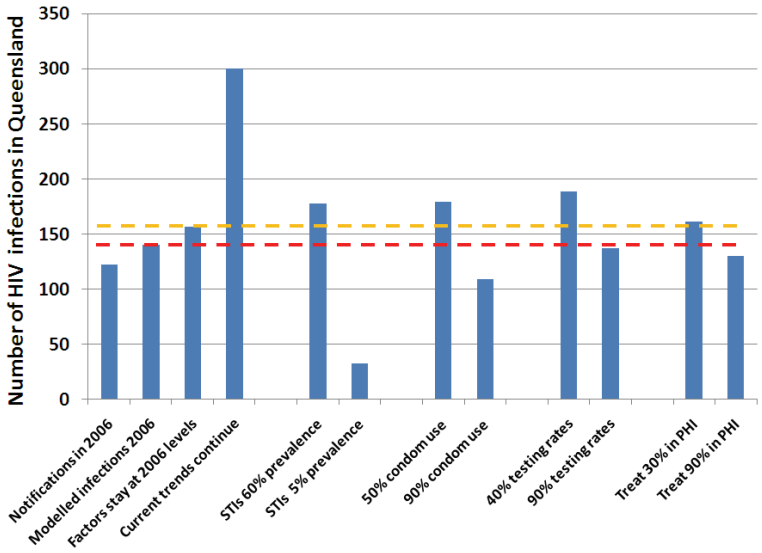


Figure 6.23: Bar graph of the simulated number of infections in 2006 in QLD compared with the projected number in 2015 according to various scenarios. For comparative purposes the dashed red line is the estimated level of new HIV infections in 2006 and the dashed orange line is the projected number of HIV infections in 2015 if all factors remain constant at their 2006 levels.



Chapter 7: Back-projection estimates of HIV incidence

7.1 Background

To assess whether the observed increases in HIV notifications truly reflect increases in underlying HIV incidence, we conducted an independent analysis using statistical back-projection modelling techniques. In Australia, HIV is monitored through notification of cases of newly diagnosed HIV infection, including cases with evidence of newly acquired HIV infection, and notification of AIDS diagnoses. In this chapter, we used a modified back-projection method which links these data sources to estimate HIV incidence in MSM, for all Australia, and by three largest States, New South Wales, Victoria and Queensland.

7.2 Data

Analyses were based on the following data sources :

- HIV surveillance data :
  - First HIV positive diagnoses by year of diagnosis,
- Newly acquired HIV infection:
  - Recent infections among new HIV diagnoses with evidence of a prior negative test or a diagnosis of primary HIV infection or an indeterminate western blot within 12 months of HIV diagnosis.
- AIDS case reporting surveillance data:
  - Based on physicians' reporting on diagnoses of clinical events subject to AIDS Case Definition

It is assumed that all people infected with HIV in Australia are eventually diagnosed with HIV, either close to infection and be reported as newly acquired HIV, later during chronic HIV infection and be notified as a new HIV diagnosis, or much later during infection at the onset of clinical symptoms close to a diagnosis of AIDS.

To be consistent with the transmission modelling, back-projection analyses were limited to HIV infections reported to be acquired through male homosexual contact. Back-projection analyses were performed for all of Australia, and then for NSW, Victoria and Queensland separately.

7.3 Modified back-projection approach

The Back-projection method was originally proposed by Brookmeyer and Gail and used in western countries in the late 1980's and early 1990's to estimate trends in HIV infections based on reported AIDS diagnoses (59). This methodology used data on reported AIDS cases, combined with an assumed rate at which people progress from HIV infection to AIDS diagnosis (the incubation period), to estimate the most likely pattern of past HIV incidence.

The availability of effective antiretroviral therapies in 1997 has altered the distribution of the incubation period in ways that are difficult to quantify. As a result, an application of the method to current AIDS diagnosis data is unlikely to give reliable estimates of HIV infection rates. Some researchers (60) have modified the incubation function to account for the treatment effect, but this approach has generally been unsuccessful because of the difficulty in capturing the complexity of treatment regimens and their effects. Others (61) have incorporated HIV diagnosis data into the back-projection method to improve the reliability of estimation.

The modified back-projection method used in this study is based on a parametric formulation of the duration of time between the time of acquisition of HIV infection and the time of earliest diagnosis of HIV infection through laboratory confirmed testing. This distribution is estimated through the combination of two separate progression rate sub-models.

SUB-MODEL 1: HIV TESTING DURING ASYMPTOMATIC INFECTION

It is assumed that a proportion of people infected with HIV will be diagnosed with HIV prior to clinical symptoms or AIDS. A heterogeneously mixed exponential model was used to model the rate at which people in this group are diagnosed with HIV. Each individual in this group was assumed to have a constant testing rate that varies across individuals. The duration between HIV infection and HIV diagnosis was assumed to have a distribution with decreasing hazard function of the Pareto form. This distribution forms a decreasing step function of the probability of diagnosis over time form infection. The assumed hazard can be used to model the proportion of new HIV diagnoses that are reported to be newly acquired in each year.

SUB-MODEL 2: HIV TESTING DRIVEN BY CLINICAL SYMPTOMS AT LATE STAGE OF HIV PROGRESSION

A proportion of HIV diagnoses are assumed to be made at a late stage of HIV infection, essentially as a result of clinical symptoms close to or at AIDS diagnosis. For this group, we assumed that the progression from HIV infection to the earliest HIV diagnosis follows a distribution similar to the progression to CD4 counts of <200cells/μL without any treatment. A Weibull distribution was adopted, with median time to HIV diagnosis of 6.5 years and shape parameter 2.08 (62). In a Weibull distribution the hazard increases with increasing time from diagnosis, which intuitively mirrors the risk of progression to HIV-related symptoms in untreated HIV infection.

OVERALL RATE OF PROGRESSION TO HIV DIAGNOSIS

The overall rate of progression to HIV diagnosis was then based on combining the two progression rate distributions described above. Combining these two distributions results in an overall “bath-tub” shaped hazard, with a relatively high rate of HIV diagnosis in the first year following HIV infection, which then decreases over time, before increasing again as clinical symptoms appear. The combination of the two distributions is allowed to vary over time, essentially in a manner so that the proportion of diagnoses due to clinical symptoms decreases with time. Finally, the combination of the two distributions is left-truncated at 1985, prior to which HIV testing itself was unavailable in Australia and HIV diagnosis was only made on the basis of AIDS symptoms.

The HIV incidence curve was then re-constructed by combining two back-projection estimated HIV incidence curves from AIDS diagnostic data (up to 1994 prior to which effective antiretroviral treatment was not available) and HIV diagnostic data using the combined progression rate distribution.

Software for this methodology, written in the R language, is available, together with further technical and methodological information (contact authors of this report for details).

7.4 Results

Back-projection estimates of HIV incidence in MSM, along with the model predicted HIV and AIDS diagnoses, for all Australia and for NSW, Victoria and Queensland individually are summarised in Figures 7.1-7.4 respectively.

Over all Australia (Figure 7.1), the back-projection analyses suggest a peak in HIV incidence in MSM at over 2000 new infections in the early 1980s followed by a rapid decline to a nadir a little under 500 new infections in the early 1990s. This is in broad agreement with previous, conventional back-projections (63, 64). HIV incidence was then estimated to increase gradually thereafter. Back-projection analyses by State suggest that HIV incidence was largely consistent with the observed pattern of HIV diagnoses. In NSW, HIV incidence in MSM is estimated to be stable during 2001-2005 (Figure 7.2), while consistent increases in in HIV incidence from 1998 onwards are estimated for both Victoria and Queensland (Figures 7.3 and 7.4 respectively).

These back-projection analyses estimate that to the end of 2006 a total of 19,686 men have been infected with HIV through male homosexual sex, of whom 13% were estimated to have not been diagnosed with their HIV infection (Table 7.1). The model estimated that a total of 9,629 and 4,725 men have been infected through male homosexual sex in New South Wales and Victoria respectively, of whom 10% of the infections have not been diagnosed in each State. A total of 4,725 men were estimated to be infected through male homosexual sex in Queensland and 16% of the infections were estimated to have not been diagnosed.

Australia has an established national surveillance system to monitor newly acquired HIV infections. These are defined as either newly diagnosed HIV infections with either a negative or indeterminate antibody test result or as a diagnosis of seroconversion illness within one year prior to HIV diagnoses. For individuals with negative or indeterminate antibody test results within one year prior to HIV diagnosis, the actual infection time could thus be much closer to the date of HIV diagnosis. The same argument applies to individuals with diagnosis of seroconversion illness within one year prior to HIV diagnoses. The theoretical link between these kind of data along with the HIV diagnoses produces additional estimates regarding the proportion of people who were diagnosed in a selected year and were also estimated to be infected in that year. Table 7.2 presents the results for the time period of 2000-2006. For example, 634 MSM (all regions) were estimated to be newly diagnosed in 2006, of whom 39% of them were also estimated to be infected within the previous year.

Figure 7.1: The estimated number of HIV infections, diagnoses and AIDS cases by year (1981-2006) based on back-projection model predictions for Australian MSM.

