Using mathematical modelling to evaluate drivers and predict trajectories of HIV and STI epidemics in South East Asian and Australian populations

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Using mathematical modelling to evaluate drivers and predict trajectories of HIV and STI epidemics in South East Asian and Australian populations

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It's been widely misattributed to the mathematician Paul Erdös, but I think over the course of my candidature I have embodied this quote: "A mathematician is a machine for turning coffee into theorems." Well, perhaps not theorems, but definitely MATLAB code.

Table of Contents

Preface

This thesis uses the tool of mathematical modelling to address timely research questions in the field of HIV and sexually transmissible infections (STI) population health. An evaluation of the drivers of epidemics in South East Asia and Australia is conducted along with projection of epidemic trajectories according to various scenarios. Economic implications of public health and clinical decisions in HIV and STI control and care are also assessed. The main chapters of this thesis have been reproduced from papers that have been published or submitted for peer-review. The citations to these papers are provided at the start of each chapter. At the time of writing, Chapter 1 had not yet been published but was in preparation for submission to an international scientific journal. Content of all chapters appear as published but minor alterations were made to the format of the papers; these include the placement of figures and tables and references to supplementary material now refer to the appropriate appendix. Reference styles were also changed to be made consistent throughout the thesis.

Introduction and review of relevant literature

Approximately 4.1 million people, of the estimated 33.3 million people living with HIV worldwide, live in South and South East Asia [1]. The Asia-Pacific region is vast and diverse, and being home to 60% of the world's population there is no single "Asian HIV Epidemic"[2]. However, HIV epidemics in Asia have tended to follow patterns which are distinct from HIV epidemics in other regions. The primary drivers behind the epidemics in Asia have been identified as commercial sex between female sex workers and male clients, anal sex (commercial and non-commercial) between men / transgendered men, and drug injection [2, 3]. The distribution of HIV infection in countries that are classified as having a "generalised epidemic" is not homogeneous throughout the general population. Most infections still remain in subpopulations that participate in the higher-risk activities already mentioned or through sexual contact with those who do, for example, spouses of men who are clients of female sex workers.

This thesis utilises mathematical modelling to answer a number of different questions that arise from a common theme of sexually transmitted infections.

Firstly, modelling is used to investigate answers to the question of how effective the implementation of a public health policy can be in mitigating an HIV epidemic. Models are applied in two widely differing epidemiological settings: one country that is high-income, the other that is low-income; one that has an epidemic that is predominantly within the population of MSM, the other where heterosexual intercourse if the cause of the majority of infections. We then use mathematical modelling from a fiscal point of view to evaluate the implementation of public health strategies in terms of cost-effectiveness. These strategies cover the frequency of testing specific populations such as sex workers and men who have

sex with men, changing the criteria for the eligibility for antiretroviral treatment and the provision of antiretroviral therapies for free.

HIV in Cambodia

Cambodia is a country which has experienced an HIV epidemic following chains of transmission among different at-risk population groups. The first documented case of a positive HIV diagnosis in Cambodia was in 1991. The number of new HIV infections rapidly expanded with an estimated (via sentinel surveillance) peak epidemic prevalence of 3% among the adult population in 1998. By 2003, it was estimated (also via sentinel surveillance) that prevalence decreased to 1.9% and through a large household survey HIV prevalence is currently estimated to be approximately 0.6% [4]. The primary driver behind the initial epidemic has been identified to be heterosexual transmission between female commercial sex workers (FSWs) of both the direct (establishment-based) type (DSW) and the indirect (karaoke bar, massage parlour) type (ISW) and their male clients, with onward transmission to the regular sexual partners of male clients [5]. Motivated by the important need to design HIV prevention responses that are based on evidence, decision-makers should be informed by knowledge of the dynamics and modes of HIV transmissions in a population and understanding of the effectiveness of past HIV responses as well as the combination of strategies likely to have greatest impact in the future. To meet this need, a new tool was developed to evaluate and project Cambodia's HIV epidemic. In Chapter 1 background information is provided about the response to Cambodia's HIV epidemic, evaluation of the impact of this response, as well as description of the development of the tool used to conduct evaluations and projections and some summary results. In Chapter 2 we present an evaluation

of the impact of the Global Economic Crisis on the spread of HIV in Cambodia and Papua New Guinea.

Test and treat as an intervention and cost effectiveness

There is growing evidence showing that by reducing the viral load in an HIV-positive patient through the administration of antiretroviral treatment, this will reduce the rate of onward transmission. Whilst the primary motivation of treatment is usually for the health and well-being of the patient, this secondary benefit of decreased transmission is significant and should be considered as an intervention in appropriate settings. Evidence of this beneficial effect is largely obtained from epidemiological and observational studies, a few of which will be reviewed briefly below. Most recently however, for the first time, a large-scale randomised clinical trial demonstrated that early initiation of antiretroviral treatment to HIV-infected persons reduced transmission to uninfected sexual partners by 96% [1].

Viral load in the blood of an HIV-positive person has been found to be a key indicator of how likely transmission is to occur. The major finding of the study of heterosexual transmission by Quinn et al. [2] was the strong association between increasing transmission risk with increasing serum levels of HIV-1 RNA, with an increase in risk of a factor of 2.45 for each log increase in viral load.

Whilst the amount of HIV-RNA in blood is routinely monitored in developed nations, it is likely that the level of virus in genital fluids is of greatest importance for influencing infectiousness associated with sexual transmission. The findings of Vernazza et al. [3] show

that in patients that have reduced their viral load to less than 400 copies per millilitre of blood due to ART, the probability of having detectable HIV in semen is less than 4%. In a recent study Baeten et. al [17] examined the relationship between viral load in blood, endocervical swabs, semen and risk of sexual transmission. They found for each log HIV-1 RNA copies/mL increase in plasma, there was an associated with a 0.52 log copies/swab increase in endocervical viral load and a 0.46 log increase in semen. In terms of transmission, for each log increase in endocervical viral load there was an associated 2.20-fold increase in risk and similarly, a 1.79-fold risk for each log increase in seminal viral load. Overall they found higher genital viral concentrations were associated with greater risk of heterosexual HIV-1 transmission, and this effect was independent of plasma HIV-1 concentrations.

In addition to seeing the positive effect of antiretroviral treatment at the micro-level within an infected individual and to their potential for transmission to their partners, it is possible to take a macro-view of the benefit at the population level. In 2010, Montaner et al.[4] aimed to estimate the association between HAART coverage, plasma HIV-1 viral load, and number of new diagnoses of HIV in a population-based study of the Canadian province of British Columbia (BC). The drivers of the localised HIV epidemic in BC have been identified as three key sub-populations: MSM, IDUs and FSW [5]; these risk-groups carry the bulk of the disease burden. For the years 1996-2009, surveillance data were obtained for the number of HIV tests performed, the number of new HIV diagnoses, the number of individuals actively receiving HAART, CD4 cell count and viral load (from the British Columbia Centre for Disease Control and British Columbia Centre for Excellence in HIV/AIDS). These data were then analysed for associations using Poisson log-linear regression models. They found that in the population, for every 100 additional persons put onto HAART, the number of new HIV cases decreased by 3%. Similarly, for every log10 reduction in estimated average community

viral load, there was a corresponding 14% decrease in new diagnoses. It is important to note that this is purely an ecological study and does not mean there is causation at the population level. However, the large-scale randomised clinical trial that demonstrated a 96% reduction in transmission due to ART is a study of higher rigor and produced comparable qualitative results and quantitative implications [1].

Demonstrating the benefit of a healthcare intervention for a population is not enough for it to be implemented as policy. For this, it is usually necessary to demonstrate that the intervention being considered would also be cost-effective, that is, cost no more than a pre-defined "willingness to pay" threshold per quality-adjusted (QALY) or disability-adjusted (DALY) life year gained.

In British Columbia, a revision of guidelines for the provision of HAART in 2008 led to a substantial increase in the number of those eligible to receive treatment. Based on the new guidelines, Lima et al.[5] explored the potential impact of differing coverage scenarios in comparison to the previous eligibility guidelines. They constructed a transmission model comprised of four ordinary differential equations (ODEs) for three most-at-risk groups: men who have sex with men, injecting drug users and female sex workers. Each ODE represented a disease and treatment state, and also incorporated stage-dependent infectiousness. The scenarios explored were 50%, 60%, 75% and 100% of those medically eligible to receive HAART, with an assumption that 25-30% of those infected are undiagnosed. In terms of cost effectiveness, disability-adjusted life years were used to estimate HIV-related morbidity and mortality, costs were in terms of provision of first-line therapy for one individual in BC for one year disregarding inflation or discounting. Their results showed that an intervention

leading to even a marginal increase in HAART coverage to 50% of eligible individuals, in 5 years at least 1360 infections could be averted, in addition to the gain of 4155 DALYs and approximately CAD$ 21 million in costs. According to this simulated scenario, such an intervention would initially be cost-effective and cost-saving within a decade.

Whilst there is obvious benefit gained from using targeted interventions in concentrated epidemics, there remains the possibility that such an intervention could also be beneficial in a generalised epidemic. In their paper "Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model" [6], Granich et al. simulated an intervention of universal voluntary HIV testing followed with immediate treatment with ART upon diagnosis. Using this strategy, they then analysed conditions under which the elimination of the HIV epidemic could be achieved, where elimination is defined to have occurred when incidence is fewer than one case per 1000 people per year. In order to achieve this goal, the case reproductive number R0 would need to be reduced to less than one. Two mathematical models were implemented to explore the effect of the intervention strategy proposed: a stochastic model of R0; and a deterministic transmission model of the long-term disease dynamics. In the stochastic model, CD4 count determined the stage of infection, and transmission varied between the acute and chronic phases of HIV infection with an adjusting factor for those who were currently on ART. Initially, a person's CD4+ cell count and expected survival time were sampled from an observed population distribution. It was then assumed that cell count immediately decreased by 25% post-infection and linearly thereafter. The deterministic compartmental model was fitted to an observed Weibull survival distribution model. The model tracked the infected but untreated as well as the treated populations' progression from infection to AIDS stage but this component of the model was decoupled from the infectivity of the acute and final phases that

were modelled stochastically. As disease progresses, infected persons in the model can switch from untreated to treated at a rate equal to that of the treatment rate and return due to treatment failure or non-adherence. It was also assumed in the model that transmission decreases with the overall population prevalence.

Universal testing and immediate treatment was modelled independently and in unison with other combined adult interventions such as: adult male circumcision, condom promotion, treatment of other sexually transmitted infections and behaviour change programmes. When being modelled with the same roll-out rate as the ART programmes, it was assumed that the combined interventions would reduce transmission by 40%. Their model suggested that whilst other interventions could reduce HIV incidence substantially for a generalised heterosexual epidemic, universal voluntary HIV testing and immediate initiation of ART was necessary to reduce transmission to the defined elimination point within ten years.

It is equally important, if not more so, to consider the cost-effectiveness of interventions in developing countries with generalised epidemics. With the availability of less expensive medications due to the advocacy and financial support from large international organisations, the financial benefit has the potential to be much greater than what could be realised in industrialised countries with localised epidemics. In their study, Vickerman et al. [7] estimate the epidemiological impact and cost-effectiveness of interventions with various combinations of periodic presumptive treatment (PPT), syndromic management of bacterial STIs and provision of condoms to female sex workers in Johannesburg, South Africa. Using a deterministic compartment mathematical model to calculate the expected number of new HIV and other STD infections in one year with and without the intervention, they then use

economic analysis to determine the cost-effectiveness. They found that by correctly treating a large number of STIs, the full intervention resulted in 3.1% decrease in HIV incidence in FSWs with a corresponding 2% reduction in the general population. An expected 53 HIV infections and 1413 DALYs were averted at a cost of $78 per DALY, well below the recommended upper bound of $141 per DALY as a willingness to pay threshold. Their analysis shows that such an intervention has the potential to be even more cost-effective if it is implemented earlier in an epidemic.

In their paper "Examining the promise of HIV elimination by `test and treat' in hyperendemic settings" [8] Dodd et al. also examined the possible impact of test-and-treat interventions in the context of a generalised epidemic. Their deterministic partial-differential equation model included variation over the course of an infection in HIV transmissibility and sexual risk behaviour and incorporated observed HIV survival rates. The model considers transmission via heterosexual sex with and without ART, where men and women are categorised into low or high-sexual activity groups. Modelled interventions were evaluated for when the epidemic was sustained in either both sub-populations or in the high-activity group only. This was in conjunction with extensive or limited sexual mixing between the groups, giving rise to three epidemic scenarios with differing degrees of robustness. Key to the model is the assumption that those on treatment are less infectious and have a survival time dependent upon the promptness of treatment initiation, and those who are untreated survive for 11 years post infection. As would be expected, they found that earlier initiation of treatment with higher levels of coverage had the greatest impact. For example, they found that an intervention that results in testing 80% of the population every 2 years with immediate treatment could be expected to reduce incidence by more than 95% for an epidemic where risk is evenly distributed. However, this decrease in incidence is reduced to 85% in an epidemic that is

sustained in the smaller population group at higher risk where sexual mixing was assumed to be random. Incidence reduced further to 60% when the sexual mixing was assumed to be assortative (that is, people mix with people of the same population group). In these last two scenarios, such an intervention would fail to reduce the epidemic to elimination, and similar impact could be achieved with less frequent testing. Overall, the findings from their model highlight that whilst an intervention such as test and treat can reduce HIV transmission significantly, it is highly context specific. The impact of a proposed intervention on HIV transmission may be less for one epidemic type than another, or conversely, the same results may be achieved with less expenditure of resources. When the cost-effectiveness of a scheme is crucial for its implementation, a highly epidemiologically-effective intervention such as testing every year and treating immediately, may not necessarily be the most efficient fiscal strategy. Additionally, they showed that test-and-treat interventions that do not reach full implementation or coverage could potentially increase ART costs in the long-term.

In Chapter 3 we present a modelling study that evaluates the effectiveness of a test and treat intervention amongst men who have sex with men in South Australia. In the following chapter we present an economic argument for the provision of free antiretroviral medication in South Australia. In Chapter 5 we demonstrate that the frequent mandatory screening of female sex workers in Victoria is not cost-effective for the prevention of disease in their male clients.

Serosorting

The practice of choosing a preferential sexual partner based on the concordance of HIV serostatus is known as serosorting [6-8]. The primary purpose of serosorting is to reduce the risk of HIV transmission occurring. This practice is becoming increasingly common among men who have sex with men (MSM) in various locations around the world when seeking to form casual sexual partnerships and enables unprotected anal intercourse without fear of risk of HIV transmission [8-14]. In addition to choice of partner, the disclosure of serostatus is likely to influence negotiated safety and strategic positioning, that is, the use of a condom and which sexual position each man will take [8-14]. In a discordant partnership, the receptive role carries more risk than the insertive position. In sexual acts where the partnership is thought to be concordant, HIV-negative men are less likely to use condoms and are more likely to take a receptive role [15]. As such, the safety of the serosorting practice is highly dependent on the rate of undiagnosed infections. It is possible that serosorting may lead to an increased risk if a partner's status is misreported [15]. In a recent modelling study, serosorting was found to be partially effective in Seattle, Washington [16]provided the proportion of men unaware of their infection is less than 20%. In Chapter 6 we assess the effectiveness of serosorting at reducing the transmission of HIV in a variety of settings with different levels of undiagnosed infections. We investigate the expected effectiveness of serosorting using a mathematical model. Threshold levels at which serosorting increases transmission risk are estimated for different settings.

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Chapter 1: The Cambodian HIV Epidemic Model (CHEM): Evaluating the drivers of the past epidemic, understanding the present and assessing the impact of interventions in the future.

Introduction

In this chapter background information is provided about the response to Cambodia's HIV epidemic, evaluation of the impact of this response, as well as description of the development of the tool used to conduct evaluations and projections and some summary results.

Cambodia has seen a substantial decrease in overall HIV prevalence. The reasons for this are likely a combination of natural epidemic dynamics and specific HIV prevention programmes. In response to their epidemic, Cambodia has implemented two key health strategies: (i) the promotion of 100% condom use in transactional sex for female sex workers and (ii) access to antiretroviral medications for pregnant women, which was subsequently expanded to include access for other HIV-infected people. The degree to which these programmes contributed to declines in HIV prevalence, versus other programmes or natural epidemic dynamics, is unknown. In this study, these programmes are evaluated.

In 1998, the 100% condom use program (CUP) among DSW was initiated in Cambodia in the Sihanouk Ville province and expanded nationally in 1999 [1]. This intervention provided outreach support to FSWs, facilitated access to regular STD check-ups, Voluntary Confidential Counselling and Testing (VCCT) centres and other services, education about sexual health and ensured availability of condoms at all sexual-entertainment venues [2].

Between the years of 1998 and 2003, condom use in DSW for transactional sex increased from 53.4% to 96% and continued to do so until 2007 to 97-99% and then dropped to 89-98% in 2010 [3-5]. Average levels of condom use among ISW followed a similar trend, starting at approximately 30% in 1998, increasing to 84% in 2003, continued upwards to 93% in 2007 and decreased to 82-95% in 2010. Ecological associations between condom usage and prevalence among sex workers suggest that 100% CUP may have had an epidemiological impact. Over the period of increased condom usage there was a corresponding decrease in HIV prevalence in DSW, from 45.8% in 1998 to 20.8% in 2003 to 14% in 2006. Similarly, prevalence in ISW decreased from 15.6% in 2000 to 11.7 % in 2003. However, with the increase in non-brothel sex-work and DSWs becoming ISWs, prevalence in entertainment workers is dependent upon the number of sexual partners per week. Women who have seven or less partners per week are reported to have a prevalence of 3.6% in 2010, and women with more than seven partners per week had 14%. An association does not necessarily imply causation and the decline in prevalence may have been expected due to epidemic dynamics. Therefore, more rigorous investigation is required.

Treatment of HIV-infected pregnant women at the time of delivery with nevirapine was implemented in the Cambodian capital of Phnom Penh in 1999[6]. Providing access to antiretroviral treatment to all HIV-infected people with advanced disease became a priority in 2003 with the launch of the Operational Framework for the Continuum of Care for People Living with HIV/AIDS that August. This programme initially provided treatment to 2230 people at four sites and has continued to expand ever since. Currently, for a patient to qualify for the receipt of antiretroviral medication his/her CD4 count (key immune cell measure) must be less than 350 cells per millilitre of blood. Antiretroviral treatment not only substantially reduces HIV-related morbidity and mortality among those receiving it, but it

also acts to reduce transmission. The preventative impact of treatment programmes in Cambodia, in terms of infections averted, has not been assessed.

In addition to evaluation of these past programmes, for informing public health planning, in this study, projections of HIV epidemic trajectories for Cambodia are carried out according to numerous intervention conditions. Interventions that could be considered in the future in Cambodia include male circumcision, needle and syringe exchange programs (NSPs) and scaling-up of the existing HIV testing and treatment framework. Increasing testing and treatment frameworks and implementing NSPs have already commenced in Cambodia. However, programmes around male circumcision have not been implemented in Cambodia. It has been shown that in countries with generalised epidemics, that male circumcision can reduce the risk of men acquiring HIV by 60% for female-to-male sexual transmission [7, 8][12, 13].

In an assessment of the potential effects of male circumcision on HIV incidence at the population level as predicted by mathematical modelling [9], it was shown that in countries such as Uganda that have lower HIV incidence and prevalence, the number of male circumcisions required to avert an infection is greater than in high-prevalence settings. A modelling consensus reaching process led to the conclusion that interventions with a focus on subpopulations with a high HIV incidence and prevalence such as men who have multiple sex partners (e.g. clients of female sex workers) could have substantial impact on HIV incidence. It was also identified that subpopulations with low rates of male circumcision would also benefit from such a programme. In a country such as Cambodia where male circumcision is not custom, there are little data on what proportion of the male population are circumcised. It has been estimated that the rate of circumcision in Cambodia is as low as 1.6%, but is generally agreed that it is less than 20% [10]. Since male circumcision is one of the few

proven HIV prevention strategies, it may be worth consideration of the potential benefit that could be achieved by increasing circumcision rates in a setting like Cambodia.

The evaluation of the epidemiological impact of these past programmes is extremely difficult through purely empirical means. Mathematical models, informed by setting-specific programme, epidemiological and behavioural data, can be used to estimate the possible impact of these programmes. Similarly, epidemic models can be used to make projections of epidemic trajectories under different scenarios which may represent relative changes associated with new intervention strategies. There are a limited number of mathematical models that have been applied to the HIV epidemic in Cambodia and the most important of which are reviewed in brief before describing a new tool that was developed specifically for this purpose.

In 2004, the UNAIDS Estimation and Projection Package (EPP) [11] was released. This Java-based software package, under construction since 2001, was used for countries with generalised HIV epidemics as a tool for estimating and projecting HIV prevalence levels. The package allows users to define the overall epidemic in terms of population subgroups and/or geographical regions, allowing for modelling of the disproportionate contribution a certain risk- or geographical-group may have on the spread of HIV. Available HIV surveillance data (such as prevalence estimates from BSS and DHS surveys or from antenatal clinics) are then input into the model for all groups that are of interest. The model behind the package is numerical, employing four key epidemiological parameters to best fit an epidemic curve to the input data points via least squares minimisation. These four parameters are: the start year of the epidemic, the proportion of the population that are at risk of infection at the beginning of the epidemic, the epidemic growth rate, and the net change in the at-risk population size. If it is determined by the user that the curve fitted, whilst mathematically the best fit, is not epidemiologically appropriate it is possible for the user to change any or all of the key four

parameters to change the shape. “EPP smoothing” is still commonly applied to sentinel surveillance reporting in Cambodia, despite the change in the epidemic profile.

Also in 2004, Brown et al. presented their work “The Asian Epidemic Model: a process model for exploring HIV policy and programme alternatives in Asia” [12]. Rather than implementing the curve fitting of surveillance data techniques of the EPP, the Asian Epidemic Model (AEM) is a transmission-based model that includes inputs such as HIV transmission probabilities, risk behavioural data, and regionally-appropriate cofactors such as the prevalence of other STIs. The model incorporates the dominant routes of transmission seen in Asian epidemics and separately includes components for each of the key at-risk groups: direct female sex workers, indirect female sex workers, male sex workers, males who are clients of sex workers, men who have sex with men who are not sex workers, injecting drug users (divided into higher and lower risk sharing networks) and males and females of the general population. Inputs are specified annually such that important changes in behaviour can be captured and include frequency of sexual acts for each partnership type, as well as the applicable condom usage rate, rate of sharing and frequency of injections for IDUs, the prevalence of other STIs for each sexual/shared injection partnership and the size of each key population. Curves are then fitted according to the input data and applied to the underlying transmission model. Like the EPP, this model is most appropriate for a generalised epidemic setting. Additionally, a much larger number of more complex inputs is required for the AEM than EPP which can limit the ease in which it can be applied. This model was initially applied successfully in Thailand [13] and Cambodia [14] (and then also applied to other settings throughout Asia) and is still used in Cambodia for annual reporting of prevalence [15].

Motivated by the notion that in-country decision makers should base public health policy and program decisions on evidence, UNAIDS promoted the Know Your Epidemic / Know Your

Response activities [26, 27]. As part of this, a modelling tool was created and released called "The Modes of Transmission" (MoT) spreadsheet [16]. This model has been applied to Cambodia. The purpose of the model is to calculate the expected incidence of HIV infections for the coming year. The distribution of new infections is also calculated by classifying the adult population into groups according to their predominant exposure to HIV. Inputs to the spreadsheet are: current HIV and other STI prevalence, sizes of the relevant populations, number of partners and acts an individual in each population has, the proportion of acts that are protected by condoms and the appropriate transmission probability. The model assumes that a member of the population can only belong to one risk category, even though they may have several different exposure risks. Also, as this model is static and calculates point estimates via risk equations, to estimate short-term incidence levels, individuals cannot move between risk-group categories.

The simplistic nature of the EPP makes it highly accessible to the end user but due to its development as a tool for use in settings of generalised epidemics, its on-going use may be less informative in the Cambodian context. It is also not possible to incorporate behaviour change explicitly, and hence evaluate modes of transmissions. The AEM addresses this gap and adds extra important inputs, but with its large data requirements, need for a deep understanding of the model framework for implementation and analysis, and best applicability to only generalised epidemics, this reduces its usability and relevance. Addressing this disparity motivates the development of the Cambodian HIV Epidemic Model (CHEM) as a new evaluation and projection tool. In this study we aim to evaluate the effectiveness of previous prevention interventions upon the HIV epidemic in terms of the expected prevalence and number of infections averted and forecast epidemic trajectories according to a variety of scenarios related to combinations of interventions appropriate to the Cambodian setting. These projections are made via the design and implementation of a

mathematical model specific for the unique behavioural and epidemiological context of Cambodia.

Methods

Determined through a consultative process with the National Center for HIV/AIDS, Dermatology and STD (NCHADS), the following key distinct population groups of importance in Cambodia were determined for inclusion in CHEM: direct female sex workers (DSW), indirect female sex workers (ISW), clients of female sex workers, men who have sex with men (MSM), men who have sex with men and women (bisexual) (MSMW), injecting drug users (IDU), (non-injecting) amphetamine-type stimulant users (ATS), and males and females in the general population. Many of these groups exist in other countries but some groups are not common elsewhere, for example, the ATS drug users are of interest because their sexual risk behaviour is influenced by their drug use and they make up a larger proportion of the population than IDUs. Additionally, men who have sex with men are split into two types: “longhairs” (MSM) - men who are exclusively homosexual many of whom are transgendered in appearance and “shorthairs” (MSMW) – bisexual men who generally are masculine in appearance. These two groups have differing risk behaviours and therefore are likely to influence the epidemic in varying ways. The CHEM was designed to be a deterministic compartmental model that uses behavioural, clinical and biological data to track for each priority group the number of new infections and the number of those in each progressive stage of HIV disease over time.

CHEM was developed to capture transmission and disease history of HIV in Cambodia. In the model, ordinary differential equations (ODEs) track the number of people in the population over time in each state of HIV disease stage: uninfected, infected but not yet diagnosed, diagnosed but not on treatment and on ART. For each subpopulation, all HIV-infected individuals are classified according to their stage of HIV disease, based on CD4 count: CD4 count greater than 500 cells per mL, between 350 cells and 500 cells per mL, between 200 cells and 350 cells per mL, less than 200 cells per mL. Additionally, the model tracks the number of people who initiate first-line ART, the rate of treatment failure, and progression to second- and subsequent-lines of ART. HIV/AIDS-related deaths and other causes of death are also included in the model. A schematic diagram of the natural history described by the model is presented in Figure 1, how each of the subpopulations mix is shown in Figure 2 and the governing equations of the model are presented in Equation 1.