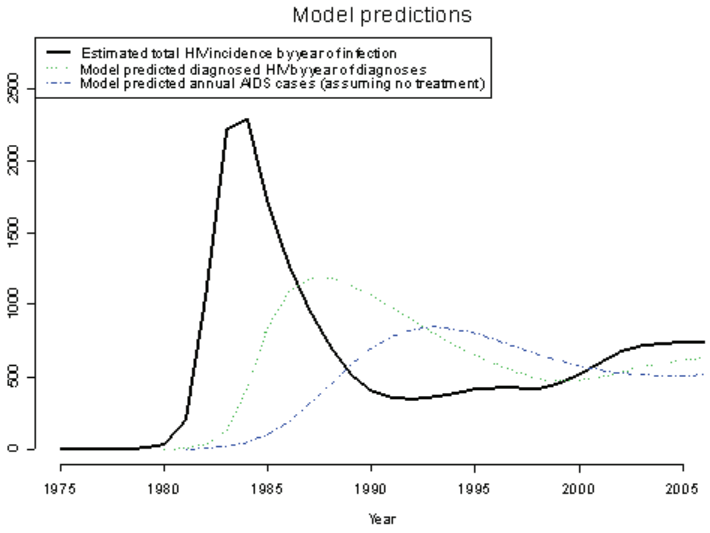


Figure 7.2: The estimated number of HIV infections, diagnoses and AIDS cases by year (1981-2006) based on back-projection model predictions for MSM in NSW.

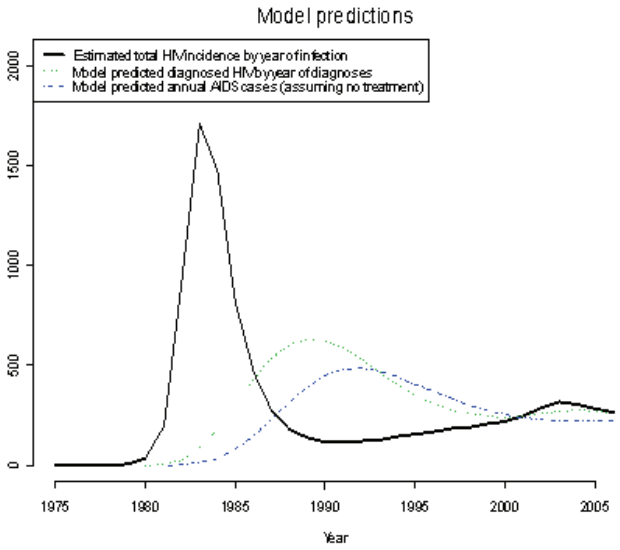


Figure 7.3: The estimated number of HIV infections, diagnoses and AIDS cases by year (1981-2006) based on back-projection model predictions for MSM in Victoria.

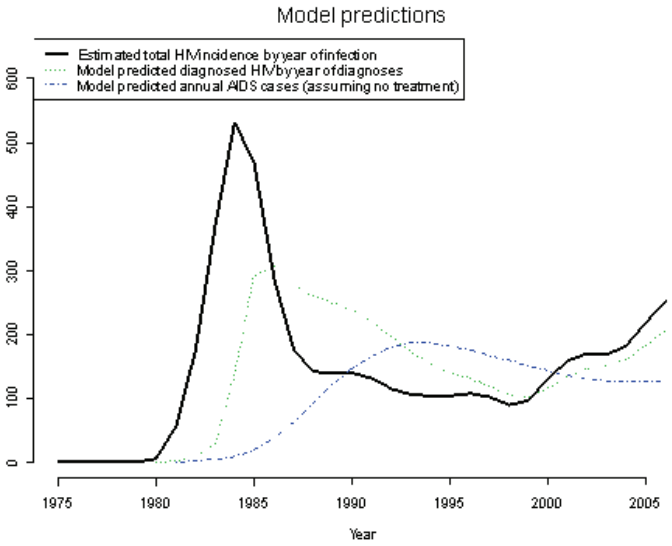


Figure 7.4: The estimated number of HIV infections, diagnoses and AIDS cases by year (1981-2006) based on back-projection model predictions for MSM in Queensland.

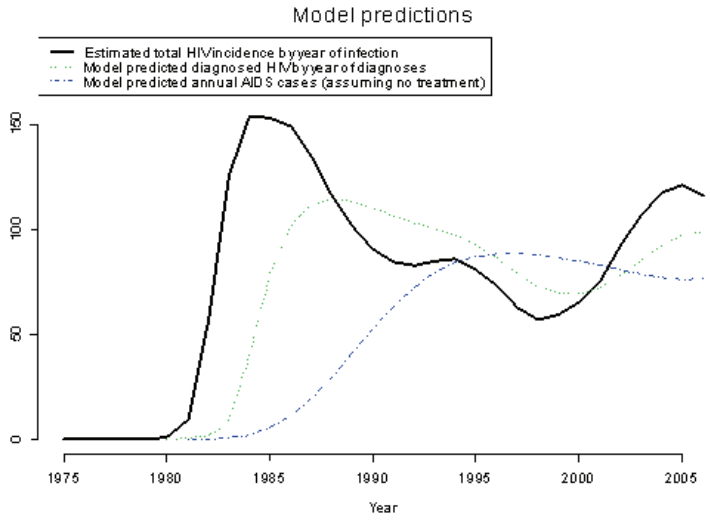


Table 7.1: Back-projected number of HIV infections in MSM, and estimated percentage of infections not diagnosed, according to time periods: before 1990, 1990-2000. 2000-2006, and for all Australia, and for NSW, Victoria, and Queensland

	Model based Estimates Back-projected HIV infections				
Population	**Before 1990**	**1990-2000**	**2000-2006**	**Total**	**% infections not diagnosed yet**
MSM – All regions	11381	3574	4731	19,686	13%
MSM – NSW	6312	1397	1920	9,629	10%
MSM – Queensland	1092	672	693	2457	16%
MSM – Victoria	2352	1091	1282	4,725	10%

Table 7.2: Model estimated new HIV diagnoses and % new diagnoses estimated to be recently acquired 2000-2006 for all MSM in Australia, and for New South Wales, Victoria, and Queensland.

Calender year		MSM – All regions	MSM – NSW	MSM – VIC	MSM – QLD
2000	Newly diagnosed infections in 2000	474	242	116	69%
	New diagnoses estimated to be infected in 2000	36%	29%	57%	33%
2001	Newly diagnosed infections in 2001	499	246	135	72%
	New diagnoses estimated to be infected in 2001	40%	33%	59%	38%
2002	Newly diagnosed infections in 2002	535	260	146	78%
	New diagnoses estimated to be infected in 2002	42%	38%	58%	43%
2003	Newly diagnosed infections in 2003	567	272	151	85%
	New diagnoses estimated to be infected in 2003	42%	39%	55%	45%
2004	Newly diagnosed infections in 2004	593	274	160	92%
	New diagnoses estimated to be infected in 2004	41%	38%	56%	46%
2005	Newly diagnosed infections in 2005	616	269	183	97%
	New diagnoses estimated to be infected in 2005	40%	36%	60%	45%
2006	Newly diagnosed infections in 2006	634	261	208	99%
	New diagnoses estimated to be infected in 2006	39%	34%	61%	42%

7.5 Discussion of back-projection results

The back-projection analyses presented in this chapter suggest that the differences between NSW and Victoria and Queensland in trends in HIV diagnoses in MSM reflect underlying differences in HIV incidence. HIV incidence was estimated to have been generally flat in NSW, but to have consistently increased in Victoria and Queensland since 1998. The analyses estimated that 13% of all MSM infected with HIV in Australia were undiagnosed with their infection at the end of 2006.

The modified back-projection method used in this study is the first time in Australia that data on newly acquired infections along with HIV diagnosis data and AIDS cases (up to 1994) have been used. This observed data represents percentages of recent actual infections among those who are newly tested HIV positive for a selected diagnostic year. The back-projection model based on HIV diagnostic data and recent infections also yields a useful relational matrix to determine the percentage of newly diagnosed infections in a given year that are estimated to be infected in that year.

Back-projection analyses do have limitations, chiefly in the assumptions required to generate a rate of progression from HIV infection to diagnosis. Although this rate of progression was allowed to vary over time, it was assumed to be in an increasing manner. Furthermore, although the relationship between newly acquired HIV, HIV diagnosis and AIDS is to some extent exploited in generating the progression rate distribution, it is not possible for external information, for example rates of HIV testing, to be built into the models using the current formulation.

One advantage of back-projection analyses is that they provide a completely independent, statistical method for estimating HIV incidence that can be the compared with results from mathematical models. Both back-projection models and transmission mathematical models are based on a number of uncertain, but different, assumptions. The extent to which these very different approaches agree provides some corroboration of results.

Overall, this approach produced promising results for obtaining HIV incidence estimates by combining HIV and AIDS notifications to maximise the data available from an established national surveillance system. These results were also consistent with the results from the mathematical modelling approach as well as with observed pattern of HIV diagnoses amongst MSM in Australia in recent years.

Chapter 8: Recommendations for future data collection

Mathematical models of epidemiology heavily rely on the behavioural, social, epidemiological, clinical, and biological data available. They are only as good as the quality of input data provided. For this report we have sufficient data accessible for model inputs. But if the data is biased, particularly if trends in data over time are not truly reflective of the real world population, then this will directly bias the results and implications of the model. We have incorporated uncertainty analyses, with each parameter sampled over appropriate ranges given the data available. But some parameters used in the model were based on assumptions and inferences from expert opinion, intuition, or interpretation of non-optimal data sources. We recommend that collection of future data include the following information in order to maximise the use of mathematical modelling:

- The average number of casual sex partners MSM have per month in which there is penile-anal intercourse
- The average number of insertive/receptive acts per casual partnership
- Frequency of anal intercourse acts with regular partners
- Average duration of regular relationships
- The approximate percentage of insertive/receptive acts with casual partners in which condoms are used
- The proportion of new sexual partnerships that form on the basis of serosorting (disclosure of serostatus as a means of establishing seroconcordant partnerships)
- The proportion of regular sexual partnerships in which disclosure of serostatus is carried out in negotiating protection
- How behaviour changes post-diagnosis of HIV infection and upon commencement of antiretroviral therapies
- Average compliance of MSM to ART drug regimens
- Prevalence (not just incidence) of other STIs that are thought to amplify HIV incidence; e.g. infectious Syphilis, HSV-2, and other genital ulcer diseases
- Patterns of treatment decisions based on disease progression and how these patterns change with time
- Degree of assortativity or disassortativity with regards to age-mixing of sexual partners
- Information on the underlying sexual network; for example,
  - the proportion of MSM with concurrent partnerships as opposed to serial relationships
  - the average rate of partner change
  - the duration of time between serial relationships
  - behaviour and known sexual contacts of interviewees partner(s)

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Appendix: Description of mathematical transmission modelling methods

A.1 Model assumptions and parameter estimates

The transmission model is formulated at the population-level; that is, it does not track individual people but rather the change in the number of people in various compartments related to their diagnoses/ treated or HIV-disease status. The flows in the number of people between these compartments are due to biological, behavioural, clinical, or epidemiological parameters. Our model simulates the population of men who have sex with men (MSM) in Australia. The structure of the model is illustrated schematically in Figure A.1. We consider men who are HIV-negative to be susceptible, and denote the number of these men as S. The number of men who are infected with HIV but remain undiagnosed in primary, chronic, or AIDS stages of disease are denoted by I_P , I_C , and I_A respectively. The number of men who have been diagnosed as infected (number of notifications) with HIV and are in primary, chronic, or AIDS stage disease are denoted by I_P^N , I_C^N , and I_A^N respectively. The corresponding notation for the number of HIV-infected individuals that are treated with combination antiretroviral therapy in each disease stage is T_P , T_C , and T_A. That is, we include one compartment for the number of uninfected MSM and nine categories of HIV-infected MSM (3 disease stages each for undiagnosed, diagnosed, or treated individuals) for a total of ten compartments. The flows between these compartments are represented by the arrows in Figure A.1 and denoted by the various Greek symbols. We track the change in the number of people in each compartment mathematically by formulating a system of ten ordinary differential equations, one for each compartment. The parameters that drive the flow between compartments are specified in detail in Table A.1, along with available references from the epidemiological, clinical, behavioural, and biological literature. For each model parameter we explored a range of input values to account for the intrinsic heterogeneity and for the uncertainty in the parameter. We efficiently sampled over the entire parameter space and conducted detailed uncertainty and sensitivity analyses. Thus, we developed a model of homosexual transmission of HIV. The model includes HIV-infected MSM who upon diagnosis may change their sexual behaviour or may initiate treatment of disease. All infected MSM progress in their disease from primary infection to chronic infection and then to AIDS stage. In each stage we model different viral load levels, which influence differential transmission probabilities. Treated MSM have substantially lower viral load levels which also significantly slows disease progression.

Figure A.1: Schematic diagram with mathematical notation of our HIV compartmental model for MSM in Australia

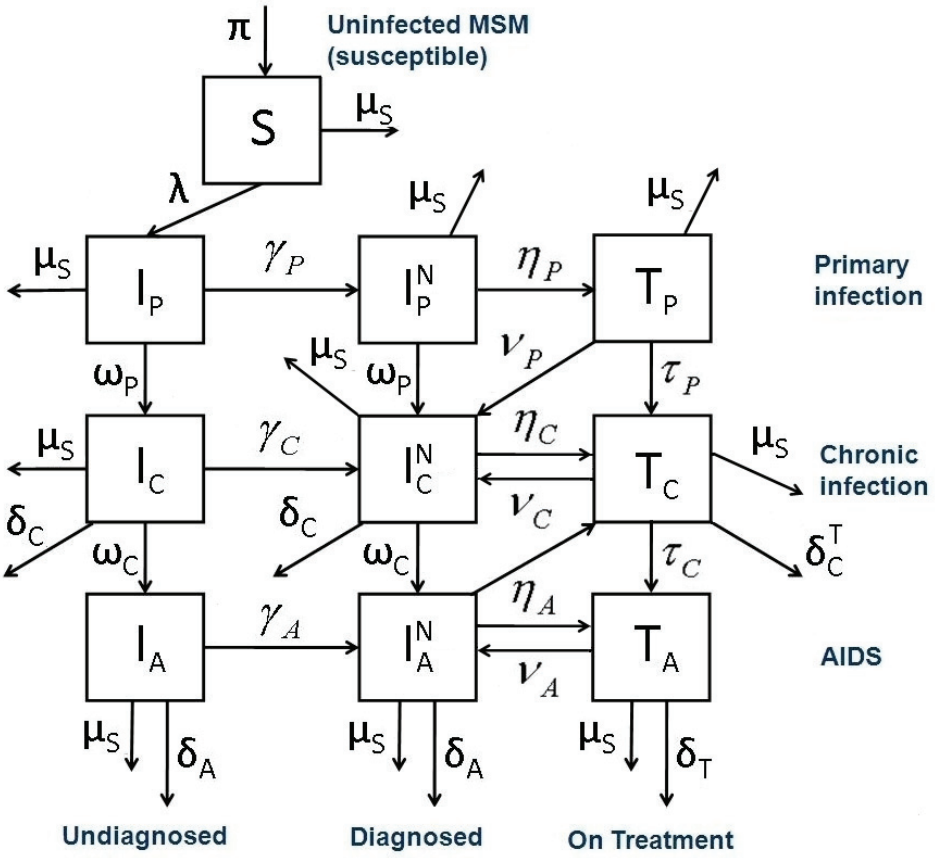


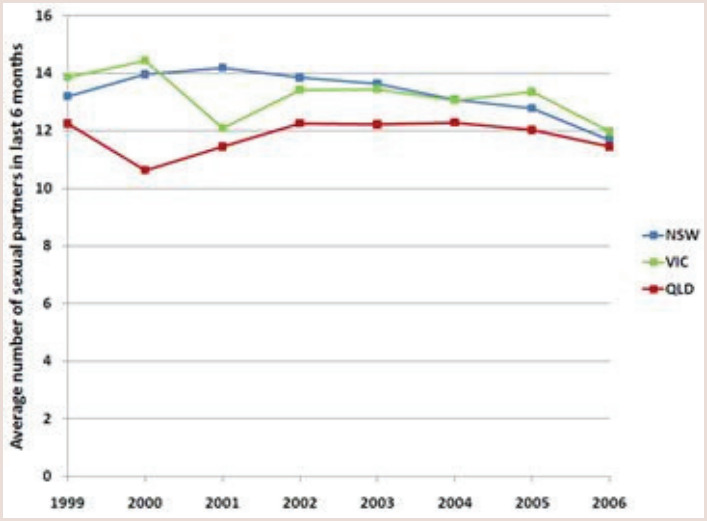
Table A.1: Definitions, ranges, and references for input parameters used in our mathematical model

Parameter	Description		Value	Ref
c	Average number of sexual partnerships per year (undiagnosed MSM)		a^*,(21, 46, 47)	
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%	(21)
f	Multiplying factor for the 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	(20-28)
p_{disclose}	Proportion of partnerships in which serostatus is disclosed (in negotiating condom usage)	Regular	0.8 – 0.9	(9 – 12)
		Casual	b^*	
p_{condom}	Proportion of acts in which condoms are used		c^*,(9, 11)	
ε	Efficacy of condom protection per act		0.85 – 0.9	(65 – 69)
W	Baseline viral load during chronic infection		10^4 – 10^5 copies/ml	(30, 32 – 34, 36)
V_{PI}	Average viral load at primary infection stage		$10^{6.5}$ – 10^8 copies/ml	(30, 32 – 35)
V_A	Average viral load at AIDS		$10^{5.5}$ – $10^{6.5}$ copies/ml	(32, 37, 38)
V_T	Average viral load in effectively treated individual		10 – 100 copies/ml	(70 – 72)
p_S	Proportion of individuals on antiretroviral therapy in which viral load is suppressed		d^*, (20, 44 – 46)	
β_C , β_C^N	Probability of HIV transmission per act from an individual in chronic stage of infection		0.0015 – 0.0025	(73 – 78)
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		e, (79)	
β_P^T , β_C^T , β_A^T	Probability of HIV transmission per act from a treated individual		e, (79, 80)	
p_{STI}	Proportion of HIV-negative MSM who have other STIs		0.05 – 0.15	f, (15, 43)
b_{STI}	The multiplicative increase in transmission probability due to the presence of other STIs		2 – 5	g, (13, 16 – 18, 81 – 83)
n_{reg}	Average number of anal intercourse acts per regular partner per week		1.6 – 2.4	(84)

n_{cas}	Average number of anal intercourse acts per casual partner (over duration of casual relationship)	1 – 2	(12, 84)
p_{test}	Proportion of MSM that test for HIV infection each year	h^*,(9)	
$1/\gamma_A$	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	(29 – 31)
$1/\omega_C$	Average time for individuals to progress from chronic infection to AIDS	8 – 12 years	(34, 37, 39 – 42)
p_P	Proportion of people diagnosed in primary infection that will commence treatment	i	
$1/\nu_P$	Average time to cease treatment for individuals with primary infection	6 – 12 months	i
p_P^C	Proportion of people who started ART in primary infection and continue ART after finishing dosing schedule	65 – 75%	i
p_C	Proportion of people in chronic infection that will commence treatment	65 – 75%	(8, 9, 11, 46)
p_A	Proportion of people with AIDS that 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	(46)
$1/\nu_A$	Average time to cease treatment for individuals with AIDS	8 – 14 years	(46)
$1/\mu$	Average time for individuals to 'retire' out of sexually active population (no longer obtaining new partners)	30 – 35 years	j,(41)
δ_C	Proportion of untreated MSM in chronic infection who die each year	1 – 2%	(85 – 89)
δ_C^T	Proportion of treated MSM in chronic infection who die each year	1 – 2%	(85 – 89)
$1/\delta_A$	Average time until death from the onset of AIDS for untreated individuals	0.5 – 1.5 years	(89 – 92)
$1/\delta_T$	Average time until AIDS-related death for individuals in AIDS stage but on ART (with treatment failure)	0.5 – 5 years	(41, 89, 91, 93 – 99)