Figure 1: HIV health states in CHEM

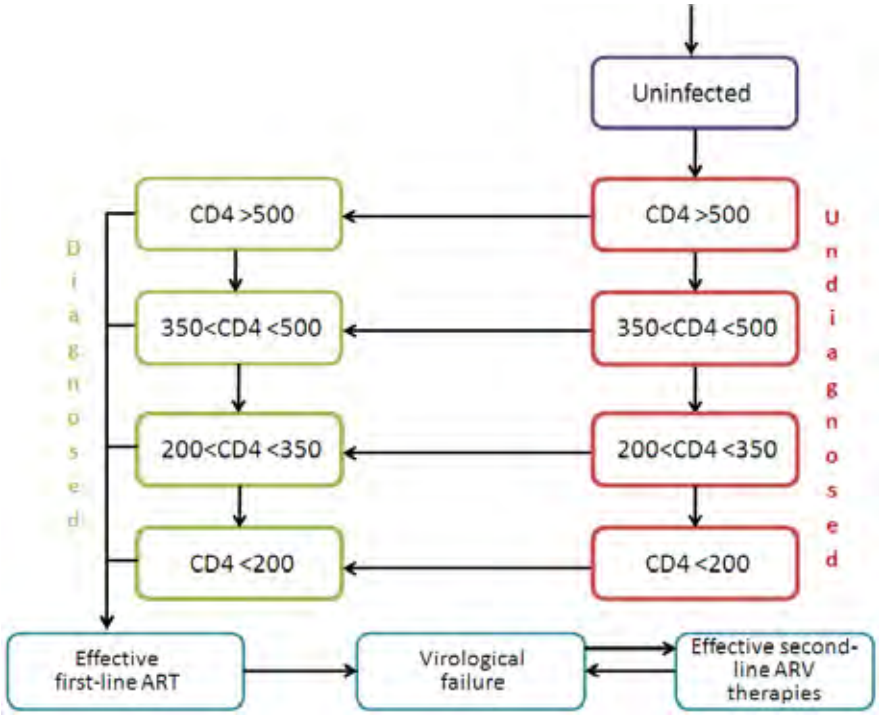
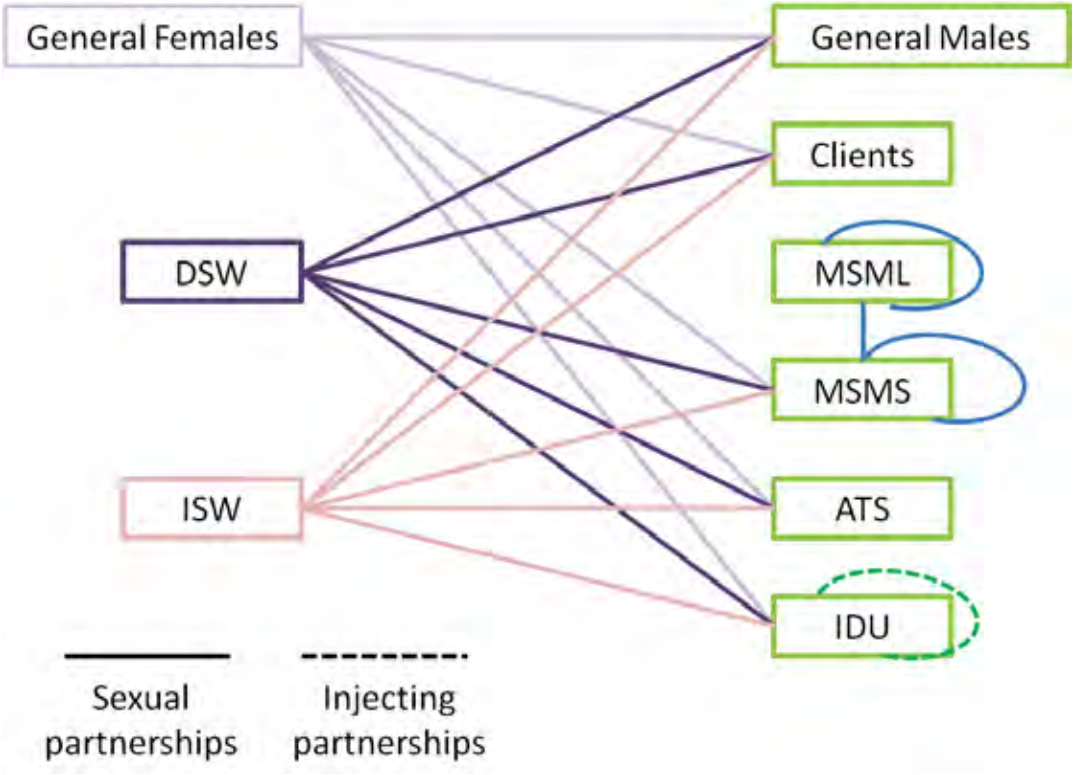


Figure 2 - Partnership mixing between populations



Equation 1: Governing equations of the model

Change in number of uninfected people

$$\frac{dS}{dt} = \underbrace{\pi}_{\text{New entry into population}} - (\underbrace{\mu}_{\text{Background death}} + \underbrace{\lambda}_{\text{Per-capita rate of acquiring HIV}}) \cdot S$$

Change in number of people with undiagnosed infection (CD4>500)

$$\frac{dU_{500}}{dt} = \underbrace{\lambda S}_{\text{New infections}} - (\underbrace{\mu}_{\text{Background death}} + \underbrace{\mu_{500}}_{\text{HIV-related death (CD4>500)}} + \underbrace{\tau_{500}}_{\text{Progression to 350<CD4<500}} + \underbrace{\eta_{500}}_{\text{Testing/diagnosis rate (CD4>500)}}) \cdot U_{500}$$

Change in number of people with diagnosed infection (CD4>500)

$$\frac{dD_{500}}{dt} = \underbrace{\eta_{500} U_{500}}_{\text{New diagnoses}} - (\underbrace{\mu}_{\text{Background death}} + \underbrace{\mu_{500}}_{\text{HIV-related death (CD4>500)}} + \underbrace{\tau_{500}}_{\text{Progression to 350<CD4<500}} + \underbrace{\sigma_{500}}_{\text{Treatment rate (CD4>500)}}) \cdot D_{500}$$

Change in number of people with undiagnosed infection (350<CD4<500)

$$\frac{dU_{350\_500}}{dt} = \underbrace{\tau_{500} U_{500}}_{\text{Progression from CD4 >500}} - (\underbrace{\mu}_{\text{Background death}} + \underbrace{\mu_{350\_500}}_{\text{HIV-related death (350<CD4<500)}} + \underbrace{\tau_{350\_500}}_{\text{Progression to 200<CD4<350}} + \underbrace{\eta_{350\_500}}_{\text{Diagnosis rate (350<CD4<500)}}) \cdot U_{350\_500}$$

Change in number of people with diagnosed infection (350<CD4<500)

$$\frac{dD_{350\_500}}{dt} = \underbrace{\eta_{350\_500} U_{500}}_{\text{New diagnoses}} + \underbrace{\tau_{500} D_{500}}_{\text{Progression from CD4>500}} - (\underbrace{\mu}_{\text{Background death}} + \underbrace{\mu_{350\_500}}_{\text{HIV-related death (350<CD4<500)}} + \underbrace{\tau_{350\_500}}_{\text{Progression to 200<CD4<350}} + \underbrace{\sigma_{350\_500}}_{\text{Treatment rate (350<CD4<500)}}) \cdot D_{350\_500}$$

Change in number of people with undiagnosed infection (200<CD4<350)

$$\frac{dU_{200\_350}}{dt} = \underbrace{\tau_{350\_500} U_{350\_500}}_{\text{Progression from 350<CD4<500}} - (\underbrace{\mu}_{\text{Background death}} + \underbrace{\mu_{200\_350}}_{\text{HIV-related death (200<CD4<350)}} + \underbrace{\tau_{200\_350}}_{\text{Progression to CD4<200}} + \underbrace{\eta_{200\_350}}_{\text{Diagnosis rate (200<CD4<350)}}) \cdot U_{200\_350}$$

Change in number of people with diagnosed infection (200<CD4<350)

$$\frac{dD_{200\_350}}{dt} = \underbrace{\eta_{200\_350} U_{200\_350}}_{\text{New diagnoses}} + \underbrace{\tau_{200\_350} D_{200\_350}}_{\text{Progression from 200<CD4<350}} - (\underbrace{\mu}_{\text{Background death}} + \underbrace{\mu_{200\_350}}_{\text{HIV-related death (200<CD4<350)}} + \underbrace{\tau_{200\_350}}_{\text{Progression to CD4<200}} + \underbrace{\sigma_{200\_350}}_{\text{Treatment rate (200<CD4<350)}}) \cdot D_{200\_350}$$

Change in number of people with undiagnosed infection (CD4<200)

$$\frac{dU_{200}}{dt} = \underbrace{\tau_{200\_350} U_{200\_350}}_{\text{Progression from 200<CD4<350}} - (\underbrace{\mu}_{\text{Background death}} + \underbrace{\mu_{200}}_{\text{HIV-related death (CD4<200)}} + \underbrace{\tau_{200}}_{\text{Progression to CD4<200}} + \underbrace{\eta_{200}}_{\text{Diagnosis rate (CD4<200)}}) \cdot U_{200}$$

Change in number of people with diagnosed infection (CD4<200)

$$\frac{dD_{200}}{dt} = \underbrace{\eta_{200} U_{200}}_{\text{New diagnoses}} + \underbrace{\tau_{200\_350} D_{200\_350}}_{\text{Progression from 200<CD4<350}} - (\underbrace{\mu}_{\text{Background death}} + \underbrace{\mu_{200}}_{\text{HIV-related death (CD4<200)}} + \underbrace{\tau_{200\_350}}_{\text{Progression to CD4<200}} + \underbrace{\sigma_{200\_350}}_{\text{Treatment rate (CD4<200)}}) \cdot D_{200}$$

Change in number of people on 1st-line ART

$$\frac{dT_{1st}}{dt} = \underbrace{\sigma_{200\_350} D_{200} + \sigma_{200\_350} D_{200\_350} + \sigma_{350\_500} D_{350\_500} + \sigma_{500} D_{500}}_{\text{Rate of initiating ART from each CD4 stage (high CD4 levels may have zero rates)}} - (\underbrace{\mu_{treat}}_{\text{Death rate while on effective ART}} + \underbrace{\nu}_{\text{ART failure rate}}) \cdot T_{1st}$$

Change in number of people experiencing treatment failure

$$\frac{dT_{fail}}{dt} = \underbrace{\nu T_{1st}}_{\text{1st-line ART failure rate}} + \underbrace{\nu_2 T_{2nd}}_{\text{2nd-line ART failure rate}} - (\underbrace{\mu_{fail}}_{\text{Death rate while failing ART}} + \underbrace{\sigma_{2nd}}_{\text{Rate of initiating 2nd-line ART}}) \cdot T_{fail}$$

Change in number of people on 2nd-line ART

$$\frac{dT_{2nd}}{dt} = \underbrace{\sigma_{2nd} T_{fail}}_{\text{Rate of people initiating 2nd-line ART}} - (\underbrace{\mu_{treat}}_{\text{Death rate while on effective ART}} + \underbrace{\nu_2}_{\text{2nd-line ART failure rate}}) \cdot T_{2nd}$$

The model was informed by biomedical inputs such as (1) infectiousness due to disease stage (which is strongly associated with viral load) (2); type of exposure to HIV (heterosexual or homosexual intercourse; injection), effectiveness of condoms, circumcision, ART, and needle-syringe cleaning in preventing transmission; and (3) rates of natural and HIV-related death. Behavioural inputs for sexual transmission included changing rates of condom use and HIV testing over time, average number of casual and regular homosexual and heterosexual partnerships per person, and the average frequency of sexual acts per partnership. For intravenous transmission, parameters included the number of injecting partners per person per year, frequency of sharing injecting equipment, the percentage of shared syringes that are cleaned prior to re-use, and the number of injection acts per year.

In order to effectively predict possible epidemic trajectories for the future, it is essential that the model is able to reflect observations of the past and present. In order to achieve this, given the uncertainty around all parameter values, within confidence intervals or plausible bounds, an optimization procedure was used. This procedure determines how the complex interactions of all the parameters can be reconciled together to match the available population-level data. To calibrate the model, weights were assigned to each of the input and output parameters (e.g., condom usage rates and prevalence, respectively). A goodness-of-fit function was defined as the sum of squared differences between the available data and the model inputs and outputs, multiplied by the assigned weights. A trust-region-reflective algorithm [17, 18], a gradient-descent method with a dynamically updating step size based on the curvature of parameter space, was used find an optimal set of input parameters. Briefly, this method perturbs each input parameter in turn, evaluates the model and its goodness-of-fit after each perturbation, calculates the gradient of the resulting set of goodness-of-fits, and modifies the parameter values in the direction of the gradient. Starting from the modified parameter set, the process repeats, until one of the following stopping criteria is met: (1) the

gradient is always positive (i.e., a local minimum has been reached), (2) the goodness-of-fit is within a predetermined tolerance limit, or (3) the number of iterations has exceeded a predetermined maximum. In the present case, optimization usually terminated due to the second stopping criterion.

Since parameter values used in the model are not precisely known, it is necessary to conduct uncertainty analyses to determine the range of possible model outcome values related to the range of input parameter values. In order to carry out this analysis, minimum and maximum plausible limits are assigned to input parameters. The estimated 2.5, 50, and 97.5 percentiles were used to numerically define a nonparametric distribution for each parameter, with first- and second-order continuity provided by spline interpolation mapped onto the desired interval by means of an inverse error function. Time-varying parameters were assigned uncertainty bounds in the model up to ± 20% of the best parameter estimates. Furthermore, all parameters were defined to have 'hard' limits to their bounds to ensure realism (e.g. all fractions must be bounded between 0 and 1). Uncertainty in outcomes were generated by running 40 simulations, each simulation using a different set of parameters sampled from the defined uncertainty distributions associated with each model input. In this model we used a 95% uncertainty limit defined by the 2^{nd} and 39^{th} values of 40 simulations at each time step.

By matching the available epidemiological and behavioural data for the years 2000 to 2010, the model can evaluate the effectiveness of past campaigns by calculating how many infections could have been expected otherwise had they not been put into place. Then by predicting future epidemiological trajectories under current conditions, the possible impact of future interventions can also be measured. Projections are carried out to represent the time period from the year 2011 to 2020.

It is not possible to know for certain all indirect effects an intervention had on behaviour through its implementation. For example, the 100% CUP for direct sex workers increased condom use for both direct and indirect sex workers in commercial and non-transactional acts. This increase was a direct result of the education and support provided to FSWs. This education however, may have possibly increased condom use in general females with FSWs educating their female relatives and friends in turn. Another possible flow-on effect could be increased condom use in clients for non-transactional sex-acts, with clients becoming more aware of the risk of contracting HIV through their interaction with FSWs. In order to assess the effectiveness of the 100% CUP campaign, we therefore take a conservative approach and only consider the effect of retaining condom use rates in FSWs at the same level as they were in 1998. It is also possible that other programmes in operation over this period may have had an impact on increasing condom use among FSWs, however, 100% CUP was the only intervention specifically targeted FSWs. Therefore, it is argued that an assumption that condom use would have remained at 1998 levels in the absence of 100% CUP is reasonable. Similarly, we can evaluate the impact that the introduction of ART in 2003 had upon the epidemic. As reviewed in Chapter 2, a person's infectivity is greatly reduced with effective antiretroviral treatment. It could be assumed that without the scale-up of antiretroviral treatment the reduction in infectiousness for those receiving effective antiretroviral treatment would not occur.

To estimate the number of infections averted due to these programmes the CHEM can be simulated over the relevant historical time periods according to the assumptions without the programmes and compared with the epidemic trajectories under the optimized, calibrated model. The difference in the estimated incidence provides an indication of the expected number of infections averted due to the programmes. The CHEM is also used to project epidemic trajectories according to changes in conditions, associated with the implementation

of different interventions. Intervention types investigated with CHEM are described in the following paragraphs.

Heterosexual condom use outside of transactional-sex is low. According to the 2010 Cambodia Demographic and Health Survey [19], approximately 2.7% of married women have used condoms at some stage during the previous year. In MSM, condom use is much more consistent, with 83% of 'short-hair' MSM reporting condom use at last sex and 94% of 'long-hair' MSM in the 2007 Behavioural Sentinel Surveillance [3]. We take the efficacy of condoms to be 95%, and simulate epidemic trajectories according to condoms being used in 2% of acts to 10, 20 and 40%.

Circumcision levels in Cambodia are unknown, but are estimated to be very low. For modelling purposes, it is more conservative to overestimate the prevalence of circumcision, which in turn would lead to an underestimation of new infections, particularly in males. Therefore, we assume the current circumcision level in sexually active males in Cambodia is five percent. We examine a potential intervention that would result in small increases in circumcision prevalence to 10, 15 and 20%, as large increases are not likely to be attained. As circumcision is of greater benefit to men, especially those with low condom use, we focus on targeting circumcision to adult men of the general heterosexual population that do not belong to any higher-risk groups.

Therapeutic replacement of heroin to reduce injection frequency, education about safer injecting habits and increased access to clean needles and syringes for those who inject drugs could be an efficient means of reducing HIV incidence in that population. As the current enrolment in the MMT program is very low, we focus solely on needle and syringe programs. In the model we assume that for those who share injection equipment, approximately 60% of injections are shared. We evaluate an intervention that through the provision of equipment

and education, reduces the proportion of injections that used shared equipment for those injectors who share from 60% to 45%, 30% and 15%. Sharing rates of 15% are still common in settings of high access to needle and syringe programmes [25], and therefore this sharing rate is considered as a best target.

Changing guidelines on access to antiretroviral medications such that more people qualify as eligible for treatment benefits not only the HIV-infected individuals but also reduces the community viral load. A reduction in community viral load reduces the average infectiousness and therefore population incidence. Those diagnosed with HIV infection are currently deemed eligible when their CD4 count drops below 350 per millilitre of blood. We use CHEM to investigate the impact of raising this criterion to treating those with levels less than 500/mL and also treating all of those that are diagnosed. Whilst it is not feasible to enforce treatment upon all of those diagnosed, it is a useful exercise to evaluate the full benefit of antiretroviral medication. The evaluation is also conducted in combination with an increase in testing rates in general males and females from 2% to 10% and 20%.

Clearly, a public health response to an epidemic affecting multiple population groups and for which there are different intervention options should involve the implementation of more than one targeted strategy concurrently. We project the relative impact of combinations of initiatives which are thought likely to be effective and feasible to implement and maintain, in terms of acceptance and adherence in the targeted population. As testing rates in general males and females are low, we recommend a target of a relatively small increase in testing to 10% per year, in conjunction with providing antiretroviral medication to all of those diagnosed with a positive infection and reducing the percentage of shared injections for those who shared from 60% to 30%. We then evaluate the same scenario with a 20% testing rate in general males and females and then once more with the addition of increasing condom use in non-transactional heterosexual acts from approximately 2% to 10%.

Results

For the years 2000 to 2010, the model calculated that there were approximately 72427 (95% confidence interval: 32607, 164536) new infections in the population overall. The breakdown of infections by risk-group can be seen in Table 1. The proportion of new infections incurred in and attributed to each sub-population can be seen in Figure 2 (a-d). General females (who cannot be classified in a behavioural most-at-risk population group) account for the largest proportion, with 47% of new infections between the years 2000-2010. The large absolute number of infections in this group is due to the large population size compared to the relatively small population groups most at risk that have high per-capita rates of infection. General males and clients of sex workers are the next most-at-risk groups with 36% and 11% of incident cases respectively. The proportions are similar for attribution of infections; overall general females are the largest group with 49%, general males follow with 37% and clients contribute 11%. The profile does change over time, with infections caused by female sex workers in 2010 less than half the proportion in 2000. Prevalence in general males, general females and ATS users remains low and relatively constant. The model suggests there has been a continual reduction in prevalence in direct and indirect sex workers and their clients. Populations at higher risk, such as MSM and IDU, had a delayed peak in their prevalence with a noticeable decline in prevalence among MSM and a more modest decline among IDU that could be tending towards a plateau. Injecting drug users have the highest prevalence overall by 2010, estimated at 22.8%.

In Table 2 we present the results from evaluating the effectiveness of the 100% CUP campaign, the introduction of antiretroviral treatment and the two programmes in

combination. In the absence of 100% CUP, the model predicts there would have been an approximate 78415 (34860, 181517) new infections for the years 2000-2010, meaning there would have been 5988 (2253, 16981) or 8.3% more infections than what would have been expected otherwise. The majority of these extra infections would likely have occurred in male clients of FSWs, with an extra 3381 (1480, 8039) (42.1%), followed by general females with an extra 1466 (399, 5124) (4.3%) and FSW with 632 (267, 1570) (69.8%). Had ART not been implemented, in the population overall the model predicts there would have been 81994 (36744, 185140) HIV infections between 2000 and 2010 which equates to an extra 13.2% (9567) more infections than otherwise expected. Broken down into key risk groups, general females would have accounted for 3872 (17243, 85777) of these infections (an extra 13.5% for that risk group), 9127 (4258, 19847) among clients of FSWs (extra 13.7%), and1040 (488, 2389) HIV or 14.8% more infections among FSW. These two interventions did not occur in isolation, but concurrently. However, the number of infections averted due to the two interventions will not be the sum of the separate estimated impact as they both affected the same population sub-groups but in different ways. In absence of both interventions, there would have been an expected 88882 (39350, 204256) infections in the population overall, of which 39903 (17684, 91418) would be in general females, 13099 (5997, 29116) in clients and 1776 (799, 4185) in FSW. That is, the two interventions were estimated to result in an aversion of 16455 HIV infections in total, or 22.7% of all incident infections.

Table 1: Matching available past epidemiological data years 2000 - 2010 (Baseline).

	Risk Group									
Cumulative Incidence	Overall Population	General Females	General Males	DSW	ISW	Clients	MSML	MSMS	ATS	IDU
Upper	164536	76055	60617	186	720	17478	3262	2267	81	2676
Median	72427	33714	26366	90	338	8028	1274	933	19	1160
Lower	32607	15263	11719	1669	164536	3772	520	412	6	471

Table 2: Evaluating the effectiveness of past interventions 2000 - 2010.

	Baseline	Without 100% CUP			Without ART			Without 100% CUP or ART		
		Cumulative Incidence	Additional Infections		Cumulative Incidence	Additional Infections		Cumulative Incidence	Additional Infections	
			no.	%		no.	%		no.	%
All Pops										
Upper	164536	181517	16981	10.3	185140	20604	12.5	204256	39720	24.1
Median	72427	78415	5988	8.3	81994	9567	13.2	88882	16455	22.7
Lower	32607	34860	2253	6.9	36744	4137	12.7	39350	6743	20.7
General Females										

Upper	76055	81179	5124	6.7	85777	9722	12.8	91418	15363	20.2
Median	33714	35180	1466	4.3	38272	4558	13.5	39903	6189	18.4
Lower	15263	15662	399	2.6	17243	1980	13.0	17684	2421	15.9
General Males										
Upper	60617	62858	2241	3.7	68018	7401	12.2	68018	7401	12.2
Median	26366	26872	506	1.9	29760	3394	12.9	29760	3394	12.9
Lower	11719	11826	107	0.9	13167	1448	12.4	13167	1448	12.4
FSW										
Upper	2072	3642	1570	75.8	2389	317	15.3	4185	2113	102.0
Median	906	1538	632	69.8	1040	134	14.8	1776	870	96.0
Lower	428	695	267	62.4	488	60	14.0	799	371	86.7
DSW										
Upper	403	821	418	103.7	451	48	11.9	925	522	129.5
Median	186	378	192	103.2	207	21	11.3	429	243	130.6
Lower	90	175	85	94.4	99	9	10.0	198	108	120.0
ISW										
Upper	1669	2821	1152	69.0	1938	269	16.1	3260	1591	95.3

Median	720	1160	440	61.1	833	113	15.7	1347	627	87.1
Lower	338	520	182	53.8	389	51	15.1	601	263	77.8
Clients										
Upper	17478	25517	8039	46.0	19847	2369	13.6	29116	11638	66.6
Median	8028	11409	3381	42.1	9127	1099	13.7	13099	5071	63.2
Lower	3772	5252	1480	39.2	4258	486	12.9	5997	2225	59.0
MSMSL										
Upper	3262	3262	0	0.0	3526	264	8.1	3526	264	8.1
Median	1274	1274	0	0.0	1382	108	8.5	1382	108	8.5
Lower	520	520	0	0.0	564	44	8.5	564	44	8.5
MSMS										
Upper	2267	2268	1	0.0	2476	209	9.2	2476	209	9.2
Median	933	934	1	0.1	1026	93	10.0	1026	93	10.0
Lower	412	412	0	0.0	454	42	10.2	454	42	10.2
ATS										
Upper	81	113	32	39.5	122	41	50.6	122	41	50.6
Median	19	48	29	152.6	53	34	178.9	53	34	178.9

Lower	6	21	15	250.0	24	18	300.0	24	18	300.0
IDU										
Upper	2676	2679	3	0.1	2984	308	11.5	2984	308	11.5
Median	1160	1160	0	0.0	1334	174	15.0	1334	174	15.0
Lower	471	472	1	0.2	545	74	15.7	545	74	15.7

Figure 3: Incident infections and infections caused by risk group 2000 - 2010

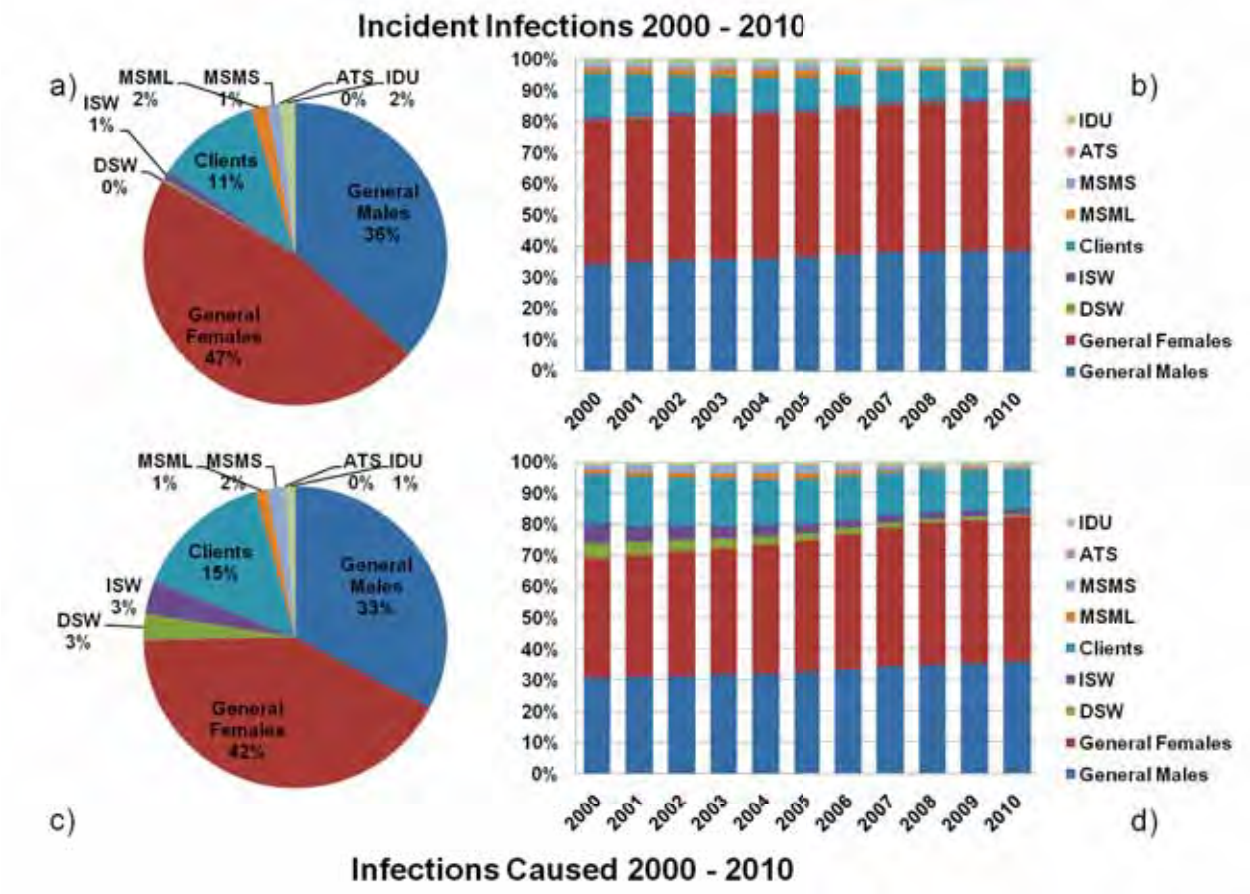
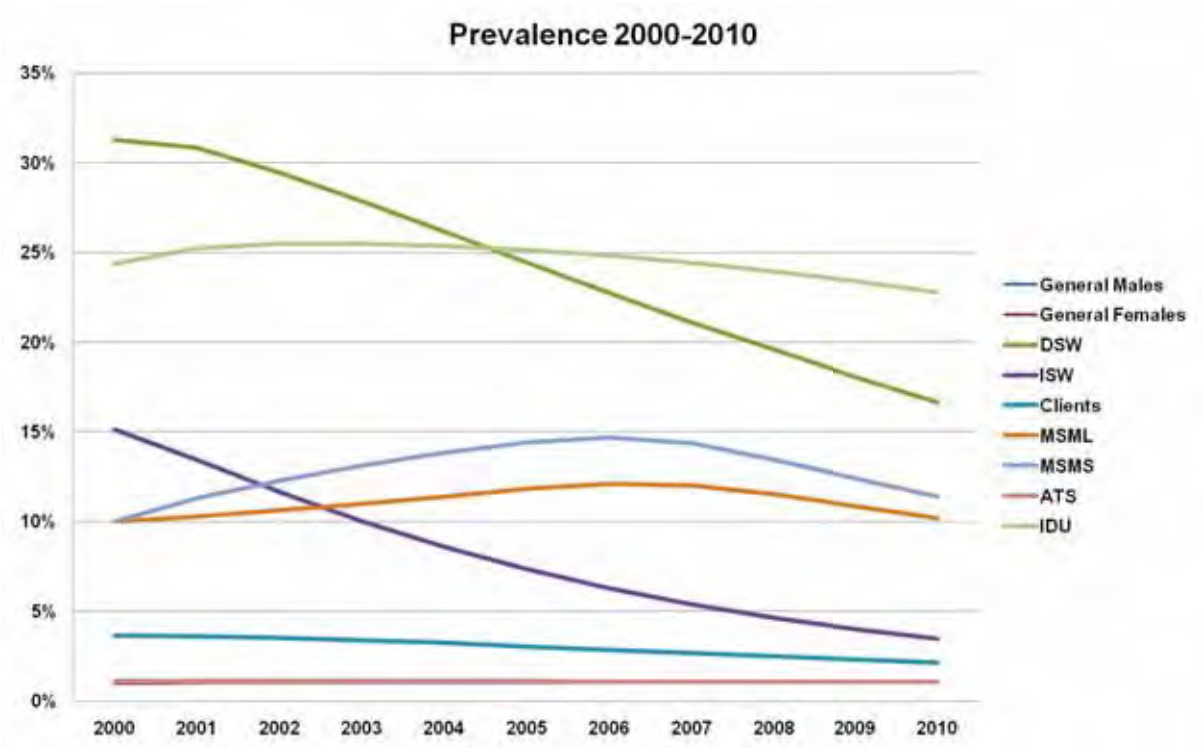


Figure 4: Prevalence by risk group 2000 - 2010



The model was then used to project trajectories under current conditions to assess the impact of other intervention strategies which may be considered for implementation in the future. The projection for future prevalence and incidence under current conditions is presented in Figures 5 & 6 and Table 3 (N.B. In Figures 5 & 6 trajectories for General Males, General Females and ATS overlap).