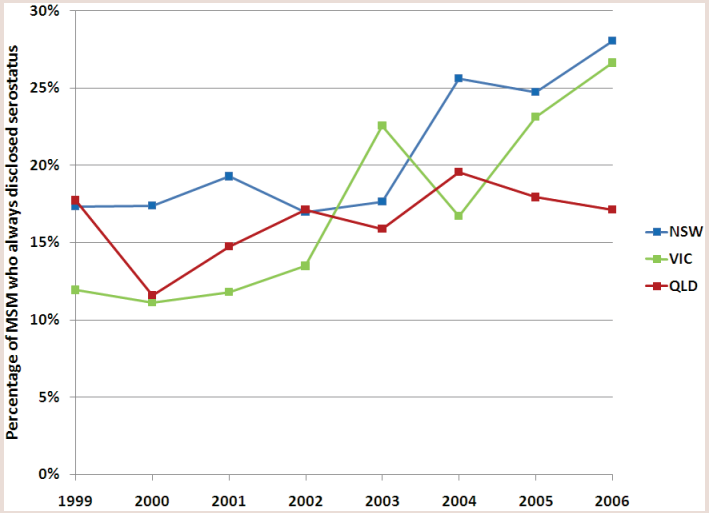
$1/\tau_C$	Average time of disease progression for treated individual with chronic infection to progress to AIDS		$1/\omega_C < 1/\tau_C < 20$	
π	Number of new susceptible individuals entering the MSM population per year (this is approximately 3-3.5% of men)	Nationally	2000 – 2500	k
		NSW/ACT	35 – 40%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

a : We use behavioural data on the proportion of men that have 0, 1, 2-10, 11-50, >50 partners to calculate a weighted average at each available time point, to obtain the following trends:

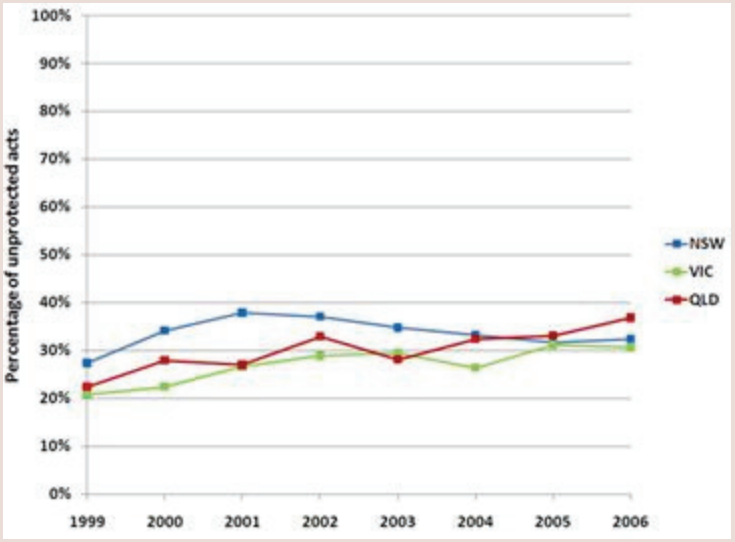


We assume that 1 partner is regular and the remaining partners are casual partners.

b : Serosorting and disclosure of serostatus are discussed in the Appendix methods section. 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 UAIC and always disclosed serostatus:

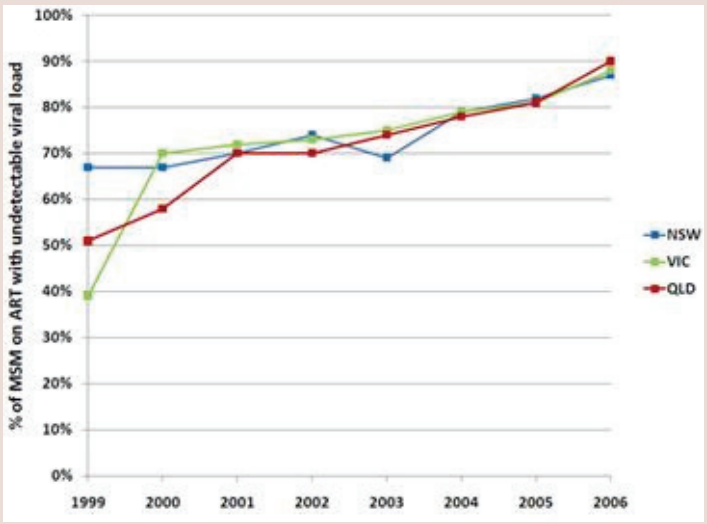


c : Condom usage will vary between types of relationships and the disclosure of HIV serostatus. For relationships in which serostatus is not ascertained we use the data from the State gay periodic surveys (9) to obtain the following trends over time:



In regular relationships that are serodiscordant we assume that average condom usage is high. Based on the Futures study (11) we assume condoms are used in 75-85% of anal intercourse acts between discordant MSM. However, in regular relationships that are seroconcordant we assume that average condom usage is relatively low; we assume condoms are used in 5-10% of acts (11). In casual relationships, serological disclosure is not as common as in regular relationships, but if the MSM in a casual relationship determine 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 $p_{\text{condom}}^{\text{reg}} < p_{\text{condom}}^{\text{cas}} < 10\%$.

d : There is evidence to suggest that the percentage of treated patients with undetectable virus has increased over time (46). This could be due to numerous factors such as greater adherence or different drug regimes. We use data from the AHOD database (46):

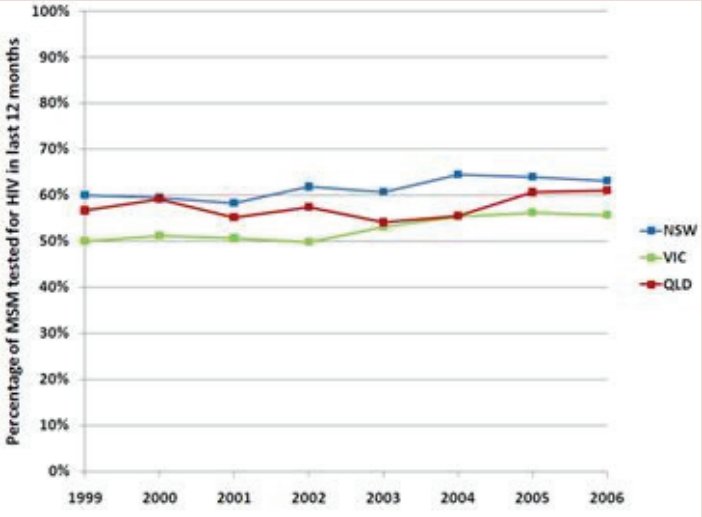


e : We use the established relationship from (79) to determine the change in transmission probability as viral load changes, namely, 2.45 $\log_{10}\left(\frac{V}{V_{CI}}\right)\beta_C$ if the viral load (V) is greater than the baseline during chronic infection (V_{CI}), and $\beta_C \Big/ \left(2.45 \log_{10}\left(\frac{V_{CI}}{V}\right)\right)$ if $V < V_{CI}$. Although this relationship was originally determined for heterosexual penile-vaginal intercourse, we use a greater baseline transmission probability for homosexual penile-anal intercourse, β_C, and assume that the same multiplicative increase in transmission holds with changes in viral load.