Figure 5: Prevalence by risk group 2011 - 2020

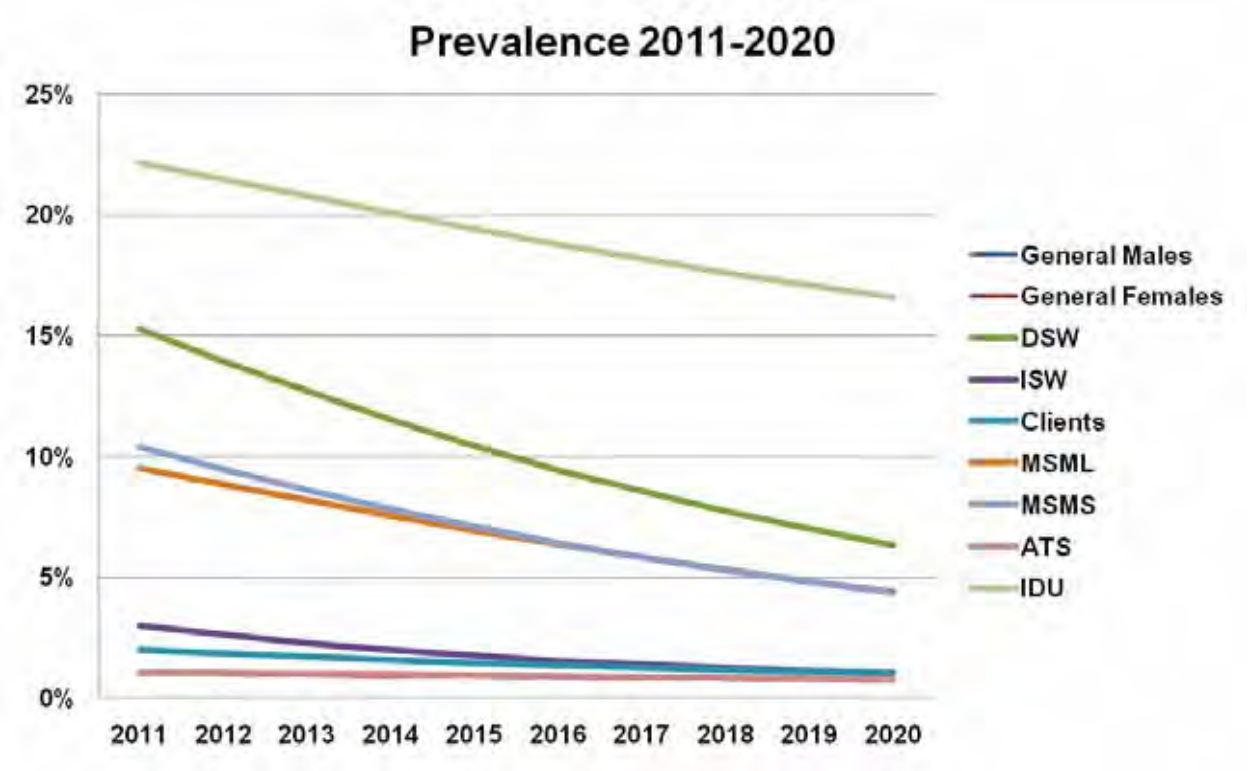
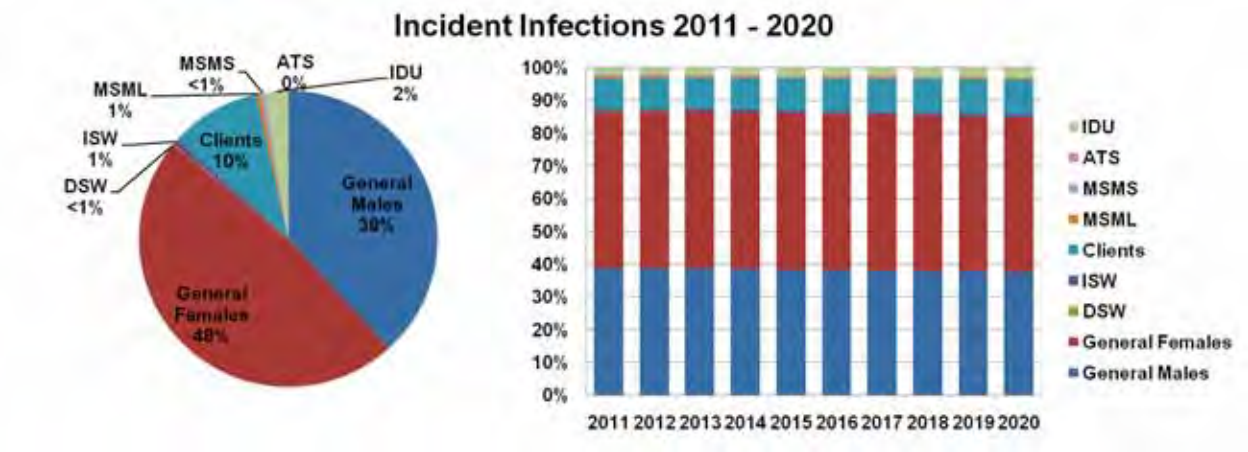


Figure 6: Incident infections by risk group 2011 - 2020



The projected incidence for increasing condom use for non-transactional sex in heterosexuals can be seen in Table 4. If condoms are used in 10% of all relevant acts, we could expect 11.2% less infections across the entire population. If condoms are used in 20% or 40% of acts, this increases to 23.7% or 44.8%. Population groups that would benefit most, in terms of absolute numbers, from such an intervention would be general males and general females who proportionally have the most infections averted due to the largest population sizes.

Increasing the prevalence of circumcision in men from 5% to 10, 15 and 20%, in the population overall would avert an estimated 708 (182, 3284), 1382 (355, 6401) and 2051(528, 9485) infections in the years 2011 to 2020 respectively, translating to 2.4, 4.7 and 6.9% as seen in Table 5. The greatest benefit is seen in general males at low-risk of infection and an increase in circumcision to 10% will avert 3.6% of infections; increasing circumcision levels to 15% is estimated to avert 7% of infections in this group and circumcision levels of 20% is estimated to avert 10.4% of infections among the general male population. Male clients of sex-workers would likely gain almost as much benefit as other males, with a corresponding 3.4% (100 infections), 6.9% (200 infections) and 10.3% (299 infections) reduction in incidence.

Decreasing the percentage of shared injections for those IDU who share, from 60% to 45%, was projected to avert 249 (55, 697) or 34.7% of new HIV infections in IDUs over the next 10 year period as show in Table 6. As the IDU population in Cambodia is relatively small, this intervention would lead to only a 1.1% reduction in incident infections the population overall. If it is possible to reduce the proportion of shared injections for those who share to 15%, 587 (138, 1761) or 81.9% of infections that would otherwise be expected for IDUs could be averted. There is a small flow-on effect for this intervention in general females with reductions in incidence from 0.5-1.3% (72-179 infections averted).

Increasing the scale-up of antiretroviral use, by raising the treatment-eligibility criteria from a CD4 count of 350 to 500, with treatment initiation for all diagnosed individuals and assuming no change in testing rates, approximately 240 (65, 1048) infections (0.8%) would be averted from 2011 to 2020 in the overall population. This reduction increases to 2.1% if testing rates in general males and females were raised from 4% to 10% and would increase again to 3.7% with a testing rate of 20%. With no change in current testing rates, by treating all of those diagnosed, approximately 3127 (791, 14494) of otherwise expected infections would not occur in the overall population, equivalent to 10.5%. This increases to 15.4% and 21.5% if the testing rate for general females and males rises to 10% and 20% respectively. These are presented in Tables 7 & 8.

As shown in Figure 6, the most at-risk populations in terms of incidence are general females and males and clients of female sex workers. In terms of HIV prevalence (Figure 5), IDUs are clearly an important risk-group with prevalence greater than 20%. It is important to ensure that all key groups are targeted when implementing health policy and no single intervention will do this. Therefore, it is necessary to combine interventions that will be effective at reducing incidence in these groups whilst still remaining feasible in terms of implementation and acceptance to those whom are targeted. The resultant trajectories for the combination of some interventions is presented in Table 9. A public health policy that results in: an HIV testing rate in the general (those not belonging to higher-risk groups) population of 10%; provides access to treatment for all of those diagnosed; and reduces the proportion of shared injection acts to 30% would reduce incidence overall by 16.9%, with reductions in individual risk groups varying between 10.5% and 70.3%. Increasing the testing rate in the general population to 20% would result in a reduction of 22.9% overall with reduction in risk groups varying between 21% and 70.6%. These increase to 31.2% and between 26.3% and 70.7% respectively with an increase in condom use for non-transactional heterosexual sex acts to 10%

Table 3: Forecasting trajectories under current conditions - Status Quo (SQ) 2011 - 2020

	Risk Group									
Cumulative Incidence	Overall Population	General Females	General Males	DSW	ISW	Clients	MSML	MSMS	ATS	IDU
Upper	123120	58336	47311	130	1188	12076	879	770	81	2350
Median	29674	14149	11352	24	211	2915	152	133	19	717
Lower	8918	4280	3401	8	67	890	47	43	6	177

Table 4 : Evaluation of increasing condom use for heterosexual non-transactional sex 2011 - 2020

	SQ	10% Condom Use			20% Condom Use			40% Condom Use		
		Cumulative Incidence	Infections averted		Cumulative Incidence	Infections averted		Cumulative Incidence	Infections averted	
			no.	%		no.	%		no.	%
All Populations										
Upper	123120	109341	13779	11.2	93907	29213	23.7	67916	55204	44.8
Median	29674	26441	3233	10.9	22733	6941	23.4	16238	13436	45.3
Lower	8918	8079	839	9.4	7085	1833	20.6	5248	3670	41.2
General Males										
Upper	47311	41753	5558	11.7	35527	11784	24.9	25043	22268	47.1
Median	11352	10051	1301	11.5	8558	2794	24.6	5944	5408	47.6
Lower	3401	3063	338	9.9	2664	737	21.7	1927	1474	43.3
General Females										
Upper	58336	51564	6772	11.6	43976	14360	24.6	31187	27149	46.5
Median	14149	12554	1595	11.3	10724	3425	24.2	7513	6636	46.9
Lower	4280	3863	417	9.7	3369	911	21.3	2454	1826	42.7
FSW										
Upper	1318	1223	95	7.2	1116	202	15.3	934	384	29.1
Median	234	219	15	6.4	201	33	14.1	169	65	27.8
Lower	75	72	3	4.0	67	8	10.7	59	16	21.3
Clients										
Upper	12076	10743	1333	11.0	9253	2823	23.4	6757	5319	44.0

Median	2915	2600	315	10.8	2239	676	23.2	1611	1304	44.7
Lower	890	810	80	9.0	715	175	19.7	541	349	39.2
ATS										
Upper	81	73	8	9.9	64	17	21.0	49	32	39.5
Median	19	17	2	10.5	16	3	15.8	12	7	36.8
Lower	6	5	1	16.7	5	1	16.7	4	2	33.3

Table 5: Evaluation of male circumcision 2011 - 2020

	SQ	10% circumcision			15% circumcision			20% circumcision		
		Cumulative Incidence	Infections averted		Cumulative Incidence	Infections averted		Cumulative Incidence	Infections averted	
			no.	%		no.	%		no.	%
All Populations										
Upper	123120	119836	3284	2.7	116719	6401	5.2	113635	9485	7.7
Median	29674	28966	708	2.4	28292	1382	4.7	27623	2051	6.9
Lower	8918	8736	182	2.0	8563	355	4.0	8390	528	5.9
General Males										
Upper	47311	45574	1737	3.7	43937	3374	7.1	42321	4990	10.5
Median	11352	10940	412	3.6	10552	800	7.0	10167	1185	10.4
Lower	3401	3284	117	3.4	3174	227	6.7	3065	336	9.9
MSM										
Upper	1649	1615	34	2.1	1579	70	4.2	1544	105	6.4
Median	285	280	5	1.8	275	10	3.5	269	16	5.6
Lower	91	89	2	2.2	88	3	3.3	86	5	5.5
General Females										
Upper	58336	57281	1055	1.8	56286	2050	3.5	55298	3038	5.2
Median	14149	13963	186	1.3	13788	361	2.6	13613	536	3.8
Lower	4280	4245	35	0.8	4213	67	1.6	4180	100	2.3
IDU										

Upper	2350	2347	3	0.1	2344	6	0.3	2340	10	0.4
Median	717	717	0	0.0	716	1	0.1	715	2	0.3
Lower	177	176	1	0.6	176	1	0.6	175	2	1.1
FSW										
Upper	1318	1294	24	1.8	1270	48	3.6	1247	71	5.4
Median	234	232	2	0.9	229	5	2.1	226	8	3.4
Lower	75	75	0	0.0	74	1	1.3	74	1	1.3
Clients										
Upper	12076	11649	427	3.5	11228	848	7.0	10812	1264	10.5
Median	2915	2815	100	3.4	2715	200	6.9	2616	299	10.3
Lower	890	862	28	3.1	833	57	6.4	804	86	9.7
ATS										
Upper	81	78	3	3.7	75	6	7.4	72	9	11.1
Median	19	19	0	0.0	18	1	5.3	17	2	10.5
Lower	6	6	0	0.0	5	1	16.7	5	1	16.7

Table 6: Evaluation of NSP resulting in lowered needle and syringe sharing rates 2011 - 2020

	SQ	45% of Injections Shared			30% of Injections Shared			15% of Injections Shared		
		Cumulative Incidence	Infections averted		Cumulative Incidence	Infections averted		Cumulative Incidence	Infections averted	
			no.	%		no.	%		no.	%
All Populations										
Upper	123120	121986	1134	0.9	121001	2119	1.7	120200	2920	2.4
Median	29674	29333	341	1.1	29064	610	2.1	28855	819	2.8
Lower	8918	8853	65	0.7	8797	121	1.4	8749	169	1.9
IDU										
Upper	2350	1653	697	29.7	1058	1292	55.0	589	1761	74.9
Median	717	468	249	34.7	275	442	61.6	130	587	81.9
Lower	177	122	55	31.1	77	100	56.5	39	138	78.0
General Females										

Upper	58336	58024	312	0.5	57749	587	1.0	57517	819	1.4
Median	14149	14077	72	0.5	14018	131	0.9	13970	179	1.3
Lower	4280	4270	10	0.2	4261	19	0.4	4254	26	0.6

Table 7: Evaluation of increasing treatment rates 2011 - 2020

	SQ	Treat CD4 < 500			Treat All Diagnosed		
		Cumulative Incidence	Infections averted		Cumulative Incidence	Infections averted	
			no.	%		no.	%
All Populations							
Upper	123120	122072	1048	0.9	108626	14494	11.8
Median	29674	29434	240	0.8	26547	3127	10.5
Lower	8918	8853	65	0.7	8127	791	8.9
General Males							
Upper	47311	46973	338	0.7	42633	4678	9.9
Median	11352	11276	76	0.7	10371	981	8.6
Lower	3401	3380	21	0.6	3157	244	7.2
MSM							
Upper	1649	1600	49	3.0	1051	598	36.3
Median	285	278	7	2.5	201	84	29.5
Lower	91	89	2	2.2	68	23	25.3
General Females							
Upper	58336	57833	503	0.9	51398	6938	11.9
Median	14149	14030	119	0.8	12601	1548	10.9
Lower	4280	4247	33	0.8	3879	401	9.4
IDU							
Upper	2350	2317	33	1.4	1806	544	23.1
Median	717	706	11	1.5	541	176	24.5
Lower	177	173	4	2.3	140	37	20.9

FSW							
Upper	1318	1299	19	1.4	1066	252	19.1
Median	234	232	2	0.9	198	36	15.4
Lower	75	75	0	0.0	65	10	13.3
Clients							
Upper	12076	11969	107	0.9	10598	1478	12.2
Median	2915	2893	22	0.8	2618	297	10.2
Lower	890	884	6	0.7	813	77	8.7
ATS							
Upper	81	80	1	1.2	73	8	9.9
Median	19	19	0	0.0	18	1	5.3
Lower	6	6	0	0.0	5	1	16.7

Table 8: Evaluation of implementing test and treat 2011 - 2020

	SQ	General Males & Females Test 10% & Treat CD4 < 500			General Males & Females Test 20% & Treat CD4 < 500			General Males & Females Test 10% & Treat All Diagnosed			General Males & Females Test 20% & Treat All Diagnosed		
		Cumulative Incidence	Infections averted		Cumulative Incidence	Infections averted		Cumulative Incidence	Infections averted		Cumulative Incidence	Infections averted	
			no.	%		no.	%		no.	%		no.	%
All Populations													
Upper	1231	120335	2785	2.3	118126	4994	4.1	101681	21439	17.4	92872	30248	24.6
Median	2967	29051	623	2.1	28572	1102	3.7	25105	4569	15.4	23305	6369	21.5
Lower	8918	8765	153	1.7	8652	266	3.0	7812	1106	12.4	7412	1506	16.9
General Males													
Upper	4731	46236	1075	2.3	45302	2009	4.2	39697	7614	16.1	35975	11336	24.0
Median	1135	11112	240	2.1	10907	445	3.9	9753	1599	14.1	8983	2369	20.9
Lower	3401	3341	60	1.8	3292	109	3.2	3019	382	11.2	2844	557	16.4
MSM													
Upper	1649	1600	49	3.0	1599	50	3.0	1049	600	36.4	1046	603	36.6

Median	285	278	7	2.5	278	7	2.5	200	85	29.8	199	86	30.2
Lower	91	89	2	2.2	89	2	2.2	68	23	25.3	68	23	25.3
General Females													
Upper	5833	57030	1306	2.2	56007	2329	4.0	48173	10163	17.4	44076	14260	24.4
Median	1414	13857	292	2.1	13639	510	3.6	11943	2206	15.6	11121	3028	21.4
Lower	4280	4208	72	1.7	4158	122	2.9	3739	541	12.6	3560	720	16.8
IDU													
Upper	2350	226	2124	90.4	2314	36	1.5	1800	550	23.4	1793	557	23.7
Median	717	61	656	91.5	705	12	1.7	540	177	24.7	538	179	25.0
Lower	177	12	165	93.2	173	4	2.3	140	37	20.9	139	38	21.5
FSW													
Upper	1318	1288	30	2.3	1274	44	3.3	1022	296	22.5	964	354	26.9
Median	234	230	4	1.7	228	6	2.6	191	43	18.4	182	52	22.2
Lower	75	74	1	1.3	74	1	1.3	64	11	14.7	62	13	17.3
Clients													
Upper	1207	11785	291	2.4	11553	523	4.3	9872	2204	18.3	8956	3120	25.8
Median	2915	2850	65	2.2	2798	117	4.0	2461	454	15.6	2266	649	22.3
Lower	890	874	16	1.8	861	29	3.3	778	112	12.6	734	156	17.5
ATS													
Upper	81	79	2	2.5	77	4	4.9	68	13	16.0	62	19	23.5
Median	19	19	0	0.0	18	1	5.3	17	2	10.5	15	4	21.1
Lower	6	6	0	0.0	6	0	0.0	5	1	16.7	5	1	16.7

Table 9: Evaluation of combining select interventions 2011 - 2020

	Status Quo	General Males & Females Test 10%, Treat All Diagnosed, 30% Injections Shared			General Males & Females Test 20%, Treat All Diagnosed, 30% Injections Shared			General Males & Females Test 10% with 10% Condom Use, Treat All Diagnosed, 30% Injections Shared		
		Cumulative Incidence	Infections averted		Cumulative Incidence	Infections averted		Cumulative Incidence	Infections averted	
			no.	%		no.	%		no.	%
All Populations										
Upper	123120	100091	23029	18.7	91294	31826	25.8	81276	41844	34.0
Median	29674	24662	5012	16.9	22864	6810	22.9	20416	9258	31.2
Lower	8918	7719	1199	13.4	7319	1599	17.9	6638	2280	25.6
General Males										
Upper	47311	39562	7749	16.4	35846	11465	24.2	31786	15525	32.8
Median	11352	9733	1619	14.3	8963	2389	21.0	7973	3379	29.8
Lower	3401	3017	384	11.3	2842	559	16.4	2567	834	24.5
	MSM									
Upper	1649	1049	600	36.4	1046	603	36.6	1042	607	36.8
Median	285	200	85	29.8	199	86	30.2	199	86	30.2
Lower	91	68	23	25.3	68	23	25.3	67	24	26.4
General Females										
Upper	58336	47756	10580	18.1	43663	14673	25.2	38742	19594	33.6
Median	14149	11854	2295	16.2	11032	3117	22.0	9825	4324	30.6
Lower	4280	3725	555	13.0	3547	733	17.1	3208	1072	25.0
IDU										
Upper	2350	801	1549	65.9	793	1557	66.3			
Median	717	213	504	70.3	211	506	70.6	210	507	70.7
Lower	177	62	115	65.0	62	115	65.0	61	116	65.5
FSW										

Upper	1318	1018	300	22.8	961	357	27.1	895	423	32.1
Median	234	190	44	18.8	181	53	22.6	170	64	27.4
Lower	75	64	11	14.7	62	13	17.3	59	16	21.3
Clients										
Upper	12076	9839	2237	18.5	8924	3152	26.1	7969	4107	34.0
Median	2915	2456	459	15.7	2262	653	22.4	2026	889	30.5
Lower	890	778	112	12.6	734	156	17.5	669	221	24.8
ATS										
Upper	81	68	13	16.0	61	20	24.7	56	25	30.9
Median	19	17	2	10.5	15	4	21.1	14	5	26.3
Lower	6	5	1	16.7	5	1	16.7	4	2	33.3

Discussion

As expected, when evaluating past interventions, the combination of 100% CUP and the introduction of antiretroviral treatment was more effective at averting infections than either programme in isolation with 18.5% (17.1%, 19.4%) infections averted. When analysing either intervention separately, it is interesting to note that whilst the introduction of ART reduced incidence more overall (11.7% vs. 7.6%), 100% CUP was more effective in FSWs (41.1% vs. 12.9% averted) and in clients (29.6% vs. 12%). This highlights the importance of continuing efforts in sexual education and condom promotion in commercial sex-acts, especially with the numbers of indirect sex workers increasing as brothels are closed down in Cambodia [4].

In terms of future interventions, as a stand-alone initiative, an increase in condom use in heterosexual non-transactional sex acts provided the highest reduction in incidence in the projected epidemic trajectories, followed by provision of treatment to all. Whilst needle-syringe programmes currently seem to not benefit the population overall, even small reductions in sharing of injecting equipment result in large decreases in incidence, making it an important harm-reduction strategy for IDUs. Additionally, if the numbers of those who inject were to increase, the potential benefit of scaling up NSPs is likely to be even greater than currently estimated.

When considering the implementation of public health policies, it is important to consider the acceptability and feasibility of their implementation. Not only do we mean in a fiscal sense in terms of funding and possible infrastructure required, but also the acceptability of the

interventions to the people to whom such policies are targeting. For example, in a country such as Cambodia where rates of male circumcision are already extremely low, it is not likely that an intervention promoting adult male circumcision would have a high uptake rate. Increased condom use may be more successfully implemented, but without continued promotion and education, there is a risk that condom-fatigue will occur and rates drop to previous levels.

Needle and syringe programs and increased access to testing and antiretroviral treatment are highly effective at reducing incidence and provide additional health benefits to the individual. Both of these schemes however, require infrastructure for their implementation and expansion. For Cambodia, this would likely require funding from government and international sources. Large financial investments required to significantly increase treatment coverage is likely to be a limiting factor in its implementation. It is not realistic to consider universal testing and treatment of all diagnosed individuals in Cambodia, as has been proposed [20]. In addition, some people may refuse to test for HIV or may refuse medication upon diagnosis. As this is the choice of the individual, it is an important ethical issue to consider the removal of such right as part of a universal testing and treatment programme. However, the substantial epidemiological benefits that can be gained through using treatment as prevention is likely to be highly worth increased investment to ensure that at least people who have advanced disease progression and need therapy to reduce the risk of HIV-related morbidity and mortality receive this life-sustaining therapy. Adherence to ART may also become an issue in the future as patients live longer, with increased risk of drug resistance development. Consequently, it is also important to procure more expensive second- and subsequent lines of antiretroviral therapy.

Our model has limitations due to the data sourced for its construction. Behavioural surveys are conducted only every 3 or 4 years, the risk groups studied change between reports and do

not cover all groups of interest in this model. Similarly, little is known about the behaviour of the general lower-risk population and the two household census surveys conducted in Cambodia are the main source of data. Population sizes of the most-at-risk groups are difficult to determine and can influence the outcomes of the model. The model can be improved by more behavioural and sentinel surveillance data, General females may have lower-risk behaviour but are most-at-risk of infection. Unknown sexual risk behaviours have been calibrated for the overall populations groups. Other studies have shown that strata of risk is important, but generally only for interventions targeting individuals. As the model had been calibrated to reflect the epidemiology of each group, unidentified strata of risk behaviour would not substantially influence the overall levels of transmission with respect to primary transmissions and prevent infections. However, there is a possibility that secondary transmissions could be affected. The emerging IDU population and the shift in sex workers from direct brothel-based type to the indirect entertainment-worker type may pose new challenges in the fight against the epidemic and should continue to be monitored. Another limitation is that we are required to estimate proportions of people in each CD4 category using best available knowledge on disease progression as CD4 count is not routinely reported for people newly diagnosed in Cambodia. As transmission probabilities are based on disease-stage, any improvements in this reporting could only improve the model predictions further. We have not conducted a cost-effectiveness analysis in this study. In addition to the considering the benefit gained from possible interventions discussed in this paper, it would be useful to determine benefit gained in terms of quality-adjusted life years gained and to investigate if any schemes would be cost effective or even, cost saving.

This modelling study has demonstrated that past public health programmes have been effective and that in order to mitigate future epidemic trends combinations of interventions should be implemented that target all populations at risk of HIV infection. As HIV still

affects numerous groups in Cambodia, it is important that public health surveillance, coupled with knowledge of routes of transmission, remain in place to inform the prioritization of public health strategies and allocation of resources. In 2009, Sopheab et al. [4] presented the findings of the first national population-based survey that was conducted in 2005. This study investigated HIV transmission in the general population to estimate patterns of prevalence in men and women aged 15-49 years, not just the most-at-risk groups. Numerous observations from this study support the hypothesis that the predominant source of new infections among men is related to sex-work and that new infections in women are generally caused by transmission from spouses. The model supports the hypothesis that sex-work was originally a predominant driver behind infections in the past and is still a source currently, but less so. Prevalence in sex-workers of both types and their clients has declined, as has the proportion of infections attributed to sex workers from ~11% to less than ~3%. The proportion of all infections represented by general females is almost equal to that represented by general males and clients, the predominant groups of whom these women would be married to. As the percentage of infections caused by FSW (and to a smaller extent, clients) has decreased, there has been a corresponding increase seen in general females and males. This also supports the hypothesis that low-risk are generally becoming infected due to their spouse or ‘sweetheart’ (term used to describe their regular sexual partners). It was also reported in the Country Progress Report for Cambodia [12] that the epidemiological data presented in the 2010 Behavioural Sentinel Surveillance (BSS) and the "Estimation of HIV Prevalence among General Population in Cambodia 2010" Report [21] shows that there is a real risk of a second wave of new HIV infections among female sex workers, men who have sex with men (MSM) and injecting drug users (IDUs). Due to forced brothel closures, Cambodia has seen a rapid increase in non-brothel-based sex work in massage parlours, beer gardens and karaoke bars. This diversification of sex-work increases the difficulty for outreach programmes to reach the

women and their clients with HIV prevention services, especially as many of these women do not identify themselves as being in the sex trade. Additionally, the BSS shows that condom use for ISW with their sweethearts remain low. As model-predicted prevalence is still high among those women who were originally classified as DSW, we believe any relaxation in their adherence to safe-sex practices, work-based or otherwise, would pose a risk for a new wave of infections. For MSM and IDU, it was identified that there is need for capacity building and additional resources in order to scale up national HIV prevention programmes. In the report "Estimation of HIV Prevalence among General Population of Cambodia" [21] it was shown that men who have sex with men and women (MSMW) consistently have higher prevalence of HIV than exclusively homosexual or heterosexual men. When prevalence is stratified by age, those aged 35-44 years have the highest prevalence in all three groups, with MSMW estimated to be at 14.3%. Similarly, survey data ([17] [27]) have revealed that whilst over 90% of IDUs knew where to get clean needles and syringes, 35.5% shared a needle and syringe at last injection (including those who never share) and only 53% were aware that Voluntary Confidential Counselling and HIV testing (VCCT) services were available in their community. With model-predicted prevalence for MSM and IDU greater than 10% and 20% respectively, we agree identification of addressing male sexual health needs in order to destigmatise MSM and the provision of quality needle and syringe programmes (NSP) and methadone maintenance treatment (MMT) to IDUs as necessary interventions and guidelines have been put into place for their implementation [12]. More recently, a small programme focusing on heroin users has been implemented. A methadone maintenance treatment (MMT) as a secondary harm-reduction intervention for IDUs was established in July 2010. As of October 2010, only 61 of the estimated 1,500-10,500 heroin users were enrolled [23].

Primary harm reduction is still lacking. As of 2009 in Cambodia there were only two non-government organisations licensed to provide a limited number of syringes to IDUs in Phnom

Penh [24]. This leaves great scope for health strategies to be targeting IDUs with the scale-up of provision of clean injecting equipment and education for needle and syringe safety for those inject.

In conclusion, it is important for any future public health policy to include strategies that protect those who have lower-risk behaviours but remain at risk of infection due to their relationship type – for example women who are spouses of men who participate in transactional sex and injecting drug users. Interventions such as promoting condom use, increasing testing rates and scaling-up the provision of ART in combination provide the most benefit.

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Chapter 2: What impact might the economic crisis have on HIV epidemics in Southeast Asia?

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Author Contributions: The design of the mathematical model was carried out by RG, KJH, AH, AJ K, HHT, DW. RG implemented the models, analyzed the results, and was involved in writing the manuscript; KJH obtained parameter estimates and calibrated the Cambodian models; AH wrote the computer code for the models; AJK provided parameter estimates for IDUs in Cambodia; HHT reviewed relevant economic literature; NL and PS provided data and guidance for contextualizing the model to the PNG setting; SS and VS provided data and guidance for contextualizing the model to the Cambodian setting; HW and JK acted in an advisory manner and assisted in ascertaining realistic assumptions; DW conceived, designed, and supervised the study and was involved in writing the manuscript.

Abstract

Objective: To evaluate the potential impact of the current global economic crisis (GEC) on the spread of HIV.

Design: To evaluate the impact of the economic downturn we studied two distinct HIV epidemics in Southeast Asia: the generalized epidemic in Cambodia where incidence is declining and the epidemic in Papua New Guinea (PNG) which is in an expansion phase.

Methods: Major HIV-related risk factors that may change due to the GEC were identified and a dynamic mathematical transmission model was developed and used to forecast HIV prevalence, diagnoses, and incidence in Cambodia and PNG over the next 3 years.

Results: In Cambodia, the total numbers of HIV diagnoses are not expected to be largely affected. However, an estimated increase of up to 10% in incident cases of HIV, due to potential changes in behavior, may not be observed by the surveillance system. In PNG, HIV incidence and diagnoses could be more affected by the GEC, resulting in respective increases of up to 17% and 11% over the next 3 years. Decreases in VCT and education programs are the factors that may be of greatest concern in both settings. A reduction in the rollout of antiretroviral therapy could increase the number of AIDS-related deaths (by up to 7.5% after 3 years).

Conclusions: The GEC is likely to have a modest impact on HIV epidemics. However, there are plausible conditions under which the economic downturns can noticeably influence epidemic trends. This study highlights the high importance of maintaining funding for HIV programs.

Keywords

Global economic crisis; Southeast Asia; HIV epidemics; Cambodia; Papua New Guinea; HIV funding; mathematical modelling

Introduction

The Asian Economic Crisis in 1997 led to a slowdown in HIV programs in many Southeast Asian countries [1, 2]. Similar reductions could occur due to the current Global Economic Crisis (GEC). While the potential impact of the GEC on the spread of HIV is unclear, falling government revenues may lead to reductions in international aid and funding for HIV programs in developing countries. Economic conditions may also have an indirect impact on HIV epidemics by affecting the behavior of some people (e.g. due to unemployment) which may influence HIV transmission. To evaluate the potential impact of the GEC on HIV epidemics we focused on two contrasting epidemics in Southeast Asia. We investigated the well-defined and generalized epidemics in Cambodia (where incidence is declining) and Papua New Guinea (PNG) (where incidence is increasing).

Cambodia is particularly vulnerable to global financial perturbations due to its reliance on international exports. After strong growth in recent years Cambodia's economy has slowed markedly [3]. It has also felt the effects of political instability in Thailand, one of the main transit points for Cambodia, and experienced similar decreases in tourist arrivals [3]. Though Cambodia's HIV epidemic is declining the infection has invaded diverse population groups. The decline in incidence and prevalence has been linked to behavioral changes in sex work with an increase in condom use between sex workers and clients and a decrease in the number of men visiting sex workers [4-8]. There has also been a strong commitment from the Cambodian government and external donors resulting in targeted public health interventions and a large scale-up of antiretroviral therapy (ART) for people with HIV infection.

The economy of PNG has been underpinned by high commodity prices in recent years, leading to relatively strong economic growth. The GEC is expected to reduce this growth

because of reductions in exports and commodity production. In addition, PNG's already high unemployment rate is expected to further increase especially in the mining industry; ~80% of adults do not have formal employment and an estimated 40% of PNG's population live in poverty [9]. Since 1994, PNG has been experiencing a steadily increasing HIV epidemic with cases detected in all regions of the country. HIV is mainly transmitted heterosexually but key factors that have been linked to HIV transmission in PNG include transactional sex, mobility, sexual violence, and gender inequality [10-12]. Recent programs have led to increases in condom use and HIV testing, with first-line ART being rolled out in numerous provinces. Most HIV programs are newly established and may be relatively fragile to economic reductions.

To investigate the potential impact of the GEC on HIV epidemics in Cambodia and PNG, mathematical models incorporating country-specific behavioral and epidemiological data were developed for both settings. These models were calibrated to accurately reflect the past and present HIV incidence, HIV prevalence, and the number of people on ART in each country. The models were then used to forecast epidemic trajectories over the next 3 years under assumptions that behavioral or program conditions may change due to economic conditions.

Methods

We carried out detailed discussions with key stakeholders and representatives from national HIV bodies in Cambodia and Papua New Guinea, as well as economists, behavioral researchers, and international policy and development experts (listed in acknowledgements). A list of major HIV-related risk factors were identified that may change as a result of the GEC (Table 1). These factors were grouped into two categories: (i) those that have direct effects on HIV/AIDS program resources and (ii) those that may affect the social and

behavioral interactions of individuals. This list is not exhaustive and other factors may be influenced by changes in the economy, however, these factors are thought to be the most important for potentially affecting HIV epidemics.

Direct effects on program resources

The GEC makes commitments of overseas development assistance more uncertain. In Cambodia and PNG only a small proportion of funding for HIV responses comes from their own governments, with the majority of assistance coming from international funding agencies such as the Global Fund and AusAID. Some donors have signaled their intention to scale back their aid budgets. Reductions in program funds may lead to:

1) *Decreases in voluntary counseling and testing (VCT) services*, resulting in a decrease in testing rates, counseling and other prevention services. This may lead to a reduction in condom use and testing of the general population.

2) *Decreases in education and prevention activities*. If there is a reduction in media campaigns and other educational activities then condom use may decline and the rate of partner change may increase.

3) *Changes in the availability of ART or slowed rate of increase in provision.* In Cambodia there is almost universal access (~85%) to first-line ART for eligible individuals. In PNG provision of ART is currently scaling up; currently ~30% in need have access and the plan is to increase this to ~50-70% over 5 years. The majority of ART provision in both countries is externally funded and external economic pressures could have a significant impact on treatment strategies.

Behavioral and social factors

The GEC could have complex behavioral and social effects on heterogeneous groups of people. Key behavioral factors relevant to HIV epidemics that may be influenced by the economy include:

1) *Increases in unemployment.* The economic downturn may lead to increased unemployment and to support themselves some unemployed women may turn to transactional sex work. The number of sex workers (supply) could increase, but the number of men engaging their services (demand) may decrease. In Cambodia it is anticipated that the total number of women seeking to engage in direct and indirect sex work will increase over the short-term, mainly due to a decline in the garment industry. Reductions in tourist arrivals in Cambodia will also decrease the demand for sex work. In PNG, a relatively large proportion of women engage in transactional sex of some form. As money is not always involved in transactional sex, it is expected that transactional sex work could increase. However, newly unemployed individuals in PNG are likely to stay with their extended family in the short term and may not initially turn to transactional sex work.

2) *Decrease in injecting drug use in Cambodia.* The majority of drug use in Cambodia involves an amphetamine type stimulant (ATS); however, there is a small population of injecting drug users (IDUs) in Cambodia. With disposable income likely to decrease, use of intravenous drugs could be expected to decrease.

3) *Change in alcohol consumption and the prevalence of violence in PNG.* There are very few IDUs in PNG [13], however, alcohol is commonly brewed at home and its consumption is expected to increase with higher unemployment. Alcohol consumption is linked with decreased condom use and increased sexual assault which also tends to be unprotected.

4) *Change in migration patterns.* A decrease in employment could lead to male migrant workers returning home in Cambodia, particularly in the declining construction industry. In PNG, there is net population growth in urban settings due to rural-to-urban migration. It is expected that increased unemployment will reduce the flow of people moving from rural to urban settings. Though people losing employment from the mining sector in PNG may go to towns and cities for other employment, the expectation is for a net decrease in migration rates to urban areas.

Table 1: Assumed change in HIV-related risk factors due to the economy

Risk factor		**Potential change within 12 months**	
HIV programs		**Cambodia**	**PNG**
VCT services	Optimistic	HIV testing steady condom use steady	HIV testing steady condom use steady
	Intermediate	HIV testing rate ↓ 5% condom use ↓ 5%	HIV testing ↓ 7.5% condom use ↓ 7.5%
	Pessimistic	HIV testing rate↓ 10% condom use ↓ 10%	HIV testing ↓ 15% condom use ↓ 15%
Education and prevention	Optimistic	condom use steady partner change steady	condom use steady partner change steady
	Intermediate	condom use ↓ 5%	condom use ↓ 5%

		partner change ↑ 3%	partner change ↑ 3%
	Pessimistic	condom use ↓ 10% partner change ↑ 5%	condom use ↓ 10% partner change ↑ 5%
Availability of antiretroviral therapy (coverage of diagnosed)	Optimistic	↑ 10% over 5 years	↑ 40% over 5 years
	Intermediate	↓ 2.5% over 5 years	↑ 25% over 5 years
	Pessimistic	↓ 5% over 5 years	↑ 10% over 5 years
Change in behavior of people		**Cambodia**	**PNG**
Unemployment	Optimistic	no. sex workers steady demand for SW ↓ 10%	no. sex workers steady demand for SW steady
	Intermediate	no. sex workers ↑ 10% demand for SW ↓ 5%	no. sex workers ↑ 5% demand for SW ↑ 5%
	Pessimistic	no. sex workers ↑ 5% demand for SW steady	no. sex workers ↑ 10% demand for SW ↑ 10%

Injecting drug use (Cambodia); Change in condom use and sexual activity due to alcohol consumption (PNG)	Optimistic	drug use ↓ 10%	condom use steady sex activity steady
	Intermediate	drug use ↓ 5%	condom use ↓ 10% sex activity ↑ 5%
	Pessimistic	drug use steady	condom use ↓ 20% sex activity ↑ 15%
Migration	Optimistic	regular partners steady	Steady, 15% in urban
	Intermediate	contact w/ partners ↑ 7.5%	14% in urban
	Pessimistic	contact w/ partners ↑ 15%	13% in urban
Absolute changes are assumed for condom use and treatment uptake; others are relative changes.			

Mathematical model

To describe the history of HIV epidemics and to forecast potential epidemic trends in the future, a mathematical transmission model and a static risk model were developed (specific details of these models are presented in the Supplemental Digital Content). These models describe the risk of HIV acquisition for six population subgroups: 1) general males, 2) male clients of female sex workers (including pimps and other core groups of men), 3) men who have sex with men (and possibly women) (MSM), 4) injecting drug users (IDUs), 5) general

females, and 6) female sex workers (FSWs). The PNG population is divided into rural (85% of total population) and urban settings, with clients and FSWs only living in urban areas. Heterogeneous interactions between all of these population groups is included to reflect the complex and polymorphous nature of sexual behavior and mixing in these settings [14]. Parameter assumptions for the models are presented in Table 2. Data specific for each setting was used to inform the mathematical models; where data was unavailable for Cambodian populations, data from Thailand was used. All model simulations and calculations were executed with Matlab® R2009a.

The transmission model describes the overall population-level transmission of HIV using four ordinary differential equations. These equations describe the temporal change in the number of people who are susceptible, HIV-infected but undiagnosed, diagnosed with HIV, and on ART. A schematic diagram of the model is shown in Figure 1; this schematic is replicated for urban and rural settings in PNG with migrating people remaining in the same disease stage. In Cambodia we assume that migration describes the movement of workers between their workplace and home. Thus, any increase in unemployment likely results in men having more contact with their regular partner at home. Any migratory increase of the number of FSWs in Cambodia is incorporated in the increasing unemployment scenario. This model was used to forecast potential trends in HIV epidemics from 2009 to 2012 for each scenario in Table 1.

To more accurately account for the variation in HIV risk and prevalence in each population group, a static risk equation model was used to estimate the probability of HIV acquisition per uninfected person per year. The static risk equations, weighted by the population sizes, were consistent with the overall population-level 'force of infection' term for incidence in the dynamic models applied to Cambodia and PNG. The annual risk of acquiring HIV infection per uninfected person was calculated for each population group and as a weighted average

across all groups. These risks were calculated for 2009 and 2012. The potential change in annual risk of acquiring HIV per uninfected person due to the GEC was then calculated. The estimated number of people on treatment in 2012 was provided by the transmission model.

Table 10

Parameter	Cambodia	Urban PNG	Rural PNG
Males			
Average number of regular sexual partners per year	0.58[a]	2[15, 16]	2[15, 16]
Average number of casual sexual partners per year	0.88 [a]	6.9[11, 17, 18]	9[a]
Condom use in casual partnerships with general females	30%[12, 19-21]	10%[16]	10%[16]
Condom use in regular partnerships with general females	30%[12, 19-21]	5%[17]	5%[a]
Prevalence of HIV	0.8% [14, 22]	1%[23]	2%[23]
Prevalence of other sexually transmitted infections	1% [a]	5%[23-26]	15.7%[25]
Male clients of female commercial sex workers			
Proportion of the population	6.5%[27]	26%	0%[a]
Number of visits to sex workers per year	62[28, 29]	18[10, 11, 15, 30]	N/A

Condom use in acts between clients and sex workers	95%[28]	60%[16, 17]	N/A
Prevalence of HIV	5% [a]	2%[23]	N/A
Prevalence of other sexually transmitted infections	1.5% [a]	1.5%[23-26]	N/A
Men who have sex with men (MSM)			
Proportion of the population	1.5%[22, 31-35]	3%[16, 17]	3%[16, 17]
Average number of male sexual partners per year	25[28, 36]	30[11, 17]	5[a]
Average number of female sexual partners per year	3[28, 36]	30[11, 17]	10[a]
Condom use in penetrative acts between MSM	80%[28, 36]	23%[11, 17, 23]	7.5%[a]
Condom use in penetrative acts between MSM and women	80%[28, 36]	50%[11, 17, 23]	7.5%[a]
Prevalence of HIV	7.5%[36]	2.5%[a]	3%[a]
Prevalence of other sexually transmitted infections	1.3%[28, 36]	20%[11]	20%[a]
Injecting drug users (IDUs)			
Proportion of the population	0.25% [37-41]	0%[a]	0%[a]

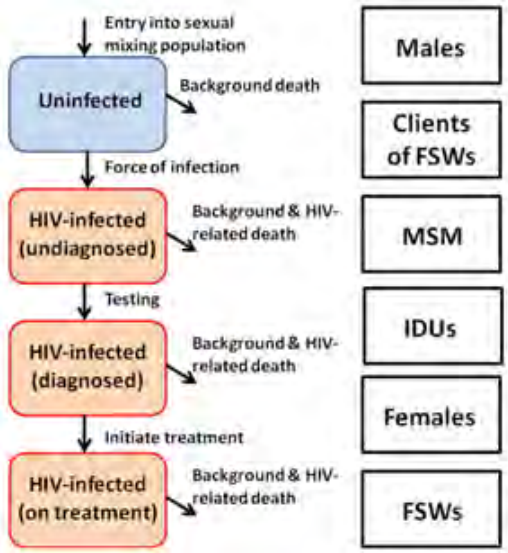
Average number of injecting partners per year	2[42]	N/A	
Average frequency of injecting per year	400[43-45]	N/A	
Percentage of injections using equipment from other IDUs	15%[42]	N/A	
Percentage of shared syringes that are cleaned before re-use	70%[46]	N/A	
Average number of regular sexual partnerships	0.5 females 0.25 FSW [21, 47, 48]	N/A	
Average number of contacts IDUs have with FSWs per year	2[21, 47]	N/A	
Prevalence of HIV	15%[46]	N/A	
Prevalence of other sexually transmitted infections	16%[46]	N/A	
Females (including those that engage in transactional sex)			
Prevalence of HIV	0.8%[49, 50]	1.5%[23]	2%[23]
Prevalence of other sexually transmitted infections	1%[51]	6%[24, 25]	15.7%[25]
Sexual behavior parameters	Balance with male behavioral values		
Female commercial sex workers (FSWs)			
Proportion of the population	1.5%[52-54]	2%[10]	0%[a]

Average number of regular sexual partnerships	0.5[28, 36]	1.4[10, 11, 55]	N/A
Condom use in acts between FSWs and regular partners	85%[28, 56]	40%[16, 17]	N/A
Average number of casual sexual partnerships, outside sex work, that FSWs have per year	3.2[28, 36]	8.9[a]	N/A
Condom use in acts between FSWs and casual partners	80%[28, 36]	60%[10, 23]	N/A
Prevalence of HIV	15%[49]	15%[30, 57, 58]	N/A
Prevalence of other sexually transmitted infections	3.5%[51]	25%[30, 59]	N/A
Sexual activity between FSWs and clients	Balance with client behavioral values		

a: Assumption. The population is split 1:1 between men and women for Cambodia and 1.2:1 for PNG [60]. The model also assumes the following. The presence of an STI increases HIV transmission risk by 4-5 fold [61-63]. A casual partnership involves 1 penetrative sex act and a regular partnership involves 75-100 acts per year. The baseline probability of HIV transmission per sexual act is 0.0008 for female-to-male transmission [64, 65], 0.001 for male-to-female transmission [64, 65], and 0.008 for male-to-male transmission [66]. Treatment reduces the transmission rate by 95% [67]. HIV transmission risk using a contaminated needle/syringe is 0.008 [68, 69]. The effectiveness of condoms is 90% [70, 71] and cleaning of syringes has effectiveness of 75% [72, 73]. People remain in the sexually mixing population for 45 years for PNG and 35 years for Cambodia, the rate of diagnosis of HIV-infection (i.e., testing rate) increased linearly from 0.14 (2003) to 0.5 (2009) for Cambodia, and is taken to be 0.2 for urban PNG and 0.12 for rural PNG. The time from infection to AIDS-related death for untreated HIV-

infected individuals is 10 years [74-76], and rate of death for treatment-eligible individuals on ART is 0.05 [77-80]. The rate at which diagnosed cases initiate therapy is taken to linearly increase from 0 in 2003 to 1.2 in 2009 for Cambodia. Before 2009, this rate is taken to be 0.25 and 0.125 for urban and rural PNG, respectively, and then increases to match treatment plans. The rate at which HIV-infected people on ART stop treatment is assumed to be 0.5.

Figure 1: Schematic diagram of mathematical model



Results

The dynamic transmission model accurately reflected the HIV epidemics in Cambodia and PNG (Figure 2). Forecasts of the expected impact of the economic crisis on HIV diagnoses, incident infections, and prevalence, for intermediate assumptions (Table 1) suggest that the GEC may have a relatively modest impact on the HIV epidemics in these countries.

In Cambodia, HIV incidence may increase moderately (by an estimated maximum of ~10% over three years) if changes in VCT and education lead to reductions in HIV testing and

condom use, and increases in partner change (Figure 2b). The increase in incidence is not expected to translate into increases in HIV diagnoses. The change in the number of HIV diagnoses due to the GEC is likely to be minimal (Figure 2c) because the GEC is expected to cause only a small increase in the overall number of undiagnosed people living with HIV, even with the expected changes to VCT.

In contrast, HIV incidence and diagnoses in PNG could be considerably affected by the GEC (Figures 2e, f). Intermediate assumptions for increased violence and alcohol use could lead to increases in incidence and new diagnoses of 17% and 11% respectively over 3 years. Pessimistic assumptions (Table 1) could lead to larger increases in incidence and new diagnoses, however, moderate assumptions for most potential scenarios lead to relatively little change (Figures 2e, f). For PNG the model predicts that there will be a slight decrease in diagnoses in the scenario of decreasing VCT as less people will be tested each year.

Figure 2: Model-based projections for Cambodia and PNG based on changes due to the economy: (a) HIV prevalence in Cambodia; (b) HIV incidence in Cambodia; (c) number of diagnoses in Cambodia; (d) HIV prevalence in PNG; (e) HIV incidence in PNG; (f) number of diagnoses in PNG. The blue dots represent available data in these countries since 2004.