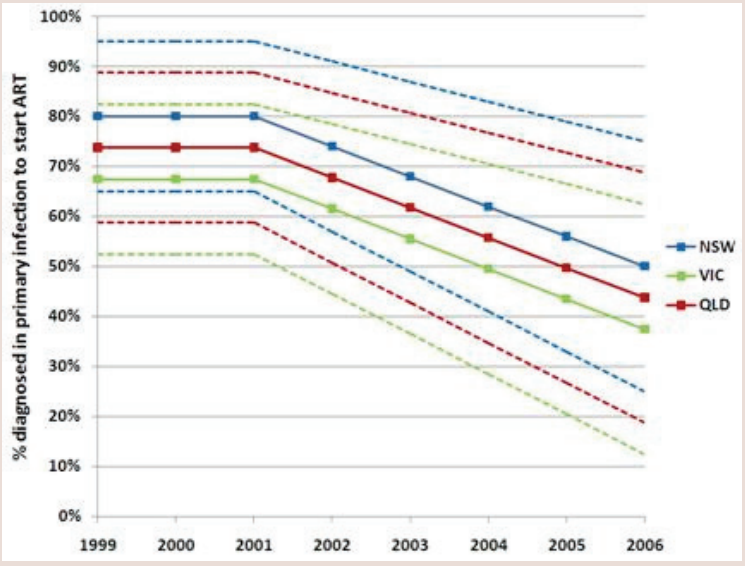
f : In order to model the impact of STIs on HIV transmission it is necessary to estimate the proportion of MSM with other STIs as well as trends over time and by State. This is problematic for a number of reasons. First, while there are indications that the prevalence of some STIs, notably syphilis, is increasing in MSM in Australia, most data is reported only as notifications, not as the proportion of tests that are positive. Furthermore, the National Centre for HIV Social Research reports significant increases in testing (10-20%) in the last few years. Second, much of the published data on STIs in MSM in Australia is from the HIM (Health In Men) study and the incidence of STIs has decreased in this Sydney-based HIV-negative cohort over the last few years. 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 HSV-2 with prevalence in the HIM cohort estimated at ~23% masking any trends that might be occurring with other STIs. 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 for which it increases HIV transmissibility is reduced. Given the uncertainty we assume that the average proportion of MSM with STIs (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 do not distinguish STI rates between States. Although there is currently no published data, the prevailing perception amongst epidemiologists and sexual health clinicians is that there has been a rise in the number of STIs in recent years. However, because the magnitude of increase is different between different STIs we do not use STI data. Our initial analyses are based on an initial uncertainty range of 5-15% but constant over time. We then investigate numerous rates of increase in the prevalence of other STIs to determine the influence of increasing STIs on the HIV epidemic.

g : There is strong evidence that both ulcerative and non-ulcerative STIs can increase the probability of HIV transmission by augmenting HIV infectiousness and susceptibility. Reciprocally, HIV infection can enhance the transmission of other STIs. This is a complex synergy and the results of several prospective studies estimate the relative risks of HIV infection due to infection with other STIS in the range 2 to 24, but largely clustering between 2 and 5. We therefore assume that the multiplicative increase in transmission probability due to concurrent infection with another STI (b_{STI}) is in the range 2 - 5.

h : Data from the Gay periodic surveys over time for the percentage of men who have sex with men who tested for HIV in the last 12 months is used as shown in the graph below:



i : We evaluated available data from primary infection cohorts of the percentage of HIV-infected MSM who commenced ART within one year of HIV diagnosis, including patients recruited to the Acute Infection and Early Disease Research Program (CORE 01) protocol established by the National Institute 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 (8)), is limited in time and only includes NSW and VIC. Sample sizes are also not sufficient (as low as 4 in some years for VIC and 6 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). We estimate the basic anecdotal trends observed over the last few years by the figure below. But since there is not 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 then 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.

j : We assume that individuals who have not been diagnosed with HIV infection, but are infected, will have the same lifetime duration (30-35 years) of sexual activity (in terms of choosing new partners) as those that are uninfected or at different disease stages (that is, $\mu_P = \mu_C = \mu_A = \mu_S$ etc). However, the number of partners chosen will differ between some disease stages.

k : This leads to approximately 150,000-175,000 MSM nationally. The proportion of new MSM in NSW/ACT, VIC, QLD each year as a subset of the total National number are indicated.

* For each of these time-dependent parameters we include an uncertainty range of ±5%

A.2 Transmission model equations

The mathematical model for the dynamic transmission model is represented by ten ordinary differential equations, one equation for each of the compartments shown in Figure A.1. The mathematical description of our schematic model is described here, each equation in turn.

Individuals enter the susceptible MSM population (S) at a rate of π per year. These individuals enter into the 'pool' of male homosexual activity, choosing sexual partners from the population. On average they leave the population of 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. Individuals newly infected with HIV will be in primary infection stage and undiagnosed (I_P). Then, the rate of change in the total number of susceptible men at time t is given by

$$\frac{dS}{dt} = \overbrace{\pi}^{\text{Entry into sexually active population}} - S(t)\left(\overbrace{\mu}^{\text{Leave sexually active population}} + \overbrace{\lambda(t)}^{\text{Force of HIV infection}} \right).$$

Here, the left hand side of this equation is the time derivative of S (representing the rate of change in the number of susceptible men). The right hand side of the equation specifies what influences the change in the number of susceptible MSM.

Once an individual has become infected with HIV, he will initially enter the undiagnosed primary infection compartment (I_P). Thus, the number of MSM that 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 of HIV serostatus at a health centre (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

$$\frac{dI_P}{dt} = \overbrace{\lambda(t)S(t)}^{\text{New infections per year}} - I_P(t)\left(\overbrace{\mu}^{\text{Leave sexually active population}} + \overbrace{\gamma_P}^{\text{Become diagnosed with HIV}} + \overbrace{\omega_P}^{\text{Progress to chronic infection}} \right).$$

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

$$\frac{dI_C}{dt} = \overbrace{\omega_P I_P(t)}^{\text{Progress from primary infection}} - I_C(t)\left(\overbrace{\mu}^{\text{Leave sexually active population}} + \overbrace{\gamma_C}^{\text{Become diagnosed with HIV}} + \overbrace{\omega_C}^{\text{Progress to AIDS}} + \overbrace{\delta_C}^{\text{Death rate}}\right)$$

and

$$\frac{dI_A}{dt} = \overbrace{\omega_C I_C(t)}^{\text{Progress from chronic infection}} - I_A(t)\left(\overbrace{\mu}^{\text{Leave sexually active population}} + \overbrace{\gamma_A}^{\text{Become diagnosed with HIV}} + \overbrace{\delta_A}^{\text{AIDS-related death}}\right)$$

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.

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

$$\frac{dI_P^N}{dt} = \overbrace{\gamma_P I_P(t)}^{\text{New diagnoses}} - I_P^N(t)\left(\overbrace{\mu}^{\text{Leave sexually active population}} + \overbrace{\omega_P}^{\text{Progress to chronic infection}} + \overbrace{\eta_P}^{\text{Commence ART}}\right),$$

$$\frac{dI_C^N}{dt} = \overbrace{\gamma_C I_C(t)}^{\text{New diagnoses}} + \overbrace{\omega_P I_P^N(t)}^{\text{Progress from primary infection}} + \overbrace{\nu_C T_C(t)}^{\text{Give up ART}} + \overbrace{\nu_P T_P(t)}^{\text{Give up ART from primary infection}} - I_C^N(t)\left(\overbrace{\mu}^{\text{Leave sexually active population}} + \overbrace{\omega_C}^{\text{Progress to AIDS}} + \overbrace{\eta_C}^{\text{Commence ART}} + \overbrace{\delta_C}^{\text{Death rate}}\right),$$

and

$$\frac{dI_A^N}{dt} = \overbrace{\gamma_A I_A(t)}^{\text{New diagnoses}} + \overbrace{\nu_A T_A(t)}^{\text{Give up ART}} + \overbrace{\omega_C I_C^N(t)}^{\text{Progress from chronic infection}} - I_A^N(t)\left(\overbrace{\mu}^{\text{Leave sexually active population}} + \overbrace{\eta_A}^{\text{Commence ART}} + \overbrace{\delta_A}^{\text{AIDS-related death}}\right)$$

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 of the stages of disease. Individuals on therapy can cease therapy until a potentially 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 disease (at rates τ) and if in AIDS-stage can still die of AIDS-related illnesses at a slower rate than 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

$$\frac{dT_P}{dt} = \overbrace{\eta_P I_P^N(t)}^{\text{Commence ART}} - T_P(t)\left(\overbrace{\mu}^{\text{Leave sexually active population}} + \overbrace{\nu_P}^{\text{Give up ART (primary)}} + \overbrace{\tau_P}^{\text{Progress to chronic infection}}\right)$$

$$\frac{dT_C}{dt} = \overbrace{\eta_C I_C^N(t)}^{\text{Commence ART}} + \overbrace{\tau_P T_P(t)}^{\text{Progress from primary infection}} + \overbrace{(1-p_A)\eta_A I_A^N(t)}^{\text{Commence ART from AIDS}}$$
$$-T_C(t)\left(\overbrace{\mu}^{\text{Leave sexually active population}} + \overbrace{\nu_C}^{\text{Give up ART}} + \overbrace{\tau_C}^{\text{Progress to AIDS}} + \overbrace{\delta_C^T}^{\text{Death rate}}\right),$$

and

$$\frac{dT_A}{dt} = \overbrace{p_A\eta_A I_A^N(t)}^{\text{Commence ART}} + \overbrace{\tau_C T_C(t)}^{\text{Progress from chronic infection}} - T_A(t)\left(\overbrace{\mu}^{\text{Leave sexually active population}} + \overbrace{\nu_A}^{\text{Give up ART}} + \overbrace{\delta_T}^{\text{AIDS-related death}}\right).$$

A.3 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 attribute 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.