Figure 2a

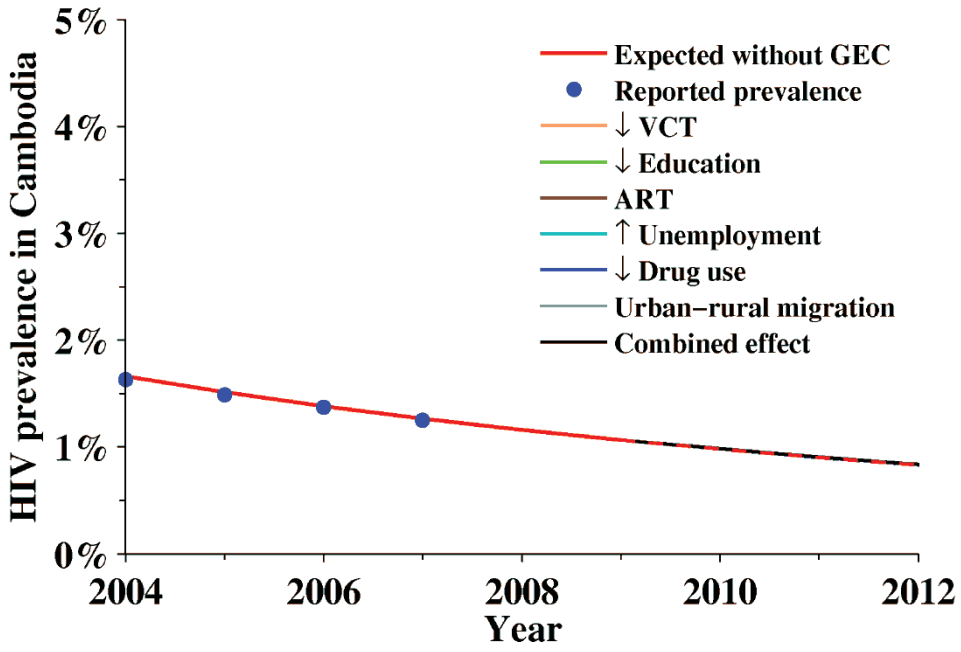


Figure 2b

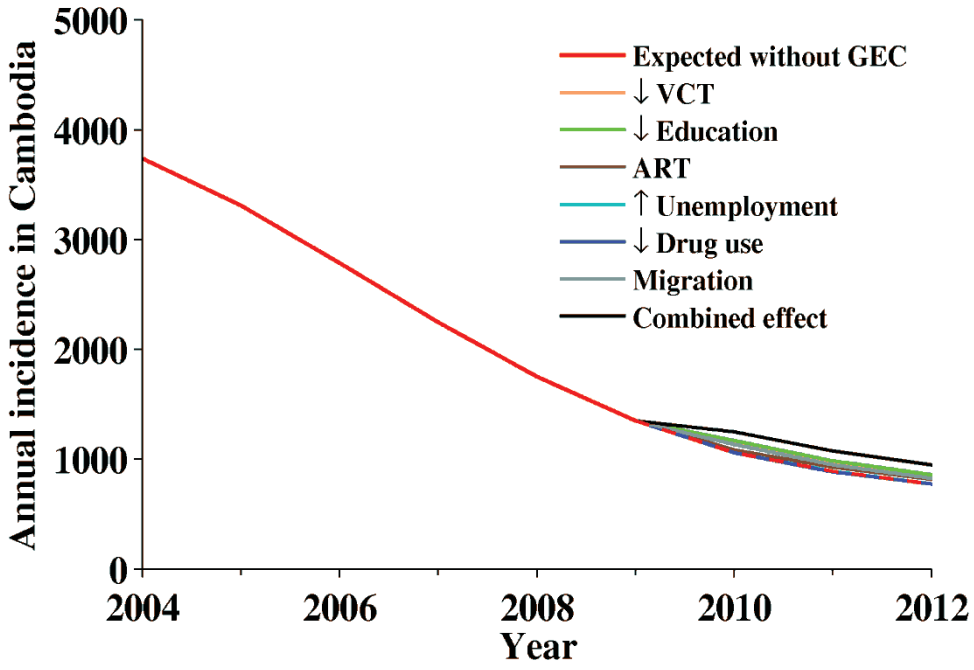


Figure 2c

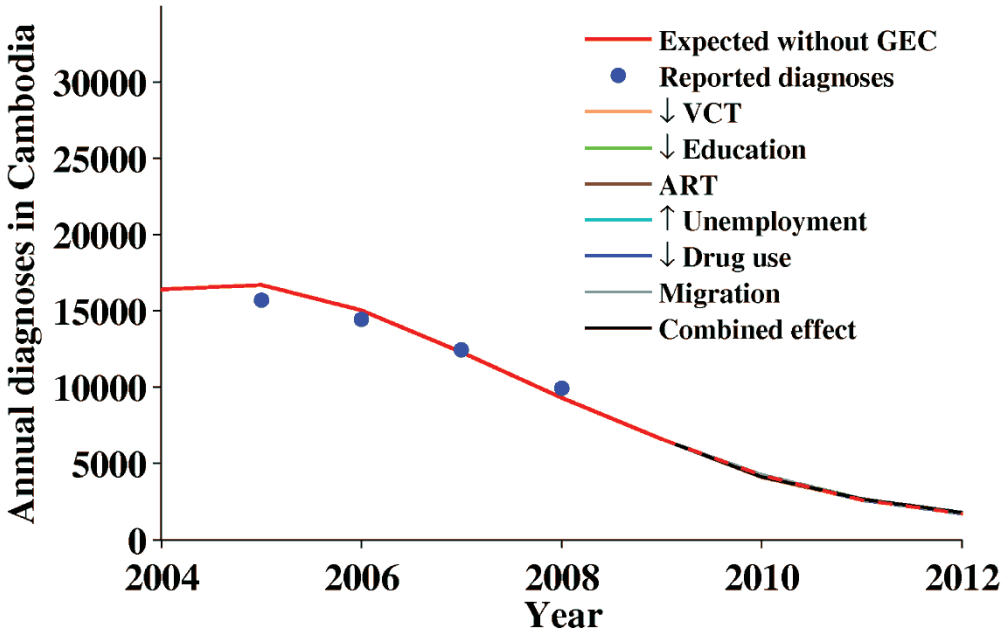


Figure 2d

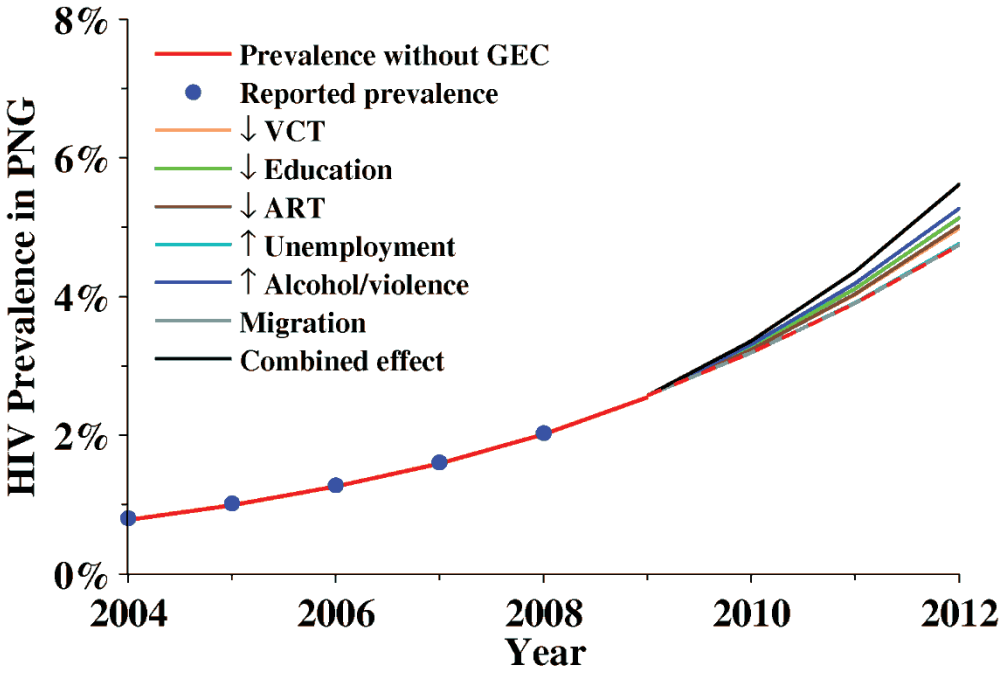


Figure 2e

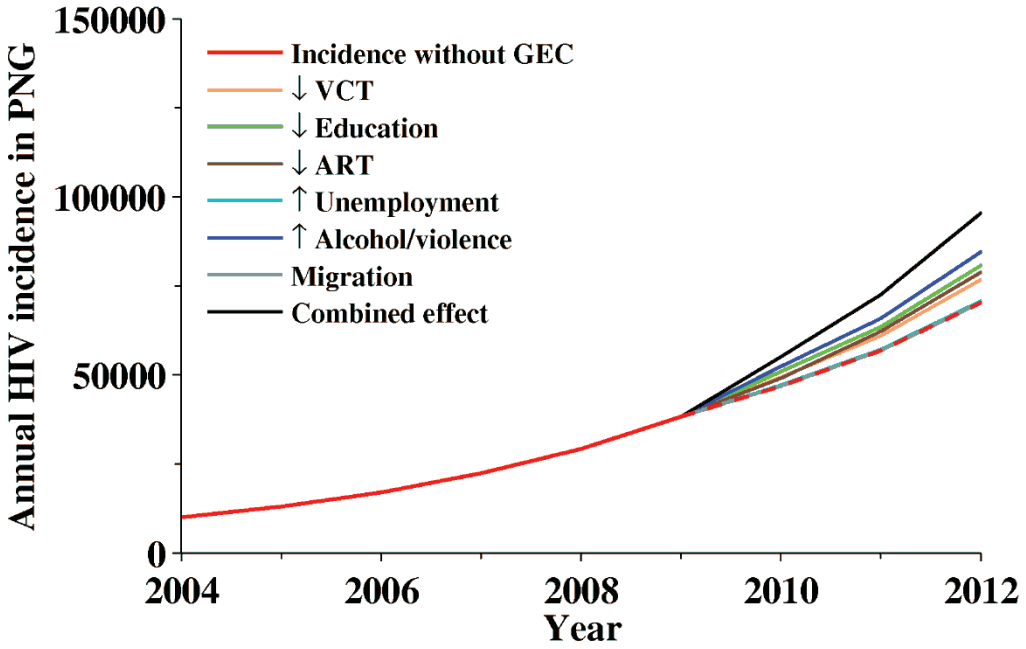


Figure 2f

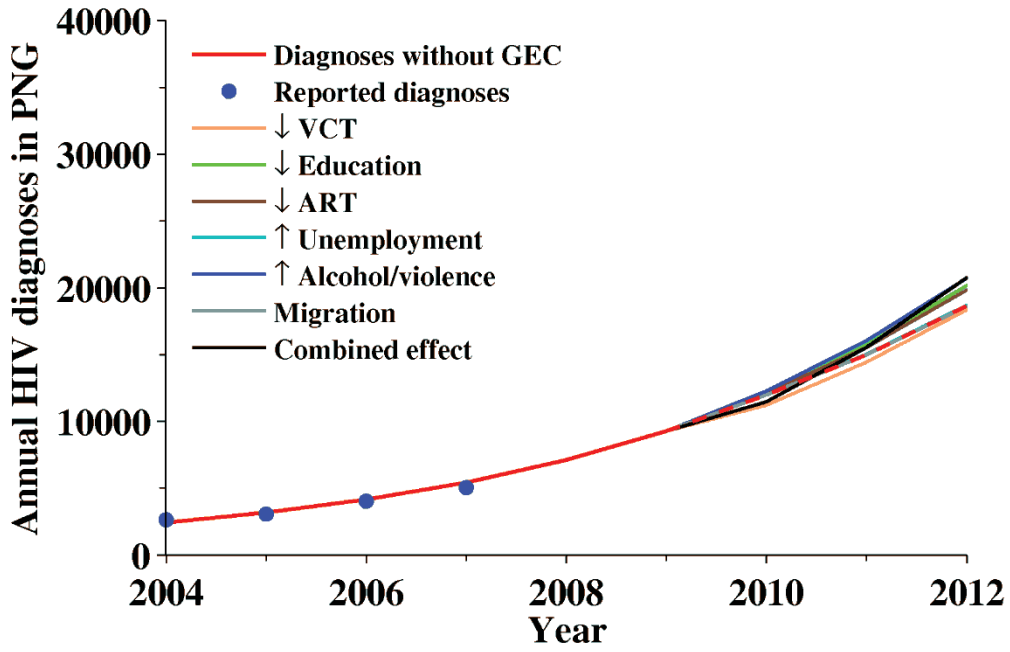


Figure 3 illustrates the estimated change in the risk of HIV acquisition for each population subgroup. The factors of greatest concern in Cambodia are decreases in VCT and education. These particularly affect male clients and FSWs. For these population groups increased unemployment is likely to reduce HIV risk due to decreased demand for sex work (Figure 3a). However, the increase in the number of sex workers in the population means that the number of new HIV infections among FSWs is expected to increase. In PNG, the factors of greatest concern are increases in violence and alcohol, decreases in ART roll out, and decreases in VCT and education (Figure 3b). Increasing unemployment in PNG is expected to lead to only a minimal increase in risk for clients and negligible change in risk for FSWs. Similarly, migration away from urban areas has minimal effect on risk because the majority of people live in rural areas. Finally, changes in ART roll out in PNG have a larger effect on clients and FSWs because treatment is more accessible in urban areas. These results suggest that the effects of the economy on HIV programs could have a greater impact on epidemics than those related to unemployment.

Figure 3: Change in HIV incident risk per person in each population group (blue dots) and overall (red dots) due to the economic crisis in (a) Cambodia and (b) PNG. Error bars denote incident risk due to optimistic and pessimistic assumptions. For PNG the results for Male Clients and FSW only apply to urban settings. For other population groups the change in risk is for the urban and rural populations combined. In our model we assumed there were no IDUs in PNG.

Figure 3a

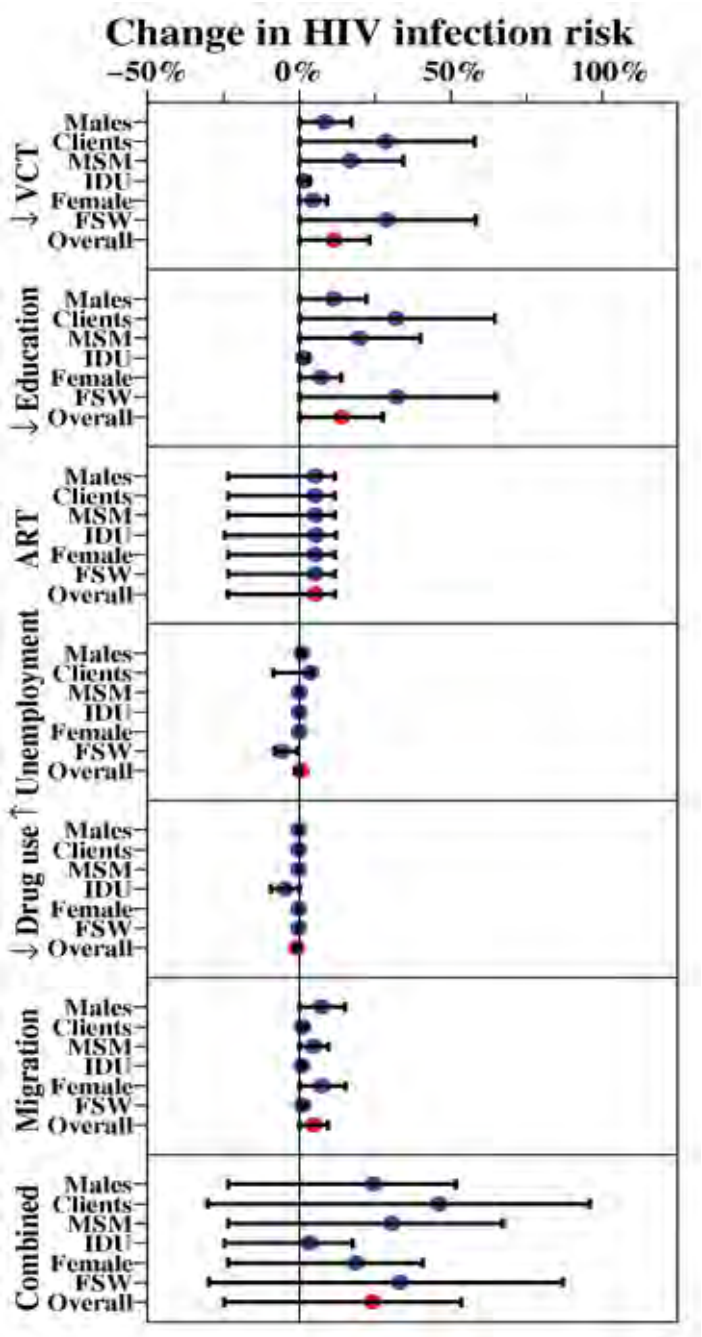
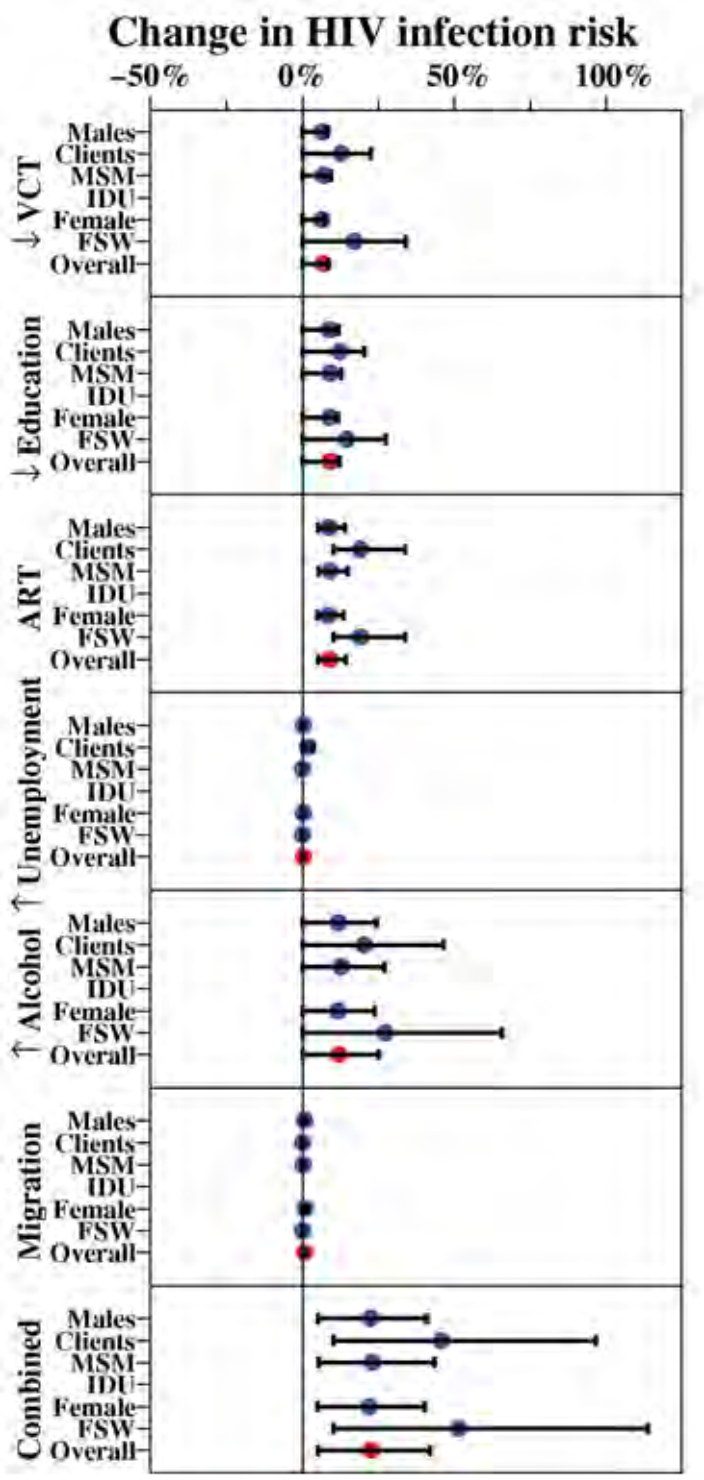


Figure 3b


Change in HIV infection risk
−50%
0%
50%
100%
↓ VCT
↓ Education
ART
↑ Unemployment
↑ Alcohol
Migration
Combined
Males
Clients
MSM
IDU
Female
FSW
Overall

The models predicted that a reduction in ART coverage or rollout has little impact on HIV incidence and diagnoses (Figure 2). However, ART may have a significant impact on the number of HIV/AIDS-related deaths. The model suggests that the coverage of ART is the most important factor determining the number of AIDS-related deaths in Cambodia over the next 3 years; however, the total number of deaths is unlikely to be highly influenced by the GEC: -1.2% in the optimistic case, ~0.4% in the intermediate case, and ~0.8% increase in HIV deaths for the pessimistic case. In contrast, the number of AIDS-related deaths in PNG could be highly affected by economic change. ART availability is being scaled-up substantially in PNG from the relatively low levels at present. If the economy reduces this planned provision of ART then it could greatly affect the number of AIDS-related deaths (by ~10%). In PNG other factors that lead to increased incidence (such as decreases in condom use) can also result in increases in AIDS-related deaths. The combined effect of all possible scenarios in PNG (Table 1) results in a ~2.1% increase in AIDS deaths in the optimistic case, ~7.5% increase in AIDS deaths in the immediate case, and ~14% increase in AIDS deaths in the pessimistic case from 2009 to 2012.

Discussion

This study estimated the effect that the GEC was likely to have on selected factors that are understood to play an important role in modulating HIV transmission rates. Pessimistic, intermediate, and optimistic scenarios were considered for each factor. Mathematical models were used to investigate the expected epidemiological effect in Cambodia and PNG to determine whether the economic crisis may potentially have a significantly adverse impact on HIV epidemics. The model-based results suggest that HIV risk, incidence, and diagnoses will be only modestly affected due to the GEC with decreases in HIV programs having a higher

impact than changes in unemployment and population movement. Overall, the model predicts that HIV epidemic profiles in established and emerging epidemics are not likely to alter significantly due to the economic crisis. For example, the effect of the economy on the HIV epidemic in Cambodia could be 'hidden' by the surveillance system (Figure 2c).

These findings are consistent with other qualitative reports on the potential impact of the global economic downturn on HIV/AIDS epidemics [81]. The current study highlights the high importance of maintaining HIV prevention and treatment programs, particularly VCT services and the provision of ART, which are largely funded by external sources. VCT and ART are well-established in Cambodia with an increase in more costly second-line therapy needed as the failure rate of first-line ART increases. In PNG, both VCT services and first-line ART are relatively new initiatives and are not well-established. Any volatility in these programs could be largely detrimental to PNG's HIV response, which aims to increase VCT services and achieve universal treatment access over the next 5-10 years. This volatility in external funding suggests that Governments will need to play a greater role in directly funding HIV programs. This is particularly pertinent for PNG, where Government expenditure for HIV has decreased (despite an increasing epidemic). However, such an increase should be considered in the context of other funding priorities such as reducing poverty and unemployment, and increasing the provision of food.

In this study, potential changes in key factors of relevance to HIV and the GEC were explored, along with sensitivity ranges around these assumptions. The models developed in this study were calibrated to accurately reflect the unique epidemiology of Cambodia and PNG and were based on the best data available, but they cannot capture the full degree of complexity that exists in transmission-related mixing, behavior, and HIV programs. Furthermore, some of the assumptions regarding the impact of the GEC (Table 1) are speculative and are not empirically based as there are limited sources of data on how the

economic crisis may affect HIV/AIDS program funds or social determinants related to HIV risk. More study is required to ascertain such behavioral shifts and to inform the response required to prevent adverse consequences for HIV incidence, morbidities and mortalities. For instance we assumed that the GEC will decrease drug use in Cambodia, however, it is possible that drug use may be stable or actually increase with unemployment [82]; though such an increase would have a similar moderate effect on our results. We also assumed that any change due to the GEC is maintained from 2009 to 2012 and ignored any potential improvements in economic conditions over the short term or behavior changes that are likely to have a short duration. Overall, the modeling highlights that prevention efforts must continue among the core groups that could be affected by the GEC in both settings (Figure 3) and among those most at risk for acquiring HIV. The trends in HIV epidemics are not expected to change markedly in the coming years. This may indicate the relative independence of HIV risk from economic fluctuations. However, one area where the GEC may have an important impact is on those living with HIV. A weaker economy may affect access to therapy (e.g., affording transport to clinics) and food security and, hence, disease progression. This was not considered in the current model.

The last decade has been strong economically, enhancing international efforts to manage the HIV pandemic [83]. For example, funds have been intensified and mobilized for the large scale-up of ART in resource-constrained countries [84]. The majority of funds for HIV prevention, care and treatment in Cambodia and in PNG are externally provided from the Global Fund, international government development organizations (such as AusAID), and non-government organizations. Despite this increased commitment, the United Nations health-related targets of the Millennium Development Goals are unlikely to be achieved by 2015 [85] and all commitments for HIV programs are unlikely to be fully realized. A downturn in the funds available for the provisions of antiretroviral drugs may result in

declining supplies, a smaller range of medications, particularly second and third line medications, and decreased availability to life-sustaining ART for the many people in need. This could also result in poorer treatment compliance, increased viral resistance and possibly transmission of resistant viral strains. HIV prevention efforts may also be unsustainable due to decreases in program funding. A judicious mix of funding sources and disbursement channels could be important for responding to HIV epidemics [86]. We are in an age where HIV still infects more people than the rate of ART roll-out [87]. It is of very high importance that funding for HIV programs are maintained, if not increased, by external donors and governments, regardless of the economic conditions.

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Chapter 3: Treatment for prevention of HIV transmission in a localised epidemic: the case for South Australia

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Abstract

There is considerable discussion currently taking place in the international HIV/AIDS community around increasing HIV testing and initiating earlier use of antiretroviral therapy (ART) among people diagnosed with HIV as a prevention method to reduce the spread of HIV infection. In this study we explore the expected epidemiological impact of adopting this strategy in a relatively small population in which HIV transmission is predominantly confined to men who have sex with men (MSM). A biologically realistic deterministic mathematical transmission model was constructed to investigate impacts of strategies that increase testing and treatment rates and their likely potential to mitigate epidemics of HIV among MSM. This model is applied to the population of MSM in South Australia and is informed by detailed location-specific data. Results from the model indicate that increasing testing rates alone, from the current high levels, will have minimal impact on reducing the expected number of infections compared to current conditions. However, in combination with increases in treatment coverage this strategy could lead to a 59-68% reduction in the number of HIV infections over the next 5 years. Targeting men who are socially engaged with the gay community would result in the vast majority of potential reductions in incidence with only minor improvements possible by reaching all other MSM. Investing in higher coverage and earlier initiation of treatment for the purposes of reducing infectiousness of HIV-infected individuals could be a highly effective public health strategy for reducing incidence in a population of MSM.

Introduction

Currently within the international HIV/AIDS community there is discussion around using antiretroviral therapy (ART) as a method of prevention for HIV infection. Results from a modelling study conducted by a World Health Organisation group suggested that annual universal testing with immediate commencement of antiretroviral therapy of all those diagnosed (a practice known as "test and treat") could if not eradicate, substantially reduce generalised heterosexual HIV epidemics [1]. This proposed strategy is an extension of available evidence that the infectiousness of a HIV-infected person is strongly associated with their viral load [2] and it is known that ART substantially reduces HIV RNA in plasma and genital fluids [3-6]. Additionally, there have been two recent studies that have shown a 92% reduction in incidence among heterosexual discordant couples in which the HIV-infected partner was on ART compared with HIV discordant couples in which the HIV-infected partner was not on ART [7, 8]. Whilst the feasibility of elimination or wide-scale implementation of a 'test and treat' strategy has been challenged, along with its ethical and clinical implications (e.g. [9-11]), a strategy such as "test and treat" should lead to a decrease in HIV incidence due to effective ART resulting in a reduction in average community viral loads and therefore infectiousness. The available evidence of ART reducing HIV transmission risk is from studies of heterosexuals and there are no available data on the effect of ART on transmission for higher risk routes of exposure, such as sharing injecting equipment and penile-anal intercourse [12]. Although there have been recent observations of decreased population incidence among men who have sex with men (MSM) coinciding with decreases in community viral load [13], HIV diagnosis rates among MSM in most resource-rich countries have increased over the last decade [14-16]. Furthermore, a recent estimate of

the per-contact transmission probability of HIV among MSM was found not to differ largely from pre-ART estimates [17].

Despite the lack of solid evidence for the relationship between HIV transmission and use of ART for activities associated with riskier exposures, there has been investment in some resource-rich settings for implementation of “test and treat” or “seek and treat” strategies to prevent HIV infections occurring from these transmission routes. An evaluation of the new guidelines of the expansion of treatment eligibility in British Columbia reports an expectation of a reduction in incidence [18] due to the increase in treatment rates where the epidemic is largely comprised of MSM and people who inject drugs. It is more feasible to expect a proactive implementation of a large-scale program like this in a resource-rich setting. It could also be expected that this strategy would be most feasible in a population that is relatively small and in which there is a concentrated epidemic among a core behavioural at-risk group. This study aims to explore the potential epidemiological impact of a strategy of increasing testing and treatment rates when applied to an HIV epidemic in such a setting, namely, South Australia.

Cumulatively to the year 2008 there were 1155 people who were diagnosed with HIV in South Australia. Of these diagnosed cases, an estimated 300-400 have died from AIDS or other HIV-related illnesses. The majority of infections are attributable to intercourse between MSM [19]. Of all diagnosed cases, approximately 76% receive antiretroviral therapy [20]. Despite this, there have been moderate but significant increases in HIV diagnoses in South Australia over the past 10 years [19]. However, the population of MSM in South Australia is also relatively small which may assist in implementation of such a universal strategy across a population. There are an estimated 12,000 homosexual and bisexual men in South Australia, based on Australian census data and the Australian Study of Health and Relationships [21]. This suggests that the HIV prevalence within the MSM population is approximately 6-7%.

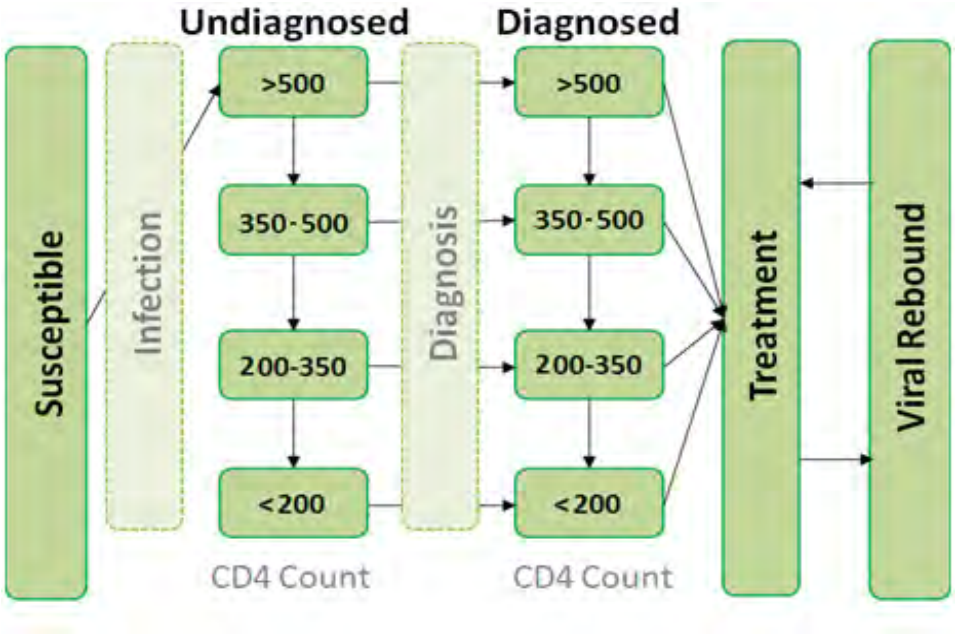
This rate is considerably lower than the HIV prevalence levels in the Eastern States of Australia [21], but substantially higher than that of the general population of South Australia at 0.1% [19].

In this study we investigate the impact of increasing testing rates and using treatment as a form of prevention on the trends of HIV infection in South Australian MSM, assuming that the relative reductions in infectiousness observed among heterosexuals also applies to homosexual exposure; we also investigate a range of relative reduction levels in an uncertainty analysis. We forecast epidemic trajectories according to current conditions and under scenarios where differing levels of testing and treatment are combined to mirror possible public health interventions being implemented. The primary method for these projections was the development and analysis of a mathematical transmission model. The deterministic compartmental model uses behavioural, clinical and biological data to track the number of MSM in South Australia over time that are in progressive stages of HIV disease infection and HIV transmission to MSM. The modelled population is also categorised into those who are socially engaged with the gay community or to other MSM to reflect the actual population as suggested by behavioural and social data [22, 23]. As far as we are aware this is the first time any mathematical model has made this distinction and we believe it is an important one because public health campaigns are likely to be more effective at reaching men who are socially engaged to the gay community. The model was calibrated to reflect the past and present epidemiology of HIV in South Australia. The differing outcomes of the scenarios were then evaluated for their expected effectiveness in reducing population-level incidence.

Methods

We developed a mathematical transmission and disease history model for HIV in South Australia. The model is based on sets of equations that describe HIV transmission risk for various transmission routes via penile-anal intercourse: receptive with ejaculation, receptive with withdrawal prior to ejaculation and insertive. These risk equations are used in conjunction with a deterministic compartmental model formulated as a system of ordinary differential equations. The ordinary differential equations track the number of MSM in South Australia over time in each possible state of HIV disease stage: uninfected, infected but not yet diagnosed, diagnosed infection but not on treatment and on ART. All HIV-infected individuals are classified according to their stage of HIV disease, based on CD4 count: CD4 count higher than 500 cells per μl; between 350 cells and 500 cells per μl; from 200 cells to 350 cells per μl; or a CD4 count of less than 200 cells per μl. A schematic diagram of this natural history described in the model is presented in Figure 1. The equations used in the model are shown in Chapter 3 Appendix.

Figure 1: Schematic diagram of HIV natural history and structure of mathematical model



The model accounts for differences in behaviour between men who are engaged with the gay community and men who are not, as sexual mixing and risk behaviour influence the risk of disease acquisition for an individual.

We define gay social-engagement to be determined by what degree the social component of a person's life is lived in the company of gay men and if they can be reached through gay male networks. Indicators used include the amount of free time spent in gay-specific venues, number of gay male friends, the amount of free time spent with them and the number of different places men go out with gay male friends. According to the E-Male survey, using a set of scales derived by Kippax et al.[24], approximately 47% of MSM in South Australia are gay socially engaged [22]. These populations are distinct in identity and behaviour. Men interviewed at the 2007 Gay Community Periodic Survey (socially-engaged MSM) self-reported sexual identities were 86.4% gay/homosexual/queer, 9.5% bisexual, 2.6% heterosexual/straight, and 1.6% other [23]. In comparison, for men who participated in the E-male survey (both non-engaged and socially engaged) the corresponding proportions of

responses for sexual identity were 76.5%, 20.8%, 1.5% and 1.2%. As these two groups have different behaviours when it comes to number of partners acquired, condom use and HIV testing, we model them as distinct groups up until the point of diagnosis. This enables us to track how many of each group becomes infected each year and enables forecasting the impact of interventions that reach different proportions of each group.

The model was also informed by behavioural inputs such as changing testing rates over time, probability of disclosure of serostatus, sexual positioning and assortativity of partners across the two groups. Biomedical inputs into the model included rates of circumcision, infectiousness due to disease stage, infectivity due to sexual position, effectiveness of treatment, effectiveness of condoms and rate of death due to HIV. All parameter values used in the model are shown in Table 1. Crucial to this modelling study is the assumption that HIV transmission due to penile-anal sex among MSM is reduced by 92% if the HIV-infected partner is on ART, the same relative reduction observed in studied among heterosexual couples. However, since there are no data on the relative reduction in infectiousness for homosexual partnerships we also conduct a second analysis where we assume an uncertainty range of 50-99% reduction in infectiousness.

Table 1: Parameter inputs for the mathematical model

Parameter Symbol	Description		Value	Reference
c_{reg}^{SE}	Average number of regular partners for socially engaged MSM (proportion of men with a regular sexual partner)		0.728	[25-27]
c_{reg}^{OM}	Average number of regular partners for other MSM (proportion of men with a regular sexual partner)		0.518	[25, 27]
c_{cas}^{SE}	Average number of casual partners per year for socially engaged MSM		11.504	[25, 27]
c_{cas}^{OM}	Average number of casual partners per year for other MSM		8.736	[25, 27]
n_{reg}^{SE} n_{reg}^{OM}	Average number of anal intercourse acts per regular partnership per year		10-50	[25, 27]
n_{cas}^{SE} n_{cas}^{OM}	Average number of anal intercourse acts per casual partnership		1	Assumption
r_{reg}^{SE}	Condom use with regular partners for socially engaged MSM	2001	69.09%	[25-27]
		2003	69.91%	
		2005	68.09%	
		2007	65.52%	
r_{reg}^{OM}	Condom use with regular partners for other MSM	2001	0.69.22%	[25-27]
		2003	70.04%	
		2005	68.22%	
		2007	65.65%	
r_{cas}^{SE}	Condom use with casual partners for socially engaged MSM	2001	88.83%	[25-27]
		2003	88.23%	
		2005	88.71%	
		2007	84.63%	
r_{cas}^{OM}	Condom use with casual partners for other MSM	2001	80.17%	[25-27]
		2003	79.63%	
		2005	80.06%	
		2007	76.37%	
d^{+}	Probability that seropositive MSM will disclose serostatus in casual acts	2001	43.2%	[25-27]
		2003	39.5%	
		2005	48.3%	
		2007	36.6%	
d^{-}	Probability that seronegative MSM will disclose serostatus in casual acts	2001	0.3575	[25-27]
		2003	0.355	

		2005	0.378	
		2007	0.3205	
ε	Efficacy of condom protection per act		90-99%	[28-32]
c_{AIDS}	Multiplying factor for the reduction in number of sexual partners for men in AIDS stage disease		0.1 – 0.4	[33]
f	Multiplying factor for the change in number of sexual partners post diagnoses of HIV infection		0.4 – 0.9	[34-42]
μ_S	Average time for individuals to 'retire' out of sexually active population (no longer obtaining new partners)		30-70 years	[43]
γ_{SE}	Percentage of socially engaged MSM that test for HIV infection each year	2001	57%	[25-27]
		2003	61%	
		2005	60%	
		2007	65%	
γ_{OM}	Percentage of other MSM that test for HIV infection each year	2001	38%	[25-27]
		2003	41%	
		2005	40%	
		2007	43%	
$1/\gamma_{lt}^{200SE}$ $1/\gamma_{lt}^{200OM}$	Average time from the beginning of AIDS before individual is likely to be diagnosed with infection		2-4 months	[33]
$1/\omega^{500}$	Average time (without ART) for HIV-infected individuals to progress from CD4 count >500 to CD4 count 350-500		2.95 (1.79-4.42) years	[44] ^{a}
$1/\omega^{350-500}$	Average time (without ART) for HIV-infected individuals to progress from CD4 count of 350-500 to CD4 count of 200-350		1.96 (1.81-2.13) years	[44] ^{a}
$1/\omega^{200-350}$	Average time (without ART) for HIV-infected individuals to progress from CD4 count of 200-350 to CD4 count <200		1.96 (1.81-2.13) years	[44] ^{a}
δ^{500}	HIV-related death rate for patients with CD4 count >500 cells per μL and detectable viral load		0.051% (0.035-0.068%)	[45]
$\delta^{350-500}$	HIV-related death rate for patients with CD4 count 350-500 cells per μL and detectable viral load		0.128% (0.092-0.164%)	[45]
$\delta^{200-350}$	HIV-related death rate per 100 person-years for patients with CD4 count 200-350 cells per μL and detectable viral load		1.0% (0.2-2.0)%	[45, 46]
δ^{200}	HIV-related death rate per 100 person-years for patients with CD4 count <200 cells per μL and detectable viral load		4.08 (0.30-7.86)%	[45, 46]
δ^{T}	HIV-related death rate per 100 person-years for patients with CD4 count <200 cells per μL and detectable viral load		1.0% (0.2-2.0)%	Experimental variable
δ^{TF}	HIV-related death rate per 100 person-years for patients with CD4 count <200 cells per μL		4.08 (0.30-7.86)%	Experimental variable

	and detectable viral load		
η^{500}	Rate at which individuals with CD4 count >500 that commence treatment for HIV each year	0.2	Assumption
$\eta^{350–500}$	Rate at which individuals with CD4 count 350-500 that commence treatment for HIV each year	0.5	Assumption
$\eta^{200–350}$	Rate at which individuals with CD4 count 200-350 that commence treatment for HIV each year	0.75-0.85	Experimental variable
η^{200}	Rate at which individuals with CD4 count <200 that commence treatment for HIV each year	0.85-0.95	Experimental variable
ν	Percentage of individuals on ART who cease therapy each year	1-5%	*b*
ρ	The percentage of times a negative man will take each role in a sex act based on disclosure of partner's serostatus (positive +, negative -, unknown ?)	See footnote *c*	[47]
α_r	Per-contact risk of transmission when negative partner takes receptive role	0.48-1.52%	[48]
α_w	Per-contact risk of transmission when negative partner takes receptive role with withdrawal prior to ejaculation	0.15-1.53%	[48]
α_i^{uncirc}	Per-contact risk of transmission when negative partner is uncircumcised and takes insertive role	0.07-1.68%	[48]
α_i^{circ}	Per-contact risk of transmission when negative partner is circumcised and takes insertive role	0.02-0.24%	[48]
p / a_{mult}	Multiplicative factor for transmission probability for people in primary/acute infection or in AIDS stage infection (due to higher viral load)	14.7	[49, 50]
t_{mult}	Relative reduction in HIV transmission probability for people on antiretroviral therapy	92%	[7, 8, 49]
ART_{eff}	Proportion of people on antiretroviral therapy with undetectable viral load	See footnote *d*	[51]
SE^{mix}	Average percentage of sex acts a socially engaged MSM will have with a non-socially engaged MSM	43%	[25, 27]
OM^{mix}	Average percentage of sex acts a non-socially engaged MSM will have with a socially engaged MSM	55%	[25, 27]

a A summary of the relation between HIV-1 RNA concentration and decline in $CD4^+$ count from the prospective study by Mellors et al. [44] is given below:

Plasma HIV-1 RNA concentration (*copies/mL*)	**Mean decrease in $CD4^+$ T cell count per year (*cells/μL*)**
≤ 500	-36. (-30.4,-42.3)

	501-3,000	-44.8 (-39.1,-50.5)
	3,001-10,000	-55.2 (-50.7,-59.8)
	10,001-30,000	-64.8 (-59.6,-70.0)
	> 30,000	-76.5 (-70.5,-82.9)

With this data, and assuming that the average viral load is ~$10^{4.87}$ copies per mL for people without treatment, the $CD4^+$ T cell count decreases by an average of 76.5 (70.5, 82.9) every year.

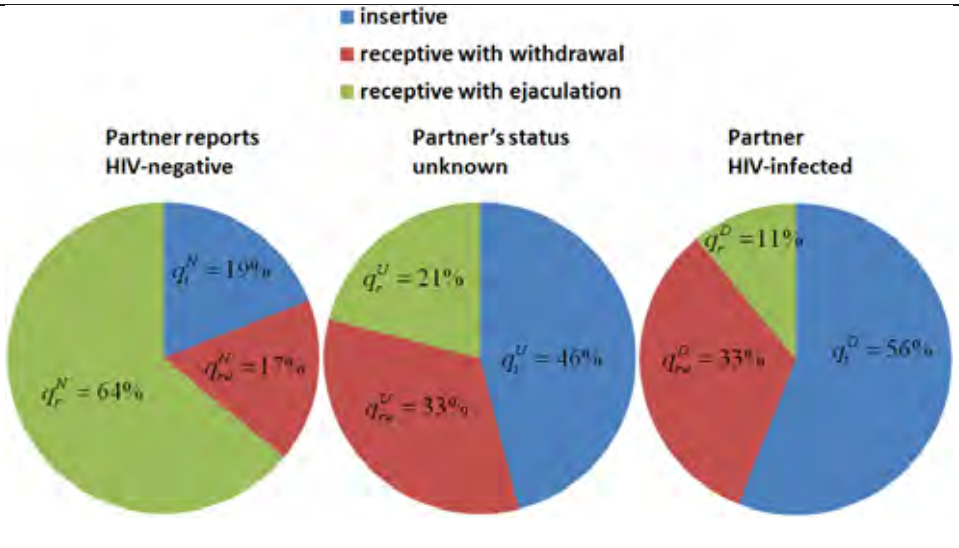
To progress through the >500 CD4 cell category, we assume that the average CD4 count is 800 cells/μL after the 2-month acute phase of HIV infection and then declines at the constant rate of 76.5 (70.5, 82.9) cells/μL each year. Then the average time to progress through this compartment is 2/12 + 300/(76.5 (70.5, 82.9)) years; that is 4.09 (3.79, 4.42) years.

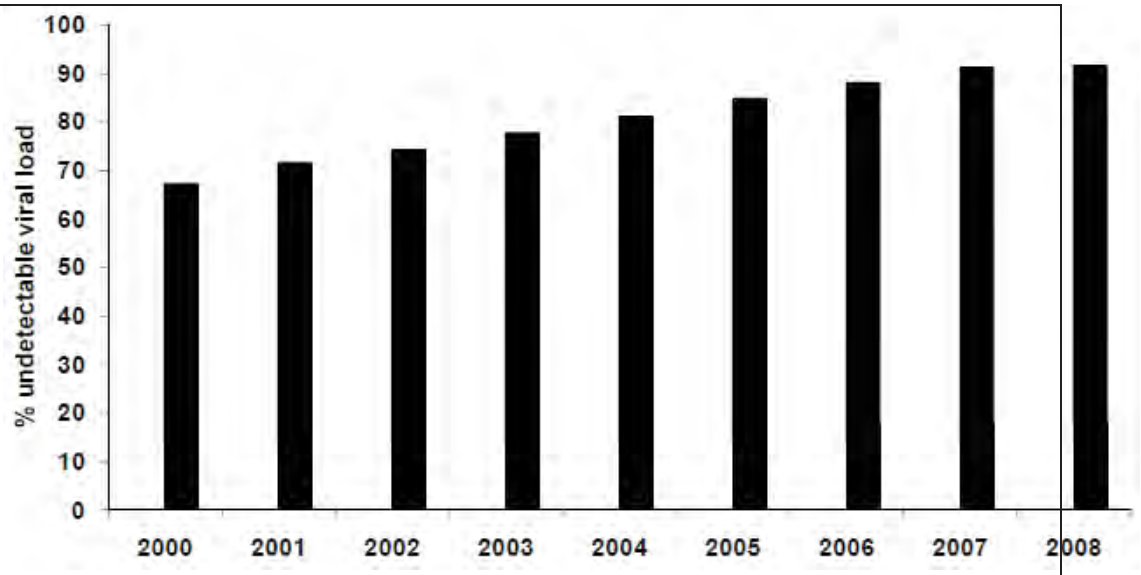
To progress through the 350-500 and 200-350 CD4 cell categories, we assume an average loss of 150 CD4 cells. Then the average time to progress through this compartment is 150/(76.5 (70.5, 82.9)) years; that is 1.96 (1.81, 2.13) years.

b

15.4/100 person years is the average rate of stopping one regime due to toxicity but the vast majority usually start another regime [52]. Very few people who commence ART stop altogether (expert opinion). Therefore, we take the absolute rate of completely stopping therapy to range from 1-5% per year as an experimental variable.

c



d	

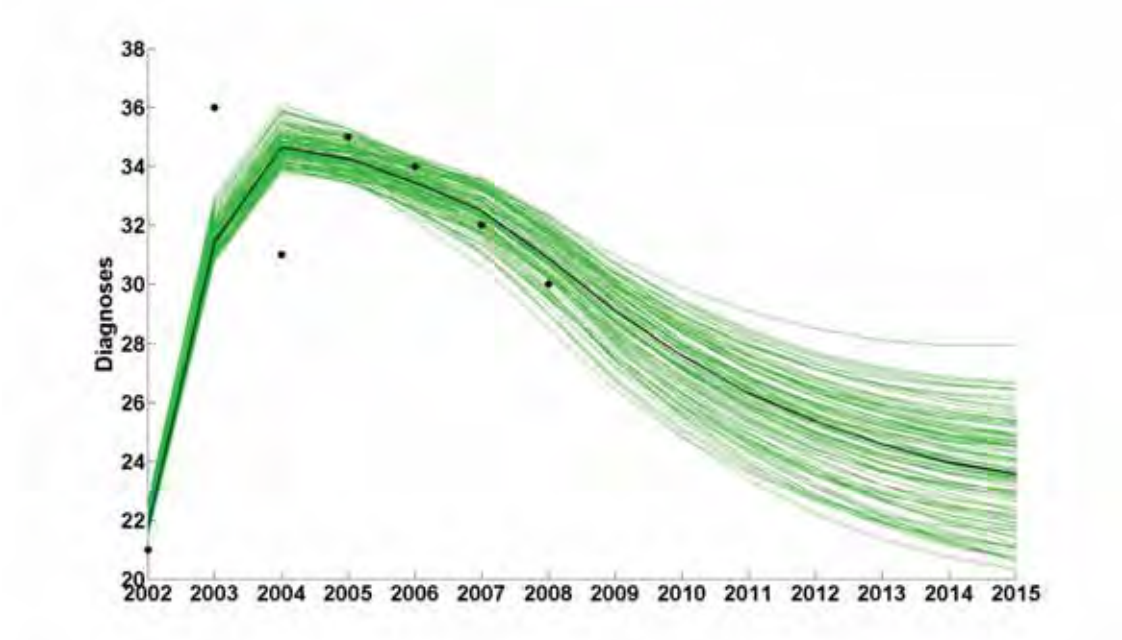
In order to model the future we need to ensure the model can accurately represent the past. Latin Hypercube sampling was used for variable parameter values and the parameter sets that led to the 100 (of 100,000) simulations that best fit all available epidemiological data/indicators were used for further analysis. Once these best parameter sets were determined, the model simulated the expected number of HIV transmissions and disease progression of HIV-infected people over the years 2010 to 2015 with all current conditions remaining the same over this period (referred to as 'status quo'). Once the results of the status quo run were established the model was re-run to simulate the outcome if different targeted interventions were achieved. The scenarios considered included increasing HIV testing rates from 55-65% testing once per year to: (i) testing 80% of socially engaged MSM, (ii) increasing HIV testing rates such that 80% of all MSM test once per year, (iii) testing 70% of all MSM twice per year. These testing scenarios were each simulated according to: (i) current treatment uptake rates, (ii) increased treatment such that all HIV diagnosed men receive ART

immediately, (iii) increased treatment such that all HIV diagnosed men who have a CD4 count less than 500 receive ART immediately. The criterion of a CD4 count of less than 500 per μL is used as this is the current requirement for those to obtain subsidised HIV antiretroviral medication under the Australian Pharmaceutical Benefits Scheme.

Results

The mathematical model was used to project the future epidemic course according to the status quo, that is, if current behavioural, testing and clinical practices remain unchanged (Figure 2). The infection time courses as predicted by the model suggest that South Australia has most likely passed the peak of its epidemic of HIV in MSM. Incidence of infection should have a modest decline from approximately 30 cases per year in 2009 to ~24 by 2015 if current conditions remain the same. The model-estimated cumulative number of new HIV infections from 2010 to 2015 is 124.76 (median, 116.78-131.68 IQR).

Figure 2: Model-projections of the expected number of HIV diagnoses among MSM in South Australia to 2015 according to current conditions from 100 simulations (median in black; dots represent HIV diagnoses data)



The model was then used to simulate over the same time period the expected disease trajectories if conditions change due to systematic increases in testing and/or treatment. By definition of the sub-population, socially engaged MSM would be easier to seek and recruit through their connections to the gay community. Consequently, for all interventions explored, targeting only socially-engaged MSM was compared against targeting all MSM.

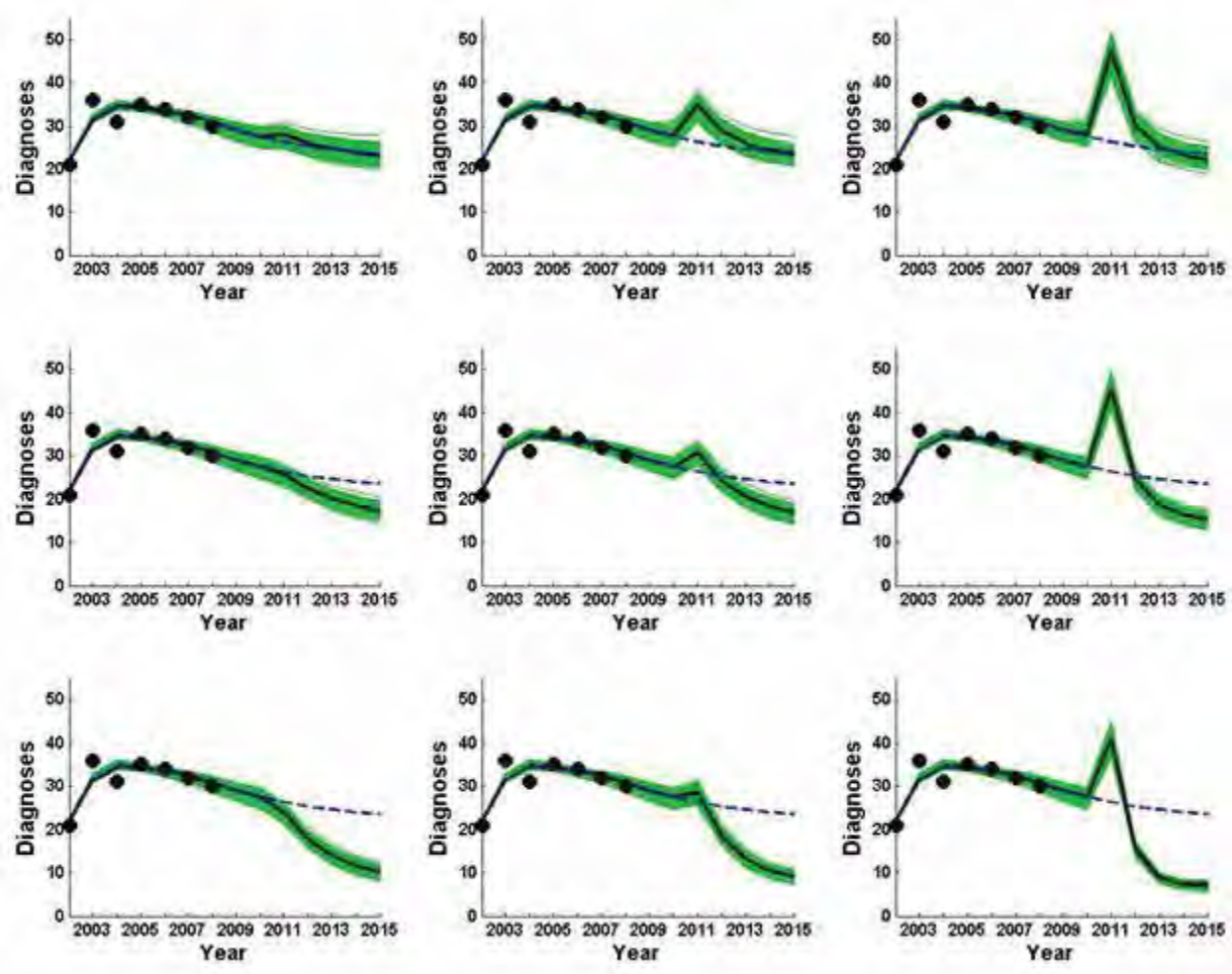
Approximately 60-65% of MSM that are socially engaged with the gay community report receiving an HIV test within the last 12 months. In order to assess the impact of an intervention that increases HIV testing rates, we simulated 80% of socially engaged gay men and 80% of all MSM testing for HIV each year (Figure 3, top row, left and centre). To investigate the impact of frequency rather than coverage, we also modelled 70% of all MSM testing twice per year (Figure 3, top row, right).The model predicts the median cumulative number of HIV infections, 2010-2015, for the three interventions would be 123.59, 122.90 and 119.99 respectively. The corresponding median reduction in new infections compared to

simulation under current conditions would be 1.17, 1.86 and 4.77. Thus, increases in testing rates alone are likely to reduce the risk of transmission; however, expected reductions in population incidence would likely be very modest.

We simulated ‘test and treat’ scenarios according to variations in testing frequencies and with all HIV-diagnosed men initiating ART if their CD4 count is less than 500 cells per µl (Figure 3, centre row). The estimated median cumulative number of HIV infections, 2010-2015, as calculated by the model is 91.26 if 70% of socially engaged MSM test once per year, 90.92 if 70% of all MSM test once per year, and 86.32 if 70% of all MSM test twice per year. This represents reductions of 33.50, 33.84 and 38.44 infections when compared to the status quo. Thus, under the assumption that infectiousness is reduced by 92% among treated MSM, earlier initiation of ART is expected to have a substantial population-level impact.

If HIV-infected people with CD4 counts greater than 500 cells per µl also initiated ART from the time of diagnosis, then an even greater reduction in incidence could be expected. The resultant median cumulative HIV infections from 2010 to 2015 are estimated to be 51.01 if 70% of socially engaged MSM test once per year, 48.52 if 70% of all MSM test once per year, and 39.41 if all MSM test twice per year (Figure 3, bottom row). The median reductions when compared to the status quo corresponding to these outcomes are 73.74, 76.24 and 85.35. Thus, removing the Australian Pharmaceutical Benefits Scheme criteria for subsidised antiretrovirals and providing ART to all HIV-diagnosed MSM regardless of CD4 count could lead to very substantial public health benefits.