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 significant levels of serosorting in the MSM population in Australia. A proportion of uninfected men serosort in seeking of new partners (p_{serosort}); but the new partner may be HIV-positive but undiagnosed with infection and thus unaware of his serostatus (that is, in the compartments I_P, I_C, or I_A). New partners for serosorting HIV-negative men will be chosen from the susceptible compartment or any of the undiagnosed HIV-positive compartments. However, men in AIDS stage disease are likely to have reduced numbers of partners due to their sickness. If healthy undiagnosed and susceptible men have c partners per year then we model the number of partners per year that men with AIDS have as $\theta_{AIDS} \cdot c$, where θ_{AIDS} is a multiplying factor for the reduction in sexual activity. Thus, for men who serosort the probability of a new partner being HIV-positive is

$$\frac{I_P + I_C + \theta_{AIDS} I_A}{S + I_P + I_C + \theta_{AIDS} I_A}.$$

The remaining proportion of men, who do not serosort, could choose partners from any compartment/serostatus. However, men who have been diagnosed with HIV may change their sexual behaviour; if undiagnosed and susceptible men have c partners per year then diagnosed men have $f \cdot c$ partners per year. Here, f refers to the multiplicative increase or decrease in sexual activity. We consider both possibilities 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, for men who do not serosort the probability of a new partner being HIV-positive is

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

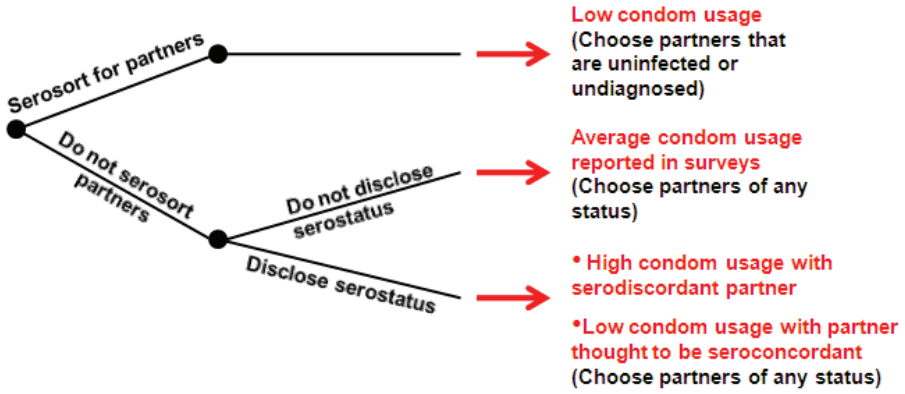
The overall average probability of a new partner being HIV-positive is then given by

$$p_{\text{serosort}} \frac{I_P + I_C + \theta_{AIDS} I_A}{S + I_P + I_C + \theta_{AIDS} I_A} + \left(1 - p_{\text{serosort}}\right) \frac{I_P + I_C + \theta_{AIDS} I_A + f\left(I_P^N + I_C^N + \theta_{AIDS} I_A^N + T_P + T_C + \theta_{AIDS} T_A\right)}{S + I_P + I_C + \theta_{AIDS} I_A + f\left(I_P^N + I_C^N + \theta_{AIDS} I_A^N + T_P + T_C + \theta_{AIDS} T_A\right)}.$$

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}. The decisions associated with disclosure and serosorting are shown in Figure A.2. 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 (11). 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 moderate 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)(11). Consequently, we simplify our model system and set $p_{\text{serosort}} = 0$, but still have the general structure in the model to allow for future studies involving non-zero serosorting. Negotiating condom use based on disclosure of serostatus is relatively common and an important aspect retained in our model.

Figure A.2: Decision tree and assumed behaviour associated with serosorting and disclosing serostatus



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 (n) and the proportion of these acts in which condoms are used (p_{condom}) to calculate the probability of transmission of infection per partnership over duration of 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 probability 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 expressed as a 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 partner per year is given by

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

This expression is valid in the case of a standard transmission probability β. But the presence of other sexually transmitted infections, both ulcerative and non-ulcerative (but particularly ulcerative), can increase the transmission probaility of HIV. Therefore, we consider the proportion of men who have other sexually transmitted 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

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

where

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

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. (79), namely,

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

where V 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_{reg}\Bigg[& p^{\text{reg}}_{\text{serosort}} \frac{\hat{\beta}^{\text{reg}\,|\,\text{low condom}}_{P} I_P + \hat{\beta}^{\text{reg}\,|\,\text{low condom}}_{C} I_C + \hat{\beta}^{\text{reg}\,|\,\text{low condom}}_{A} \theta_{AIDS} I_A}{S + I_P + I_C + \theta_{AIDS} I_A} \\
& + \left(1 - p^{\text{reg}}_{\text{serosort}}\right) p^{\text{reg}}_{\text{disclose}} \frac{\hat{\beta}^{\text{reg}\,|\,\text{low condom}}_{P} I_P + \hat{\beta}^{\text{reg}\,|\,\text{low condom}}_{C} I_C + \hat{\beta}^{\text{reg}\,|\,\text{low condom}}_{A} \theta_{AIDS} I_A}{S + I_P + I_C + \theta_{AIDS} I_A + f\left(I^N_P + I^N_C + \theta_{AIDS} I^N_A + T_P + T_C + \theta_{AIDS} T_A\right)} \\
& + \left(1 - p^{\text{reg}}_{\text{serosort}}\right) p^{\text{reg}}_{\text{disclose}} \frac{f\left(\hat{\beta}^{\text{reg}\,|\,\text{high condom}}_{P} I^N_P + \hat{\beta}^{\text{reg}\,|\,\text{high condom}}_{C} I^N_C + \hat{\beta}^{\text{reg}\,|\,\text{high condom}}_{A} \theta_{AIDS} I^N_A + \hat{\beta}^{\text{reg}\,|\,\text{high condom}}_{T} \left(T_P + T_C + \theta_{AIDS} T_A\right)\right)}{S + I_P + I_C + \theta_{AIDS} I_A + f\left(I^N_P + I^N_C + \theta_{AIDS} I^N_A + T_P + T_C + \theta_{AIDS} T_A\right)} \\
& + \left(1 - p^{\text{reg}}_{\text{serosort}}\right)\left(1 - p^{\text{reg}}_{\text{disclose}}\right) \frac{\hat{\beta}^{\text{reg}\,|\,\text{ave condom}}_{P} I_P + \hat{\beta}^{\text{reg}\,|\,\text{ave condom}}_{C} I_C + \hat{\beta}^{\text{reg}\,|\,\text{ave condom}}_{A} \theta_{AIDS} I_A}{S + I_P + I_C + \theta_{AIDS} I_A + f\left(I^N_P + I^N_C + \theta_{AIDS} I^N_A + T_P + T_C + \theta_{AIDS} T_A\right)} \\
& + \left(1 - p^{\text{reg}}_{\text{serosort}}\right)\left(1 - p^{\text{reg}}_{\text{disclose}}\right) \frac{f\left(\hat{\beta}^{\text{reg}\,|\,\text{ave condom}}_{P} I^N_P + \hat{\beta}^{\text{reg}\,|\,\text{ave condom}}_{C} I^N_C + \hat{\beta}^{\text{reg}\,|\,\text{ave condom}}_{A} \theta_{AIDS} I^N_A + \hat{\beta}^{\text{reg}\,|\,\text{ave condom}}_{T} \left(T_P + T_C + \theta_{AIDS} T_A\right)\right)}{S + I_P + I_C + \theta_{AIDS} I_A + f\left(I^N_P + I^N_C + \theta_{AIDS} I^N_A + T_P + T_C + \theta_{AIDS} T_A\right)} \Bigg] \\
+ c_{cas}\Bigg[& p^{\text{cas}}_{\text{serosort}} \frac{\hat{\beta}^{\text{cas}\,|\,\text{low condom}}_{P} I_P + \hat{\beta}^{\text{cas}\,|\,\text{low condom}}_{C} I_C + \hat{\beta}^{\text{cas}\,|\,\text{low condom}}_{A} \theta_{AIDS} I_A}{S + I_P + I_C + \theta_{AIDS} I_A} \\
& + \left(1 - p^{\text{cas}}_{\text{serosort}}\right) p^{\text{cas}}_{\text{disclose}} \frac{\hat{\beta}^{\text{cas}\,|\,\text{low condom}}_{P} I_P + \hat{\beta}^{\text{cas}\,|\,\text{low condom}}_{C} I_C + \hat{\beta}^{\text{cas}\,|\,\text{low condom}}_{A} \theta_{AIDS} I_A}{S + I_P + I_C + \theta_{AIDS} I_A + f\left(I^N_P + I^N_C + \theta_{AIDS} I^N_A + T_P + T_C + \theta_{AIDS} T_A\right)} \\
& + \left(1 - p^{\text{cas}}_{\text{serosort}}\right) p^{\text{cas}}_{\text{disclose}} \frac{f\left(\hat{\beta}^{\text{cas}\,|\,\text{high condom}}_{P} I^N_P + \hat{\beta}^{\text{cas}\,|\,\text{high condom}}_{C} I^N_C + \hat{\beta}^{\text{cas}\,|\,\text{high condom}}_{A} \theta_{AIDS} I^N_A + \hat{\beta}^{\text{cas}\,|\,\text{high condom}}_{T} \left(T_P + T_C + \theta_{AIDS} T_A\right)\right)}{S + I_P + I_C + \theta_{AIDS} I_A + f\left(I^N_P + I^N_C + \theta_{AIDS} I^N_A + T_P + T_C + \theta_{AIDS} T_A\right)} \\
& + \left(1 - p^{\text{cas}}_{\text{serosort}}\right)\left(1 - p^{\text{cas}}_{\text{disclose}}\right) \frac{\hat{\beta}^{\text{cas}\,|\,\text{ave condom}}_{P} I_P + \hat{\beta}^{\text{cas}\,|\,\text{ave condom}}_{C} I_C + \hat{\beta}^{\text{cas}\,|\,\text{ave condom}}_{A} \theta_{AIDS} I_A}{S + I_P + I_C + \theta_{AIDS} I_A + f\left(I^N_P + I^N_C + \theta_{AIDS} I^N_A + T_P + T_C + \theta_{AIDS} T_A\right)} \\
& + \left(1 - p^{\text{cas}}_{\text{serosort}}\right)\left(1 - p^{\text{cas}}_{\text{disclose}}\right) \frac{f\left(\hat{\beta}^{\text{cas}\,|\,\text{ave condom}}_{P} I^N_P + \hat{\beta}^{\text{cas}\,|\,\text{ave condom}}_{C} I^N_C + \hat{\beta}^{\text{cas}\,|\,\text{ave condom}}_{A} \theta_{AIDS} I^N_A + \hat{\beta}^{\text{cas}\,|\,\text{ave condom}}_{T} \left(T_P + T_C + \theta_{AIDS} T_A\right)\right)}{S + I_P + I_C + \theta_{AIDS} I_A + f\left(I^N_P + I^N_C + \theta_{AIDS} I^N_A + T_P + T_C + \theta_{AIDS} T_A\right)} \Bigg]
\end{aligned}$$