Figure 3: Top row, left to right: testing 80% of socially engaged MSM, testing 80% all MSM and testing 70% all MSM twice yearly with current treatment uptake rate. Middle row left to right: the same testing regime as the top row with treatment taken up by all of those diagnosed and with a CD4 count <500. Bottom row, left to right: same testing regime as the top row but with all of those diagnosed being treated. The dashed blue line shows the expected number of diagnoses in the future under the current status quo.



A summary of the effectiveness of each of the public health interventions modelled is shown in Figure 4. In this figure we present the percentage of new infections averted by each of the schemes compared to the status quo of current conditions remaining unchanged. Not

unexpectedly, the most significant and substantial savings in infections averted are made when all diagnosed HIV-positive MSM receive antiretroviral medication, with 68% reduction in infections that would otherwise be expected under current conditions for the period 2010 to 2015. The summary presented in Figure 4 is based on assumption of a 92% reduction in infectiousness once ART has been commenced. We reproduce the results for the same intervention scenarios, allowing infectiousness reduction to vary between 50 and 99% (Figure 5). We see that even with an allowance for variation in the effectiveness of treatment, there are still substantial savings to be made (51% less infections than otherwise expected) when 70% of all MSM test every 6 months and receive ART upon diagnosis.

Whilst it is clear from the Figures 4 & 5 that an increase in treatment results in greater reductions in expected incidence than testing alone, it is useful to investigate the impact of treatment relative to a fixed testing rate. In Figure 6 we present the expected reduction in HIV infections due to treatment alone for two scenarios: the first where testing remains at current levels, and in for the second scenario previously presented where all men test 70% each year. In the first scenario, the reduction in infections due to treatment are compared against a baseline of the current status quo – that being no change in testing or treatment. In the second scenario, the reduction in infections is compared against a baseline where all men who have sex with men are tested once per year. As expected, due to already high testing levels in the majority socially-engaged population, the results for change in treatment regimens reflect very closely the outcomes seen in our “test and treat” interventions.

Figure 4: Expected number of HIV infections averted among MSM in South Australia, 2010-2015, according to a number of interventions assuming a 92% reduction in infectiousness for people on ART

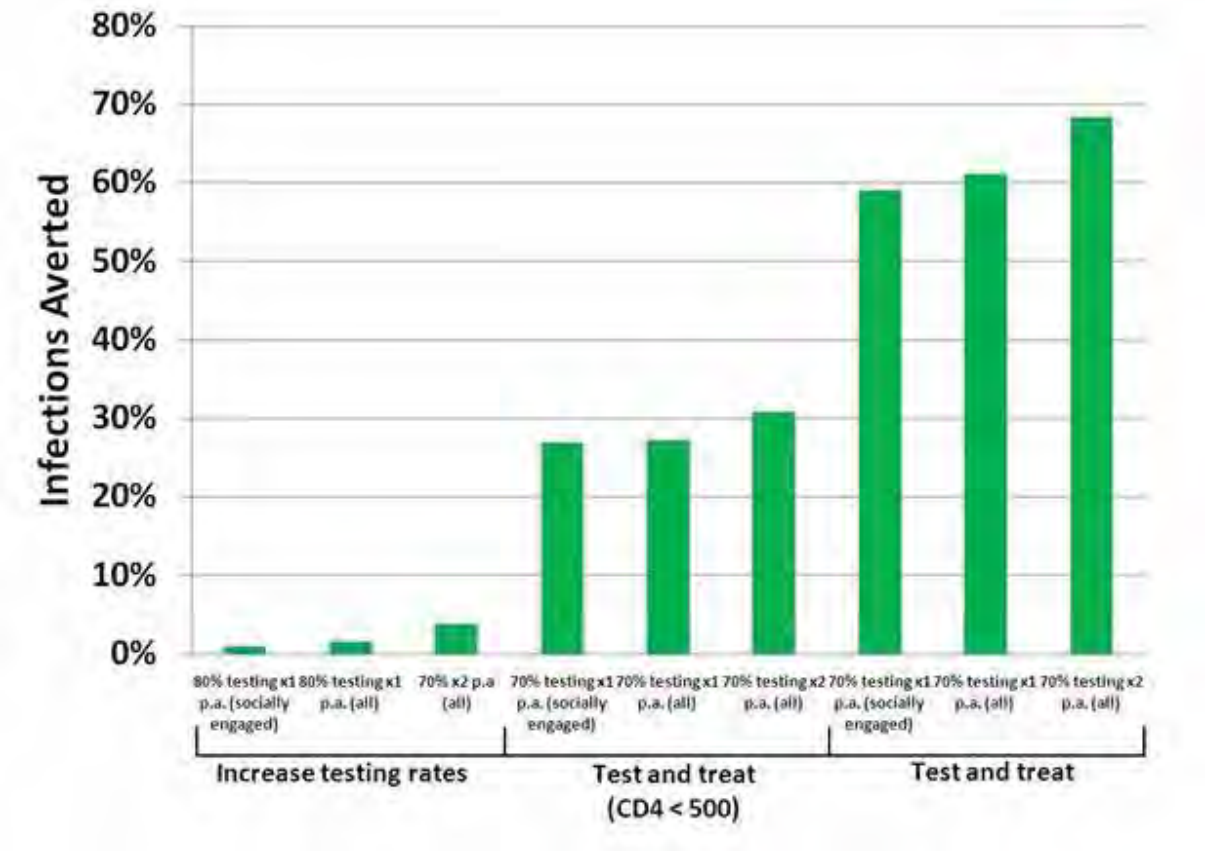


Figure 5: Expected median number of HIV infections averted among MSM in South Australia, 2010-2015, according to a number of interventions, allowing for variance of 50-99% in infectiousness reduction for people on ART (that is, these results roughly correspond to an assumption of 75% reduction in infectiousness)

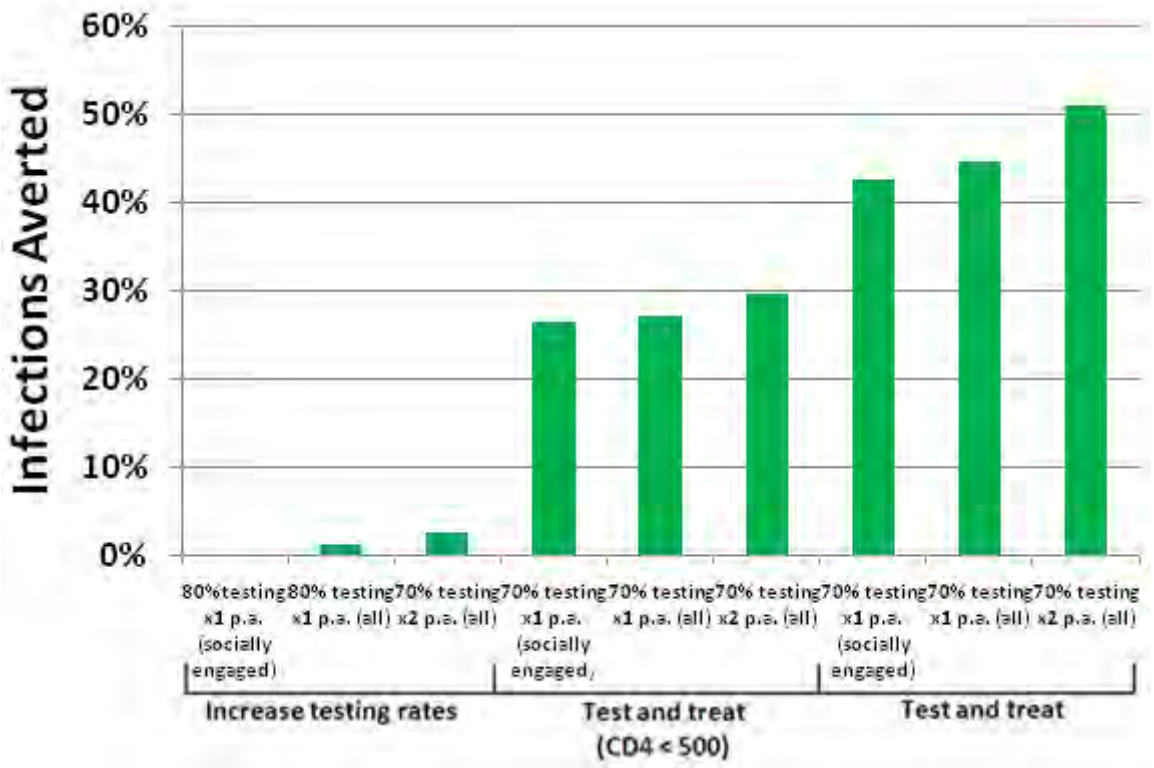
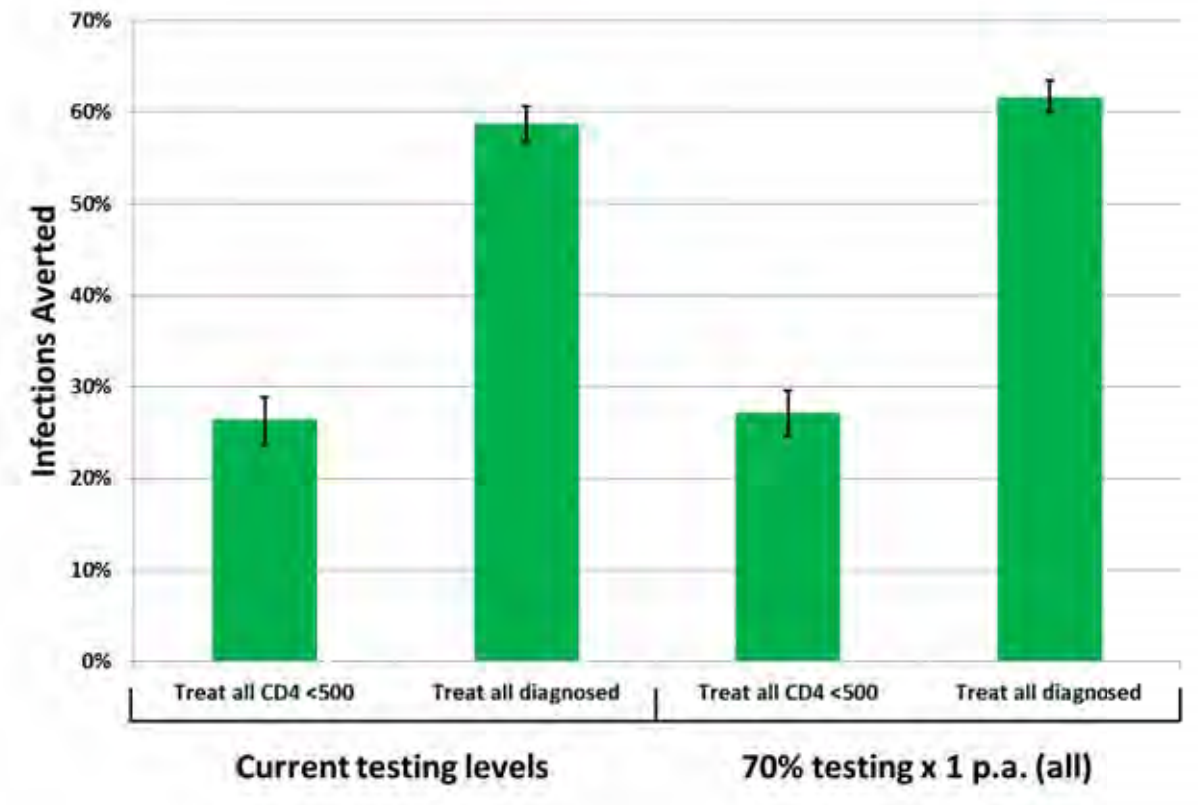


Figure 6: Expected number of HIV infections averted among MSM in South Australia, 2010-2015, according to a change in treatment relative to a fixed testing rate assuming a 92% reduction in infectiousness for people on ART



Discussion

Increases in HIV testing have numerous benefits: for the HIV-infected individual to receive care and management of infection; for public health surveillance systems to monitor epidemics; and potentially for the uninfected population as diagnosed individuals may change behaviour or receive ART to reduce transmission risks. A previous study has demonstrated the expected relationship between testing rates and HIV incidence in Australian MSM populations [53]. The relative benefit of increased testing decreases with higher testing coverage. Men who have sex with men in South Australia already have a high rate of testing for HIV with approximately 65% of men testing annually. Our results suggest that increases in HIV testing in the context of South Australian MSM are likely to have a very modest epidemiological impact.

The health care system and infrastructure in South Australia is well-equipped to conduct screening for HIV. However, there are individuals who are not regularly tested for HIV. Campaigns in South Australia have promoted regular HIV testing among MSM. However, as it is much easier to target those who are socially engaged with the gay community through gay venues or via gay-targeted events such as Adelaide's 'Picnic in the Park', innovative internet-based and offline measures would be required to reach all MSM in need of testing. For the 'e-male survey' Rawstorne et al. [22] advertised for participants using e-mail distribution lists of HIV organisations, advertisements on social networking sites, male to male hook-up sites and in local newspapers in order to reach MSM that are not directly connected to the gay community. The extra benefit gained by targeting all MSM should be evaluated against the extra expenditure of resources required in order to reach those who are not socially engaged. This is highlighted by our results that suggest only a very minor

epidemiological improvement when targeting all MSM compared with reaching just men who are socially engaged with the gay community. In order to increase coverage and frequency of HIV testing it may be necessary to extend hours of operation of sexual health clinics or to provide alternative testing mechanisms such as rapid HIV tests. If testing is not easy and convenient for those who are targeted, then it will be difficult to increase the number of people that test and the frequency thereof. MSM in Australia who have higher HIV risk exposure tend to test more frequently [54] but there may be a saturation level to the attainable frequency of testing. The levels of HIV testing among MSM in South Australia are already high and this may facilitate the relatively early detection of HIV infection, on average, and allow for the potential early initiation of ART.

Available evidence suggests that treatment reduces transmission (among discordant heterosexual couples) and modelling studies suggest that this strategy could result in significant population-level reductions in incidence [1, 53, 55-58]. A recent detailed modelling study has also indicated that treatment for prevention is likely to be a highly cost-effective public health strategy [59]. There is little evidence of the effect of ART on transmission risk among MSM. However, assuming that the same relative reduction in infectiousness found among heterosexual couples applies to MSM we have evaluated the potential population impact of increasing treatment rates among MSM in South Australia. Similar to other modelling studies, we found that expanding uptake of ART among HIV-infected people is likely to result in a substantial reduction in incidence in the population.

In Australia, people living with HIV are eligible for subsidised antiretrovirals if their CD4 count is less than 500 cells per μl. We found that if all HIV-diagnosed people with CD4 count less than 500 cells per μl are on ART then approximately 25% of infections would be averted. If testing rates increase such that 70% of MSM in South Australia are tested for HIV twice per year then ~30% of infections would be averted. However, if the Australian

Pharmaceutical Benefits Scheme restrictions were lifted and all HIV-diagnosed people received ART then HIV incidence could be expected to decrease by ~60%, most of which would be achieved if only men engaged with the gay community were reached. The proportion of potential infections averted would increase to almost 70% if all undiagnosed individuals are tested twice per year.

Our model has limitations due to the data sourced for its construction. As no detailed behavioural data for serosorting and sexual positioning is available for MSM in South Australia, this was informed by research conducted on MSM in Sydney, New South Wales [47]. Gay Community Periodic surveys are conducted only biennially in Adelaide; this is due to be increased to annual as of 2010. For non-socially engaged MSM data was obtained using the recently conducted PASH survey [60]. As this survey has only been conducted once, back projections based on behavioural trends from the Adelaide surveys were used. The rate at which MSM would switch between the socially and not-socially engaged groups post sexual debut is difficult to quantify and there are no data available to derive such a rate. Assuming the proportions of the groups remains fairly constant, by using a per-capita force of infection term that incorporates both groups, we account for switching between groups. This model was a deterministic population-level model and the large heterogeneities that exist in the population were not captured but only average behaviours and clinical outcomes were described. Lastly, the largest limitation is the absence of data on the effect of treatment on infectiousness for penile-anal intercourse. Consequently, we applied the best evidence available from heterosexual studies. This assumption may not be valid. It is actually paradoxical that in most resource-rich settings in which the majority of HIV transmissions occur among MSM, HIV diagnosis rates have been increasing over the last decade [14-16] coincidentally with increases in coverage and effectiveness of ART.

Challenges for implementation for any intervention scheme include access, adherence and choice, as well as policy and clinical opinion on what is best for the patient. Any intervention to be truly effective would need to be adopted by the majority of the targeted population for a long period of time. Whilst initial adherence may be successful, there is a risk of fatigue when it comes to maintaining any gains in testing participation and frequency. Adherence to ART is also an issue when more patients are being medicated and for longer, which also raises concerns for the development of drug resistance. Lastly, some MSM will choose not to test and others, once diagnosed, will choose not to have antiretroviral therapy. The right to choose whether to seek medical treatment is a right held by all of those that are infected; it is an important ethical issue to consider removing this right as part of a prevention program. This strategy raises numerous ethical concerns around the concepts of individualism versus utilitarianism [9].

Treatment of HIV-infected people with antiretroviral drugs for the purpose of prevention of new infections is a shift away from the normal paradigm of using ART for the sole purpose of keeping HIV-infected people alive, reversing AIDS-defining diseases and improving their health. The objective of early treatment is to preserve immune function and enhance viral control in order to attenuate long-term clinical outcomes. A randomised controlled trial of early initiation of treatment demonstrated beneficial clinical outcomes for patients receiving monotherapy with AZT for 6 months [61]. However, currently there are no data addressing the impact of early initiation of combination ART on long-term clinical outcomes. Although the World Health Organisation has changed its recommendations on when to initiate ART, from a CD4 count of 200 to 350 cells per μl, this is still a long way from treating all HIV-diagnosed individuals, many of whom are asymptomatic and generally quite healthy. Most treatment guidelines do not recommend early use of ART due to the lack of clinical trial

evidence, along with drug toxicities, the risk of selecting for drug-resistant strains of HIV, and financial implications [62].

As is true of any setting, any reduction in new infections of HIV in MSM of South Australia would not only benefit those in that population, but also indirectly benefits the broader general population also. As noted by the self-identification of sexuality and route of transmission, not all MSM participate in exclusively homosexual intercourse (especially those who are not classed as socially-engaged to the gay community). Six percent of HIV-infected MSM in South Australia identified their infection event as injecting drug use. It is plausible to consider that a reduced incidence of HIV in the most-at-risk population would have a carry on effect to others connected to this population group. Putting aside ethical debates and difficulties associated with implementation and continuation, a public health strategy based on expanded uptake of antiretroviral therapy in a highly tested population would likely be highly effective at reducing HIV incidence in an MSM population and warrants consideration.

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Chapter 4: An economic case for providing free access to antiretroviral therapy for HIV-positive people in South Australia

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Abstract

Background: As financial constraints can be a barrier to accessing HIV antiretroviral therapy (ART), we argue for the removal of co-payment requirements from HIV medications in South Australia.

Methods: Using a simple mathematical model informed by available behavioural and biological data and reflecting the HIV epidemiology in South Australia, we calculated the expected number of new HIV transmissions caused by persons who are not currently on ART compared with transmissions for people on ART. The extra financial investment required to cover the co-payments to prevent an HIV infection was compared to the treatment costs saved due to averting HIV infections.

Results: It was estimated that one HIV infection is prevented per year for every 31.4 (median, 24.0-42.7 IQR) persons who receive treatment. By considering the incremental change in costs and outcomes of a change in program from the current status quo it would cost the health sector $17,860 (median, $13,651–24,287 IQR) per infection averted if ART is provided as a three-dose, three-drug combination without requirements for user-pay copayments.

Conclusions: The costs of removing co-payment fees for ART are less than the costs of treating extra HIV-infections that would result under current conditions. Removing the co-payment requirement for HIV medication would be cost-effective from a governmental perspective.

Introduction

In South Australia, there are an estimated 750 people living with HIV that are aware of their infection [1]. Approximately 76% of these diagnosed cases are receiving antiretroviral therapy (ART) to delay or reverse disease progression and improve survival [2].Whilst it is not necessarily optimal for all patients diagnosed with HIV to be on ART, there remain a proportion of HIV-infected people who are aware of their positive serostatus, are eligible for treatment, but are not yet receiving antiretrovirals. It is an important health issue to remove barriers to treatment uptake to ensure that all in need of life-sustaining ART have access. One of the objectives in the South Australian HIV Action Plan [3] is to increase the appropriate uptake of ART. A suggested strategy to achieve this objective is to implement mechanisms overcoming any possible cost barriers to the use of ART.

In Australia, the Pharmaceutical Benefits Scheme (PBS) provides subsidised prescription drugs to Australian residents. Patients are required to contribute a co-payment for their prescription medication when purchasing under the PBS. Those who receive government pensions, are low-income earners or hold a Health Care Card (HCC) are entitled to pay a reduced "concession" co-payment amount. The co-payment for clients with a HCC is $5.30 per drug prescription and $26.30 for people without a HCC, up to an annual family threshold (inclusive of same sex couples) of $1,200. Approximately 50% of co-payments for HIV medication are at the concession level. A recent increase in co-payment costs has led to concern about patients' abilities to afford essential medications [4]. According to the HIV Futures survey, and before an increase in co-payments, 28.3% of people with HIV in Australia were living below the poverty line and over 40% of patients reported the co-payments for antiretroviral medications to be either 'a little difficult' or 'very difficult' to

afford [5]. Additionally, anecdotal reports from tertiary treatment centres affirm that due to financial reasons some patients are postponing, interrupting or even ceasing treatment [51]. Not only does this impact on the health of HIV-infected people but on the spread of the virus through the population.

Antiretroviral medications are available from public hospital pharmacies in all Australian States and Territories. Unlike other Australian states, South Australia has an additional community pharmacy agreement for dispensing HIV medications whereby the pharmacy acts as an agent for the Royal Adelaide Hospital for dispensation of Highly Specialised Drugs for HIV treatment. Previously, Centre Pharmacy charged one co-payment for a three month-supply of an HIV medication in contrast to the one co-payment per month supply charged by SA public hospital pharmacies. More recently, Centre Pharmacy has been required to charge one patient co-payment per one month supply. The increase in costs is due to the implementation of increased PBS requirements to comply with the administrative agreement between the Commonwealth and the State for the Highly Specialised Drugs Program.

The outcomes of antiretroviral treatment are of benefit at both the population and individual level. Clinical outcomes such as a slow-down or reversal of disease progression [6] benefits the patient. Furthermore, effective treatment results in successful viral suppression (reducing plasma viral load to undetectable levels, less than 50 copies per ml) in approximately 90% of cases [2]. International research (among heterosexual couples) has demonstrated that such reductions in viral load results in an average of 90-95% reduction in the infectiousness of HIV-infected people on ART compared with those not on ART [7-9]. Consequently, there has been a recent call among the HIV/AIDS global health community to substantially increase rates of treatment uptake for the purposes of preventing new infections [10].

In this study we consider the notion of providing free access to HIV medications in South Australia. We evaluate the costs associated with such a strategy and the likely treatment costs saved through averting infections due to reductions in viral load. The analysis is conducted from a health sector (government as third party payer) perspective. Specifically, a simple mathematical model based on risk equations is used to calculate the expected average number of new HIV infections caused by persons who are not currently on ART compared with the average number expected from those who are on ART. The model reflects the HIV epidemiology in South Australia and is informed by available behavioural and biological data. We compare the extra financial investment required to remove the current co-payment requirement with the total medication costs saved due to preventing HIV infections with increased treatment uptake. We then conduct a simple cost-effectiveness analysis to determine if the provision of antiretrovirals would be an appropriate healthcare intervention from a governmental perspective.

Methods

In South Australia from 2004 to 2008, 93.1% of HIV diagnoses were attributed to three dominant routes of exposure: intercourse between men who have sex with men (MSM, 60%), heterosexual sex (25.3%) and transmission via injecting drug use (IDU, 7.8 %). We developed equations that estimate HIV transmission risk for each of these transmission routes. Specifically, the risk equations conservatively calculate the average number of new HIV infections that could be attributed to one infected person each year. They are conservative because the number of secondary infections averted from ongoing chains of transmission is not estimated by our model.

The equations incorporated the risk of HIV transmission per act for each type of sexual or injecting act and the prevalence of HIV in the relevant partnership groups. The rate of circumcision among the male population and the reduction in infectiousness due to antiretroviral medication were included in the equations. To account for sexual behaviour, the model includes the average annual number of casual and regular sexual partners each person has and the frequency of sex with these partners. Similarly, for IDUs the model included the average yearly number of injecting events. HIV protection measures depicted in the model include the rate of condom use in each partnership type (with the efficacy of condoms) and the proportion of acts/partnerships in which a person discloses their HIV serostatus (and the resultant sexual position they generally perform as a consequence). In the context of transmission via injection, the rates of sharing injections and cleaning of injecting equipment (with the efficacy of cleaning) are included. Mathematically, the average number of new HIV transmissions per HIV-infected MSM per year can be expressed according to these factors as

$$
\begin{aligned}
MSM = {} & C_{cas}^{msm}(1-P_{gen}^{msm})\{(1-r_{cas}^{msm})\delta(re^{+}\beta_{re}+in^{+}(\beta_{in}^{nc}(1-c)+\beta_{in}^{c}c)+wi^{+}\beta_{wi}) \\
& +(1-\delta)(re^{?}\beta_{re}+in^{?}(\beta_{in}^{nc}(1-c)+\beta_{in}^{c}c)+wi^{?}\beta_{wi})+r_{cas}^{msm}(0.5(1-\epsilon_{c})(\beta_{re}+\beta_{in}))\} \\
& +C_{reg}^{msm}(1-P_{part}^{msm})\{0.5(1-(1-(\beta_{in}^{nc}(1-c)+\beta_{in}^{c}c))^{n_{reg}^{msm}(1-r_{reg}^{msm})}(1-(1-\epsilon_{c})(\beta_{in}^{nc}(1-c)+\beta_{in}^{c}c))^{n_{reg}^{msm}r_{reg}^{msm}}) \\
& +0.5(1-(1-\beta_{re})^{n_{reg}^{msm}(1-r_{reg}^{msm})}(1-(1-\epsilon_{c})\beta_{re})^{n_{reg}^{msm}r_{reg}^{msm}}))\}
\end{aligned}
$$

where C is the average number of partners for each relationship type (casual or regular), P is the prevalence of the relevant partnership group, r is the rate of condom use, β is the transmission risk for each act type, δ is the rate of disclosure of serostatus (+ denotes disclosed positive, - denotes disclosed negative and ? denotes unknown serostatus), c is the proportion of men that are circumcised, n is the number of acts per relationship type per year and ε is the efficacy of condoms/ cleaning of injecting equipment. The risk of male-to-female transmission (MtoF), female-to-male transmission (FtoM) and transmission via injecting drug use (IDU) have the following similar expressions:

$$MtoF = C_{reg}^{het}(1-P_{fem})\{1-(1-\beta_{mf})^{n_{reg}^{het}(1-r^{het})}(1-(1-\epsilon_c)\beta_{mf})^{n_{reg}^{het}r^{het}}\},$$

$$FtoM = C_{reg}^{het}(1-P_{mal})\{1-(1-(\beta_{fm}c+\beta_{fm}(1-c)))^{n_{reg}^{het}(1-r^{het})}(1-(1-\epsilon_c)(\beta_{fm}(1-c)+\beta_{fm}c))^{n_{reg}^{het}r^{het}}\}$$

,

$$IDU = n^{inj}\sigma(1-P_{idu})(q(1-\epsilon_q)\beta_{idu}+(1-q)\beta_{idu}).$$

These model equations are first used to calculate the risk of each exposure type prior to treatment and then recalculated with an allowance for the reduction in infectiousness (ε_t , where $\varepsilon_t\beta_{re} = \beta_{re}^{treat}$) due to treatment. The difference between the resultant risk calculations is the expected number of new infections averted per person, per year, due to initiation of treatment. From this relationship we calculated the number of people needed to treat (NNT) in order to avert one HIV infection each year and thus, the financial cost per infection averted in the immediate-to-short term. The costs of covering the required number of co-payments were then evaluated in comparison with the costs of treating the infection that would otherwise have been expected. All parameter values used in the analyses are provided in Table 1. Ethical approval was not required for this study.