where the $\hat{\beta}$ 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 effecting the transmission probabilities).

A.4 Dynamic equilibrium (Steady States)

For our system of ten ordinary differential equations we determined solutions for the system dynamic endemic equilibrium. We set the time derivatives of each compartment equal to zero and solved for the state variables. The solution specifies the equilibrium level such that if all state populations are set to the steady state value, they will remain at that constant value (the total inflow equals the total outflow). We consider the data of the number of HIV notifications in Australia to be at a local minimum at the year 1999 (Figure 1.1). We simulate the HIV epidemic in MSM starting at the year 1999 and the initial conditions of our system are set to be the steady state solutions. We then simulate the influence of the time-dependent parameter since 1999 and forecast how changes in parameter values will perturb the steady state solution, number of incident infections, and number of new diagnoses.

The dynamic endemic equilibrium solution for our system of equations is given by:

$$\bar{S} = \frac{2\bar{\alpha}\pi}{2\bar{\alpha}\mu + \bar{\delta}}$$

$$\bar{I}_P = \frac{\pi\bar{\delta}}{A(2\bar{\alpha}\mu + \bar{\delta})} \qquad \bar{I}_P^N = \frac{\gamma_P\pi\bar{\delta}}{AD(2\bar{\alpha}\mu + \bar{\delta})} \qquad \bar{T}_P = \frac{\eta_P\gamma_P\pi\bar{\delta}}{AJ(2\bar{\alpha}\mu + \bar{\delta})}$$

$$\bar{I}_C = \frac{\omega_P\pi\bar{\delta}}{AB(2\bar{\alpha}\mu + \bar{\delta})} \qquad \bar{I}_C^N = \frac{(O+P+Q+R)\pi\bar{\delta}}{ABDEJK(2\bar{\alpha}\mu + \bar{\delta})} \qquad \bar{T}_C = \frac{(L+M+N)\pi\bar{\delta}}{ABDJK(2\bar{\alpha}\mu + \bar{\delta})}$$

$$\bar{I}_A = \frac{\omega_C\omega_P\pi\bar{\delta}}{ABC(2\bar{\alpha}\mu + \bar{\delta})} \qquad \bar{I}_A^N = \frac{(Y+Z+\Gamma)\pi\bar{\delta}}{ABCDEFJKU(2\bar{\alpha}\mu + \bar{\delta})} \qquad \bar{T}_A = \frac{(V+W+X)\pi\bar{\delta}}{ABCDEJKU(2\bar{\alpha}\mu + \bar{\delta})}$$

where

$$A = \mu + \gamma_P + \omega_P,\ B = \mu + \gamma_C + \omega_C + \delta_C,\ C = \mu + \gamma_A + \delta_A,$$
$$D = \mu + \omega_P + \eta_P,\ E = \mu + \omega_C + \eta_C + \delta_C,\ F = \mu + \eta_A + \delta_A,$$
$$G = \mu + \nu_P + \tau_P,\ H = \mu + \nu_C + \tau_C + \delta_C^T,\ I = \mu + \nu_A + \delta_T,\ J = DG,\ F' = FI - \nu_A p_A \eta_A,$$
$$K = F'E^2H - F'E\eta_C\nu_C - E^2(1-p_A)\eta_A\tau_C - E(1-p_A)\eta_A\omega_C I\nu_C,$$
$$Y' = F'E^2\tau_P + F'E\eta_C\nu_P + E(1-p_A)\eta_A\omega_C I\nu_P,\ X' = F'E\eta_C\gamma_C + E(1-p_A)\eta_A\omega_C I\gamma_C,$$
$$W' = F'E\eta_C\omega_P + E(1-p_A)\eta_A\omega_C I\omega_P,\ V' = \gamma_A IE^2(1-p_A)\eta_A,$$
$$U' = Y'BCD\eta_P\gamma_P + X'CDJ\omega_P + W'BCJ\gamma_P + V'DJ\omega_C\omega_P,\ O = \gamma_C\omega_P CDJK,\ P = \omega_P\gamma_P BCJK,$$
$$Q = \nu_C U',\ R = \nu_P\eta_P\gamma_P BCDK,\ V = p_A\eta_A\gamma_A\omega_C\omega_P DEJK,\ W = p_A\eta_A\omega_C(O+P+Q+R),$$
$$X = \tau_C FU'E,\ Y = \gamma_A\omega_C\omega_P DEJKF',\ Z = \omega_C(O+P+Q+R)F';$$

$$\beta_{R1}^{(P,C,A)} = (1-p_{serosort}^{reg})\,p_{disclose}^{reg}\hat{\beta}_{(P,C,A)}^{reg|\text{low condom}},\ \beta_{R2}^{(P,C,A)} = (1-p_{serosort}^{reg})\,p_{disclose}^{reg}\hat{\beta}_{(P,C,A)}^{reg|\text{high condom}},$$
$$\beta_{R3}^{(P,C,A)} = (1-p_{serosort}^{reg})\,p_{disclose}^{reg}\hat{\beta}_{(P,C,A)}^{reg|\text{ave condom}},\ \beta_{C1}^{(P,C,A)} = (1-p_{serosort}^{cas})\,p_{disclose}^{cas}\hat{\beta}_{(P,C,A)}^{cas|\text{low condom}},$$
$$\beta_{C2}^{(P,C,A)} = (1-p_{serosort}^{cas})\,p_{disclose}^{cas}\hat{\beta}_{(P,C,A)}^{cas|\text{low condom}},\ \beta_{C3}^{(P,C,A)} = (1-p_{serosort}^{cas})\,p_{disclose}^{cas}\hat{\beta}_{(P,C,A)}^{cas|\text{low condom}},$$
$$\beta_{R2}^{T} = (1-p_{serosort}^{reg})\,p_{disclose}^{reg}\hat{\beta}_{T}^{reg|\text{high condom}},\ \beta_{R3}^{T} = (1-p_{serosort}^{reg})\,p_{disclose}^{reg}\hat{\beta}_{T}^{reg|\text{ave condom}},$$
$$\beta_{C2}^{T} = (1-p_{serosort}^{cas})\,p_{disclose}^{cas}\hat{\beta}_{T}^{cas|\text{high condom}},\ \beta_{C3}^{T} = (1-p_{serosort}^{cas})\,p_{disclose}^{cas}\beta_{T}^{cas|\text{ave condom}}$$

$$\mathrm{B}_{R1}^{(P,C,A)} = \beta_{R1}^{(P,C,A)} + \beta_{R3}^{(P,C,A)},\ \mathrm{B}_{R2}^{(P,C,A)} = \beta_{R2}^{(P,C,A)} + \beta_{R3}^{(P,C,A)},\ \mathrm{B}_{C1}^{(P,C,A)} = \beta_{C1}^{(P,C,A)} + \beta_{C3}^{(P,C,A)},$$
$$\mathrm{B}_{C2}^{(P,C,A)} = \beta_{C2}^{(P,C,A)} + \beta_{C3}^{(P,C,A)},\ \mathrm{B}_{R}^{T} = \beta_{R2}^{T} + \beta_{R3}^{T},\ \mathrm{B}_{C}^{T} = \beta_{C2}^{T} + \beta_{C3}^{T}$$

$$\Gamma = \nu_A\left(V+W+X\right),\ \Delta_R = \mathrm{B}_{R1}^{P}D + \mathrm{B}_{R2}^{P}f\gamma_P,\ \Delta_C = \mathrm{B}_{C1}^{P}D + \mathrm{B}_{C2}^{P}f\gamma_P,$$
$$\Lambda_R = \mathrm{B}_{R1}^{C}\omega_P CDEJK + \mathrm{B}_{R2}^{C}f(O+P+Q+R),\ \Lambda_C = \mathrm{B}_{C1}^{C}\omega_P CDEJK + \mathrm{B}_{C2}^{C}f(O+P+Q+R),$$
$$\Theta_R = \mathrm{B}_{R1}^{A}\omega_C\omega_P DEFJKF' + \mathrm{B}_{R2}^{A}f(Y+Z+\Gamma),$$
$$\Theta_C = \mathrm{B}_{C1}^{A}\omega_C\omega_P DEFJKF' + \mathrm{B}_{C2}^{A}f(Y+Z+\Gamma),\ \hat{\Phi} = \Delta_R BCEFKF',\ \hat{\Psi} = \Lambda_R FF',\ \hat{\Omega} = \theta_{AIDS}\Theta_R,$$
$$\hat{C} = f\mathrm{B}_R^T\eta_P\gamma_P BCDEFKF',\ \hat{D} = f\mathrm{B}_R^T U'EFF',\ \hat{E} = f\theta_{AIDS}\mathrm{B}_R^T\left(V+W+X\right)F$$

$$\dot{\Phi} = \Delta_C BCEFKF',\ \dot{\Psi} = \Lambda_C FF',\ \dot{\Omega} = \theta_{AIDS}\Theta_C,\ \dot{C} = f\mathrm{B}_C^T\eta_P\gamma_P BCDEFKF',\ \dot{D} = f\mathrm{B}_C^T U'EFF',$$
$$\dot{E} = f\theta_{AIDS}\mathrm{B}_C^T\left(V+W+X\right)F,\ \hat{J} = BCDEFJKF',\ \hat{K} = \omega_P CDEFJKF',\ \hat{L} = \theta_{AIDS}\omega_P\omega_C DEFJKF',$$
$$\hat{M} = \gamma_P BCEFJKF',\ \hat{N} = (O+P+Q+R)FF',\ \hat{O} = \theta_{AIDS}(Y+Z+\Gamma),\ \hat{P} = \eta_P\gamma_P BCDEFKF',$$
$$\hat{Q} = U'CEFF',\ \hat{R} = \theta_{AIDS}(V+W+X)F,\ \hat{S} = \hat{J}+\hat{K}+\hat{L}+f(\hat{M}+\hat{N}+\hat{O}+\hat{P}+\hat{Q}+\hat{R}),$$
$$\overline{A} = ABCDEFJKF',\ \hat{G} = c_{reg}p_{serosort}^{reg}(BC\hat{\beta}_P^{reg|\text{low condom}} + C\hat{\beta}_C^{reg|\text{low condom}}\omega_P + \theta_{AIDS}\hat{\beta}_A^{reg|\text{low condom}}\omega_P\omega_C),$$
$$\hat{H} = c_{reg}(\hat{\Phi}+\hat{\Psi}+\hat{\Omega}+\hat{C}+\hat{D}+\hat{E}),$$
$$\dot{G} = c_{cas}p_{serosort}^{cas}(BC\hat{\beta}_P^{cas|\text{low condom}} + C\hat{\beta}_C^{cas|\text{low condom}}\omega_P + \theta_{AIDS}\hat{\beta}_A^{cas|\text{low condom}}\omega_P\omega_C),$$
$$\dot{H} = c_{cas}(\dot{\Phi}+\dot{\Psi}+\dot{\Omega}+\dot{C}+\dot{D}+\dot{E});$$

$$\overline{\alpha} = BC\hat{S} + \theta_{AIDS}\omega_P\omega_C\hat{S} + C\omega_P\hat{S},\ \overline{\gamma} = ABC\overline{A} - \hat{G}\overline{A} - \hat{H}ABC - \dot{G}\overline{A} - \dot{H}ABC,$$

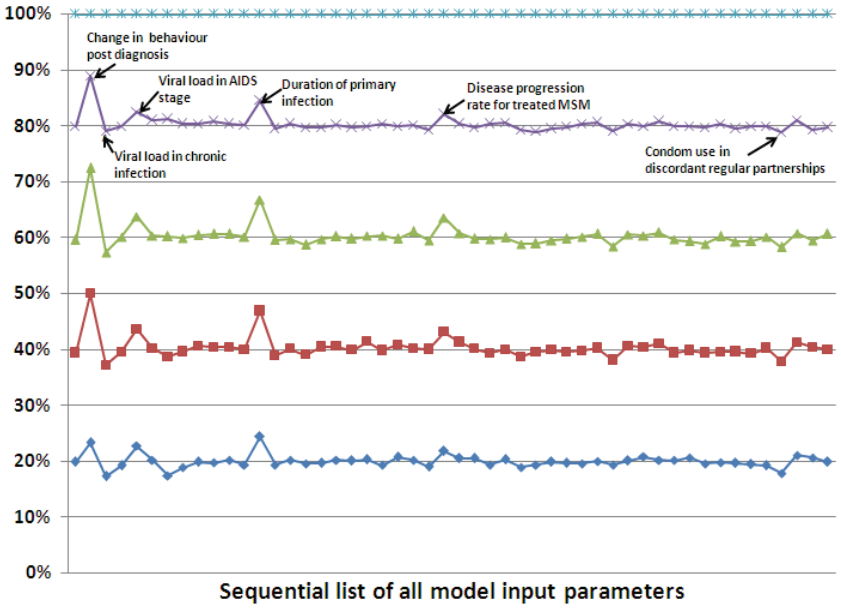
$$\overline{\beta} = C\omega_P\overline{A} + ABC\hat{S} + BC\overline{A} + \theta_{AIDS}\omega_P\omega_C\overline{A} - \hat{G}\hat{S} - \hat{H}BC - \hat{H}\theta_{AIDS}\omega_P\omega_C - \dot{G}\hat{S} - \dot{H}BC - \dot{H}\theta_{AIDS}\omega_P\omega_C - \hat{H}C\omega_P - \dot{H}C\omega_P,$$

$$\overline{\delta} = -\overline{\beta} \pm \sqrt{\overline{\beta}^2 - 4\overline{\alpha}\overline{\gamma}}\,.$$

A.5 Uncertainty and Sensitivity Analyses

Due to the heterogeneity and uncertainty in some parameter estimates we defined a probability density function (PDF) for each parameter in the model. Using Latin Hypercube Sampling (100-104), a type of stratified Monte Carlo sampling, each of these PDFs is then stratified (into N equiprobable intervals) and the value of each input parameter is randomly chosen. Each input value is used only once in the entire sampling analysis and so this is a very efficient sampling design (100, 103, 105, 106). Distributions of the outcome variables can then be derived directly by running the model N times with each of the sampled parameters. We employ this method to sample the parameter space, generating 10,000 parameter sets. We defined a PDF for every parameter except one: γ_P, the rate of diagnosis of MSM in primary infection. There was no data available for this parameter and consequently we used this parameter to calibrate the model to the notifications data. The number of new diagnoses each year is represented in our model by $\gamma_P I_P + \gamma_C I_C + \gamma_A I_A$. The number of reported HIV diagnoses in 1999 was 536. Thus, we solved the equation, $536 = \gamma_P \bar{I}_P + \gamma_C \bar{I}_C + \gamma_A \bar{I}_A$, for γ_P. But we excluded every parameter set that did not result in a solution for γ_P lying in the range 0 to 25 (which we consider to be a plausible range); this method is known as Monte Carlo filtering (107, 108). The remaining (4187) parameter sets were used in our analyses. To ensure that the filtered parameter sets used in our analyses were not in significantly biased regions of parameter space we explored the distribution of retained parameter sets (see Figure A.1) and carried out Kolmogorov-Smirnov tests (109, 110) on the dichotomous outcome of whether the original parameter set resulted in a realistic solution. The parameters of greatest importance (according to Kolmogorov-Smirnov tests) in contributing to whether or not a parameter set was retained (f, ω_P, V_A, τ_C, W, $p^{\text{reg}}_{\text{condom}}$) were consistently among the most important parameters influencing outcome variables from our uncertainty analyses (see Chapter 3); for each parameter, values were retained across the entire uncertainty range but the density of sampling across the distribution changed slightly for these dominant parameters whereas there was no substantial change in the sampled distribution for other parameters (Fig. A.3).

Figure A.3: A representation of the probability density functions for all sampled parameters in our model after the process of Monte Carlo filtering. Here, the cut-off values for the first 20%, 40%, 60%, 80%, and 100% of the cumulative density functions prior to filtering were determined, and then the percentage of simulations retained that are within these bounds are shown (20% (blue), 40% (red), 60% (green), 80% (purple)). Prior to filtering, all distributions were uniformly sampled (that is, all parameters lay on the 20%, 40%, 60%, 80% constants below). None of the parameters' distributions have changed significantly for concern of grossly biased samples. The six parameters whose distributions have changed the most are indicated.



We simulated our model under various scenarios and calculated various time-dependent outcome variables for each parameter set. Then, we conducted extensive sensitivity analyses. Sensitivity analysis is the study of how the uncertainty in the output of complex models can be apportioned to sources of uncertainty in the model inputs (100, 111). Calculating PRCCs is currently the best method for determining statistical association between two sets of variables in a large system (such as the relation between one input parameter, out of many input parameters, on a particular outcome variable) (100-103, 112-123). We also carried out other sensitivity analyses: calculation of standardized regression coefficients between model parameters and outcomes (124), and factor prioritization by reduction of variance (calculating first order sensitivity indices) (125-136). Sampling of parameter distributions using Latin Hypercube Sampling and all sensitivity analyses were performed with the SaSAT software package (137).

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