Table 1: Parameters used in our mathematical model

Parameter definition	**Range of values** [a]
Reduction in transmission risk per risk event due to treatment compared to no treatment (ε_t , where $\varepsilon_t\beta_{re} = \beta_{re}^{treat}$)	90.02 (81.13-98.72)% [7, 11]
Transmission risk per act of unprotected receptive anal act (with ejaculation) (β_{re})	1.43 (0.48-2.85)% [12]
Transmission risk per act of unprotected receptive anal act (without ejaculation)(β_{wi})	0.65 (0.15 - 1.53)% [12]

Transmission risk per act of unprotected insertive anal act (with circumcision)(β_{in}^{c})	0.11 (0.02 - 0.24)% [12]
Transmission risk per act of unprotected insertive anal act (without circumcision)(β_{in}^{nc})	0.62 (0.07-1.68)% [12]
Transmission risk per act of unprotected receptive vaginal act (β_{mf})	0.1(0.05-0.17)%[13-21]
Transmission risk per act of unprotected insertive vaginal act (w/out circumcision)(β_{fm})	0.05 (0.025-0.085)% [13-21]
Proportion of men that are circumcised (c)	65 (50.3-82.6)% [22]
Efficacy of condoms (ε_c)	95 (80-99)% [23-27]
Rate of disclosure of HIV status by HIV-positive MSM (δ)	45.9 (30-60)% [28]
Estimated population size of gay men in South Australia	12,500 [29, 30]
Condom use among heterosexual couples in which discordant HIV status is known (r^{het})	75 (69-80)% [5]
Prevalence of HIV among heterosexual population (P_{mal}, P_{fem})	0.1(0.098 - 0.148%)% [31]
Average number of regular sexual partners per year for heterosexuals (c_{reg}^{het})	1 (0.8-1.2) assumption
Transmission probability of HIV per injection with a contaminated syringe (β_{idu})	0.7 (0.56-0.84)% [32, 33]

Weighted average annual injecting frequency for IDUs in South Australia (n^{inj})	300 (256-384) [34]
Proportion of injections that are shared in South Australia (σ)	16 (10-22%)% [35]
Prevalence of HIV among IDUs in South Australia (P_{idu})	0.86 (0.5-1)% [34]
Average number of acts per year in regular MSM partnership (n_{reg}^{msm})	100 (80-120) [36]
Average number of casual partners of HIV-positive MSM (c_{cas}^{msm})	14 (10-16) [37] (b)
Average number of regular partners MSM (C_{reg}^{msm})	0.65 (0.5-0.7)% [38]
Average number of acts per casual MSM partnership (n_{cas}^{msm})	1 [36]
Condom use in casual partnerships MSM (r_{cas}^{msm})	75 (60-90)% [38]
Condom use in regular partnerships MSM (r_{reg}^{msm})	48 (30-65%)[38]
Prevalence of HIV in partners of positive MSM (P_{part}^{msm})	0.398 (0.35-0.45) [38]
Prevalence of HIV in general MSM (P_{gen}^{msm})	0.1 (0.08-0.12) [2, 31]
Number of acts per regular heterosexual partnership per year (n_{reg}^{het})	100 (80-120) assumption
Rate of needle cleaning (q)	0.75 (0.6-0.9) [34]
Efficacy of cleaning syringes (ε_q)	0.675 (0.6-0.75) [34]

Proportion of acts in which the negative partner will take role when partner is known to be positive	Receptive with ejaculation (re^{+})	0.11[37]
	Receptive with withdrawal prior to ejaculation (wi^{+})	0.33 [37]
	Insertive (in^{+})	0.56 [37]
Proportion of acts in which the negative partner will take role when partner's serostatus is unknown	Receptive with ejaculation ($re^{?}$)	0.21 [37]
	Receptive with withdrawal prior to ejaculation ($wi^{?}$)	0.33 [37]
	Insertive ($in^{?}$)	0.46 [37]
Explanatory footnotes		
a	Mean (95% Confidence Bounds) reported. A uniform distribution is applied across the 95% CBs for input into model.	
b Distribution of the number of casual partners of gay men per 6 months (percentage of men in each category) used in the calculation of C_{cas}^{msm} [37]	1-1.5	26%
	2-5	21%
	6-10	16%
	11-50	30%
	51-60	7%

Uncertainty and sensitivity analysis

Uncertainty analysis was conducted by defining a probability distribution for each of the input parameters that covers the plausible range of values based on the published literature. Using Latin hypercube sampling, the distributions were sampled 10,000 times generating the equivalent number of unique parameter sets. The expected numbers of transmissions, with and without additional provision of treatment due to removal of the copayment requirements, were then calculated for each parameter set. Due to the variability in the inputs to the model there was a subsequent range of outcomes for each of the model output variables. Sensitivity analyses were conducted through the method of factor prioritization by reduction of variance and by calculating partial rank correlation coefficients (PRCCs) to determine the importance of uncertainty in input estimates to the range in outcome variable measures.

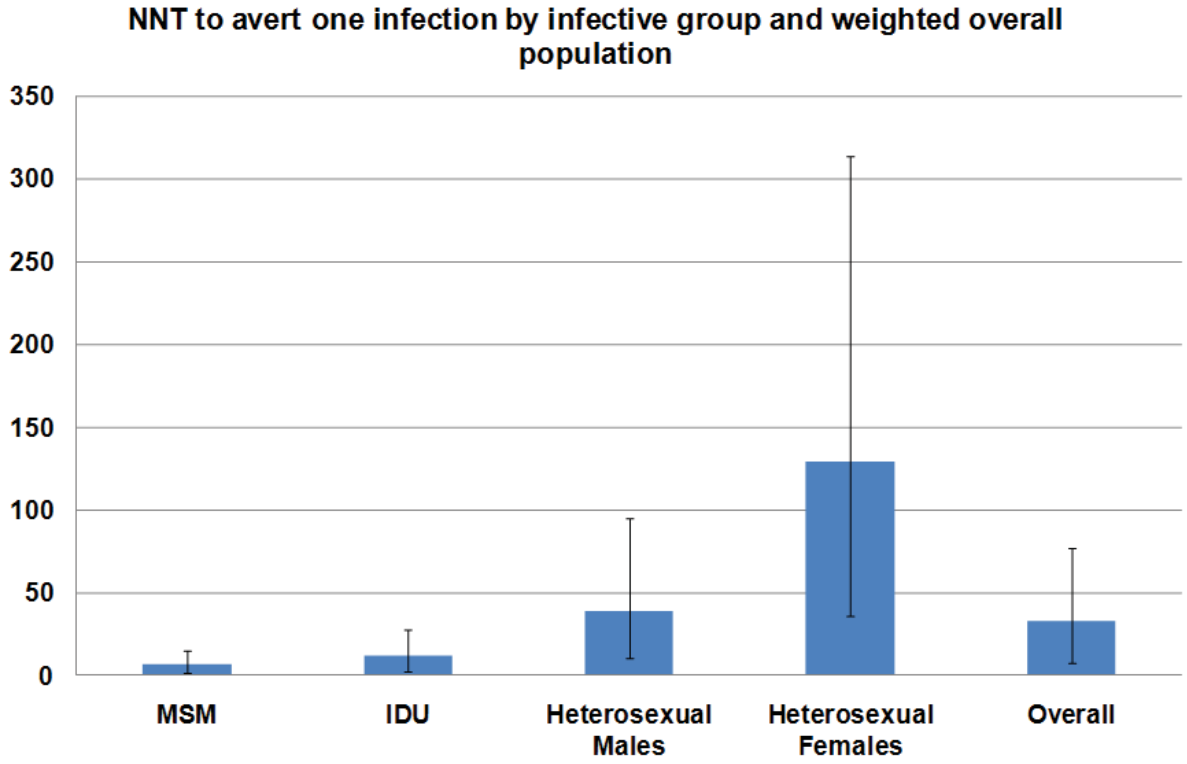
Cost-effectiveness analysis

We calculated a simple incremental cost per quality-adjusted life year (QALY) gained in order to determine if the free provision of antiretroviral medication is an efficient healthcare interventional in an economic sense. An intervention is determined to be cost-effective if the cost per QALY saved is below a pre-determined willingness-to-pay (WTP) threshold. In Australia, the WTP threshold is approximately AU$64,000 [39] and in a resource-rich setting such as South Australia, an estimated 7.5 QALYs are lost per HIV infection [40].

Results

According to the model, the expected number of new transmissions resulting from each infected person per year is much less than one, for all transmission routes even without consideration of reduction in infectiousness due to antiretroviral treatment. Men who have sex with men have the highest average transmission rate, with an average of 0.1772 (median, 0.1419 – 0.2135 IQR) new infections per year without treatment, which is equivalent to one transmission every 5.6 (median, 4.7-7 IQR) years. In comparison, without treatment one transmission would occur after an average of 5.9 (median, 4.8 – 7.4 IQR) years per IDU, 35 (median, 25.6 – 49.4 IQR) years for heterosexual males, and 115 (median, 84 – 164.9 IQR)years for heterosexual females (or equivalently, an average of one infection would occur per year for every 115 HIV-infected females). With treatment, the transmission rates are substantially reduced across the population. The model was used to estimate the per-capita rate of HIV transmission for each transmission route due to initiation of treatment for one year, adjusting for the cumulative number of exposure events and average behaviours of each population group. It was conservatively estimated that the number needed to treat in one year to prevent an HIV infection in the appropriate susceptible group is: 6.4 (median, 5.5-7.7 IQR) MSM, 38.5 (median, 28.7-53.1 IQR) heterosexual males, 126.5 (median, 94.2 – 177.2 IQR) heterosexual females, or 11.5 (median, 10.4 – 13 IQR) IDUs (Figure 1). Over the five years of reported data in South Australia (2004-2008), 60% of HIV diagnoses were among MSM, 16.7% among heterosexual males, 8.6% among heterosexual females, and 7.8% among IDUs (and 6.9% were among other categorisations). Adjusting for the proportion of diagnoses associated with each risk group as a weighted average, one HIV infection is prevented per year for every 31.4 (median, 24 – 42.7 IQR) people (Figure 1) who receive treatment in South Australia.

Figure 1: The number needed to treat to avert an HIV infection by infective group and weighted overall population



Currently, annual HIV medication costs per person in South Australia are approximately $14,000, [41-44] with an estimated average lifetime cost of the order of $400,000 [44] (assuming approximately 30 years of treatment). By providing treatment to 31.4 people each year in order to prevent one new infection, the cost of averting that infection would be 31.4 x $14,000 = $439,600. Hence, in terms of medication costs only, the expenditure currently required to prevent an infection is roughly of the same magnitude but likely only marginally more than what would be required to provide lifelong treatment to the infected person that would have resulted. Simplistically, an averted infection leads to approximately 7.5 QALYs gained. Therefore, the approximate cost per QALY is $58,613 (=$439,600/7.5), which is below the WTP threshold. Conservatively, this does not include other costs associated with healthcare services that would also be saved. Therefore, if a treatment program enables

access for people who would not have otherwise received therapy, then from a purely economic perspective, provision of full treatment is cost-effective.

As the cost of HIV medications are already partially subsidised by the government, a change in program to free access should also be considered purely in terms of the incremental cost of removing the patient co-payment requirement and not full ART costs. If ART was provided as a three-drug, three-dose regimen, it would cost just an additional $17,860 to cover current co-payment expenses in order to avert one infection. However, according to current treatment patterns, two-thirds of patients receive their three-drug regimen as a two-pill dose. This reduces the incremental cost per infection averted to $13,891.

The incremental cost to the government to remove the co-payment requirement for all 750 people currently diagnosed with HIV infection in South Australia would be approximately $331,800, of which, $79,632 would be for those (approximately 180) people who are not currently receiving treatment. This incremental cost to remove copayments for all patients is less than the estimated lifetime treatment cost of one new infection. If all of those who are currently diagnosed but not receiving ART (approximately 24%) were to uptake treatment, this would avert an expected additional 5.73 new infections each year. The annual cost in terms of medication for this sub-population would be $2,520,000, but by averting 5.73 infections, saves lifetime medication costs of $2,292,000. Therefore, in terms of co-payments costs and in terms of medicinal costs to the government, the removal of co-payments for all HIV-infected patients would likely be less than treating the additional infections that would otherwise be expected.

By conducting sensitivity analyses on the outcomes of the model, we are able to determine which of the input parameters are the most important in the calculation of transmission risk and to what extent they influence the variability in the outputs. Based on our PRCC analysis

we found that for each of the scenarios where sexual intercourse is the route of transmission, the most important parameter is the per-act risk of transmission. For people who inject drugs, the most influential parameter is the average proportion of injection acts that are shared per year. For untreated MSM, the per insertive-act risk accounts for 48.6% of the variability in the expected number of annual transmissions. For heterosexual people not on ART, the applicable gender-to-gender per-act risks caused approximately 50% of the outcome variation. For people receiving ART the effectiveness of treatment in reducing infectiousness was found to be the most influential parameter associated with sexual transmission. For MSM, male-to-female and female-to-male transmission, the effectiveness of ART caused 63.6%, 57.5% and 56.4% of variability in the expected number of transmissions respectively. In IDUs receiving antiretrovirals, the rate of needle cleaning was the parameter most influential, accounting for 62.3% of the variation in the model outputs.

Discussion

Our calculations have some potential limitations due to the data sources used. There are no data available for the South Australian MSM population for any changes in sexual risk behaviour post-commencement of treatment, only post-diagnosis. However, as shown in Chapter 3, even a small change in treatment rates alone in a subpopulation averts infections in the greater population of interest. Recently there has been discussion regarding viral load being used to negotiate condom use in serodiscordant partnerships [45]. By using post-diagnosis behaviours, we essentially take the conservative estimate for expected infections as we do not allow for an increase in unprotected acts due to belief about viral loads. In fact, it has been found that HIV-positive men who have a detectable viral load are as likely to

engage in serodiscordant unprotected anal intercourse and no less likely to restrict themselves to the receptive position as those who reported their viral load as undetectable [45]. We used the best data available to inform our calculations from comparable settings, e.g. behavioural distributions for some parameters were obtained from studies of MSM in Sydney and international studies on biological transmission rates were used, and different values may apply to South Australia. However, we used South Australian data sources wherever possible. It is possible that other STIs may act as biological cofactors to increase transmission probabilities. The average transmission probabilities used in the model were based on studies which estimated transmission rates among populations of people whilst attempting to control for numerous factors including behaviour and background rates of other STIs. Therefore, we believe it is appropriate for us to directly apply the average transmission rates without explicitly included expressions for STI factors. We assumed that treatment reduced infectiousness by 92% per exposure event, based on two recent studies conducted among heterosexual discordant couples [7, 46]. It is not known whether the same relative reduction in transmission is appropriate for transmission routes of higher risk such as sharing injecting equipment and penile-anal sex [47]. Further, although the average annual costs of antiretrovirals are known, lifetime costs of medications can only be estimated based on rough extrapolations, as have been done elsewhere. This model is static, and therefore cannot be used for the long term projection of disease progression or capture the dynamic features of infections averted. Nor could we therefore, evaluate the cumulative cost savings over time, and as such, our cost estimates have not been discounted. As the question of whether the removal of copayments would be an efficient distribution of resources is relatively simple, and with the data available, this model type is reasonable and appropriate to provide a simple and transparent assessment.

In this study we provided a simple economic argument in support of the South Australian government covering the financial cost of co-payments for HIV antiretroviral drugs. We showed that such a policy would be cost-effective. Our results are relativey conservative and directly applicable to the epidemiological context of South Australia. The quantitative outcomes of our analysis would be different for other settings but the qualitative conclusions of our analysis are likely to be broadly applicable to other similar contexts. Our mathematical framework can easily be extended to other contexts by applying appropriate epidemiological and behavioural data. Numerous economic studies carried out in a variety of different international settings have also shown provision of antiretroviral therapy to be cost-effective or cost-saving [48-50].

Financial policies and practices for provision of antiretrovirals differ across Australia. Policy in South Australia requires that the State pay for the co-payments of each one month supply of antiretrovirals dispensed, regardless of whether it is recouped from the patient. This is similar to the policy in New South Wales, Queensland, Australian Capital Territory and Tasmania, although some of these jurisdictions have no community pharmacy dispensation. In Victoria, antiretrovirals are dispensed for free from the Melbourne Sexual Health Centre; otherwise a co-payment is required from all other Victorian public hospital pharmacy outlets. In Western Australian and the Northern Territory, antiretrovirals for HIV treatment are supplied free of charge. It would not be an extreme step for South Australian policy on costs for HIV treatment to be aligned with that in Western Australia and the Northern Territory. There also exist precedents in South Australia for provision of free treatment and/or immunisation for diseases that present a public health risk. In South Australia, treatment and/or immunisation for tuberculosis, hepatitis B, seasonal influenza and sexually transmitted infections other than HIV are available without cost to the patient.

The inability for some people to access consistent treatment for HIV not only impacts upon the individual, but also the health system and the general population. By delaying treatment uptake or ceasing it altogether due to inability to finance co-payment costs, HIV-infected individuals can experience persistently increased viral load. This can have a damaging effect on the general health of individuals and the population. At a macro level, increased average viral loads in the population will lead to increased incidence of HIV. Ultimately this will lead to increased costs associated with ART, as well as more hospital admissions and outpatient appointments.

Facilitating increases in treatment rates by removing the co-payment requirement for HIV medication is likely to result in numerous beneficial outcomes including reductions in HIV transmissions and less resistance to antiretrovirals, improved health outcomes for HIV-infected individuals, and a reduced burden on public health resources. Recent discussions and recommendations about novel prevention strategies are also promoting increased treatment rates among all HIV-infected people [10]. There is strong clinical and epidemiological support for increasing treatment rates in addition to the financial benefits. We carried out a simple health economics analysis from a governmental perspective of covering co-payments for HIV antiretroviral drugs and found that this initiative is cost-effective, and we therefore recommend its implementation.

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Chapter 5: Sex workers can be screened too often: a cost-effectiveness analysis in Victoria, Australia

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Author Contributions: DPW and BD conceived the design of the study. DPW developed the mathematical framework and wrote the paper. KJH contributed to the development of the mathematical framework, carried out all analyses, produced figures, and assisted in the writing of the manuscript. JA determined all costs associated with screening and treatment, assisted with the economic calculations, and assisted with editing the manuscript. JO and CH provided data of incidence of STIs in sex workers. BD also contributed to the writing of the paper and overseeing its message.

Abstract

Objectives: Commercial sex is licensed in Victoria, Australia such that sex workers are required to have regular tests for sexually transmitted infections (STIs). However, the incidence and prevalence of STIs in sex workers is very low, especially since there is almost universal condom use at work. We aimed to conduct a cost-effectiveness analysis of the financial cost of the testing policy versus the health benefits of averting the transmission of HIV, syphilis, chlamydia, and gonorrhoea to clients.

Methods: We developed a simple mathematical transmission model, informed by conservative parameter estimates from all available data, linked to a cost-effectiveness analysis.

Results: We estimated that under current testing rates it costs over AU$90,000 in screening costs for every chlamydia infection averted (and AU$600,000 in screening costs for each quality adjusted life year (QALY) saved) and over AU$4,000,000 for every HIV infection averted (AU$10,000,000 in screening costs for each QALY saved). At an assumed willingness to pay of AU$50,000 per QALY gained, HIV testing should not be conducted less than approximately every 40 weeks and chlamydia testing approximately once per year; in comparison, current requirements are testing every 12 weeks for HIV and every 4 weeks for chlamydia.

Conclusions: Mandatory screening of female sex workers at current testing frequencies is not cost-effective for the prevention of disease in their male clients. The current testing rate required of sex workers in Victoria is excessive. Screening intervals for sex workers should be based on local STI epidemiology and not locked by legislation.

Introduction

Sex work in the state of Victoria, Australia, is decriminalised but regulated through a licensing system. Sex workers in Victoria are required to provide evidence of having regular sexual health check-ups for *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, and *Trichomonas vaginalis* and to be examined for genital warts or active herpes lesions every month, plus serology for HIV and syphilis every three months [1]. Sex workers may be prosecuted for knowingly having sex with clients while carrying a sexually transmissible infection (STI) or for not having the prescribed STI tests. The financial cost of consultations and testing for these STIs is usually covered by the government healthcare system. However, it is known that many sex workers have almost universal condom use at work and a low incidence of STIs [2]. The few STIs that they do acquire are usually attributable to private sexual partners [2]. Although it is a hallmark of public health campaigns to promote STI testing among groups with relatively large numbers of sexual partners, we postulated that the current testing rates required of sex workers in Victoria may be excessive. We conducted a simple analysis on the cost-effectiveness of these regulations and evaluated the cost-effectiveness of alternative testing frequencies. To assess the cost-effectiveness of regular STI testing we used a mathematical model to estimate the expected number of STI transmissions from sex workers to their clients based on available behavioural, biological, and epidemiological data. We used the model to explore how the expected number of sex worker-to-client transmissions of HIV, syphilis, chlamydia, and gonorrhoea changes with the frequency of STI testing and the cost of that testing. We took a health sector perspective with 3% discounting of costs and outcomes according to standard methods [3]. We only included the costs and outcomes of diseases in male clients.

Methods

If a sex worker has an STI then the expected number of transmissions of the infection to clients (per sex worker per week) can be estimated as the product of the number of clients each sex worker has per week, n, and the probability of transmission per sexual encounter with a client, β. The probability of transmission per encounter can be modelled by $\beta = \left\{ p\left[b + (1-b)(1-\varepsilon) \right] + 1 - p \right\} \beta'$ for a condom usage rate of p, condom efficacy of ε, condom breakage rate of *b*, and baseline probability of transmission per unprotected act of β'. In a population of *N* sex workers, if the incidence rate (per week) of a sex worker acquiring an infection is λ then the expected prevalence of infected sex workers at any time is approximately $N\lambda\tau$, where τ denotes the average number of weeks between tests. The total expected number of infections caused by all infected sex workers per week is

$$I = N\lambda\tau n\beta. \qquad (1)$$

That is, the modelled number of transmissions is a function of the average sexual activity level of sex workers (in terms of number of acts and condom use), the biological transmission efficiency of the organism in question (in terms of both incidence to sex workers and secondary transmissions from sex workers to clients), and the testing frequency.

The total number of infections caused by all infected sex workers per week (equation 1) can be expressed in terms of the total number of tests per week:

$$I = \frac{\lambda n \beta N^2}{\text{Total number of tests per week}}, \qquad (2)$$

or the total cost of conducting all tests:

$$I = \frac{c\lambda n\beta N^2}{\text{Total cost}}, \tag{3}$$

where c is the cost per test. The expected weekly cost of testing all sex workers every τ weeks on average is Nc/τ. Then, the cost per infection averted, for any given testing frequency, can be calculated from taking the gradient of equation (3):

$$\text{CostPerIA} = \frac{c\lambda n\beta N^2}{I^2} = \frac{c}{\lambda n\beta\tau^2}. \tag{4}$$

If each infection results in a loss of q quality-adjusted life years (QALYs) for the infected person, then the cost outlaid for each QALY saved is

$$\text{CostPerQALY} = \frac{c}{\lambda n\beta\tau^2 q}. \tag{5}$$

We also used estimates of the cost to treat infections to calculate the expected total financial loss/saving (net monetary benefit) for the health system (total savings is calculated as the cost saved on treatment from averting infections minus the cost of screening, assuming a willingness to pay of AU$50,000 per QALY gained). We also calculated the marginal cost effectiveness ratio by dividing the net monetary benefit by the net health benefit (net QALYs gained was calculated by the product of the number of infections averted and the QALYs lost per infection).

In Table 1 we present values and costs for the parameters of this model based on behavioural, biological, epidemiological, and screening cost data and literature associated with HIV [4-8], syphilis [9-18], chlamydia [19-21], and gonorrhoea [22-26] for Victoria, Australia. We estimate STI incidence in sex workers from sexual health clinic databases and recently reported estimates of incidence in Victorian sex workers [2]. But we conservatively use the upper 95% confidence bound of incidence as the mean value in our model. Specifically, we

take incidence to be 0.1/100 person-years for HIV, 0.1/100 person-years for syphilis, 3.3/100 person-years for chlamydia, and 0.7/100 person-years for gonorrhoea. Notably, no confirmed cases of HIV transmission to or from a sex worker in Australia have ever been reported. We take the efficacy of condoms to be 95% [27-31] and assume that they break or slip 2.5% of the time [32], even though an Australian prospective study suggested that 0.6% may be a more accurate measure for sex workers [33]. We also conservatively assume that a broken or slipped condom equated to unprotected sex. The actual number of sex workers in Victoria is not precisely known but we base our analysis on an estimated 2000 sex workers. This estimate is derived from studies showing that the proportion of men that access sex workers in Victoria is similar to that in the State of New South Wales [2, 34, 35] and an estimation of the size of the sex industry in New South Wales [36]. This is also in agreement with estimates based on the number of registered brothels and average number of women working from each brothel and consistent with expert opinion [37].

Table 1: Definitions and values of parameters used in our analysis

Parameter	Definition		Value
λ	Incidence of infection (per year)*	HIV	0.1 /100py
		syphilis	0.1 /100py
		chlamydia	3.3 /100py
		gonorrhoea	0.7 /100py
β'	Probability of transmission from an infected SW to a male client per unprotected penetrative penile-vaginal exposure	Primary HIV	0.003
		syphilis	0.15
		chlamydia	0.35
		gonorrhoea	0.22
p	Proportion of penetrative penile-vaginal exposures in which condoms are used		99%
ε	Efficacy of condoms		95%
b	Proportion of penetrative penile-vaginal acts using condoms where breakage or slippage of condom occurs		2.5%
n	Average number of clients per sex worker per week		15
q	Quality-adjusted life years (QALYs) lost due to an infection	HIV	7.5
		chlamydia	(3 days)
c	Cost per test(s)	chlamydia + gonorrhoea	AU$57.35**
		chlamydia + gonorrhoea + HIV + syphilis	AU$82.65**

* Using upper bounds of 95% confidence intervals
** Based on Australian MBS data

Screening costs

We used costs reported under the Australian Medicare health system for consultation and STI testing (October 2008). Costs for each clinical consultation for a sexual health check-up are AU$32.80 (assuming level B on the Medicare scheme). In addition, it costs AU$24.55 to conduct a chlamydia and/or gonorrhoea polymerase chain reaction assay (item 69316). If both HIV and syphilis testing are carried out together (item 69387) then the extra testing cost is AU$25.30, but if the tests are carried out on separate occasions then the syphilis testing cost (item 69384) is AU$13.40 and the HIV ab/ag testing cost (item 69384) is AU$13.40. For consultations in which multiple STIs are screened we apportioned the consultation costs equally across each STI.

Treatment costs

If a screening test detects an infection then we consider the treatment costs for chlamydia and gonorrhoea as the cost of one consultation for screening tests (MBS item 23) plus the cost of the relevant medication required to clear the infection (using costs under the Pharmaceutical Benefits Scheme). Similarly for syphilis, the treatment cost is composed of three consultations, one for providing medication and two follow-up serological tests.

Costs of Disease in male clients

Costs associated with each infection in male clients were estimated. There are no recent estimates of the costs of people living with HIV or experiencing complications related to chlamydia, gonorrhoea and syphilis in Australia. Therefore we used the lifetime costs of HIV infection in 2004 derived from data in the USA [38]; inflated to 2007 prices with the medical component of the US Consumer Price Index [39] and converted to Australian dollars using the Purchasing Power Parity [40]; this estimate was AU$490,370 discounted at 3%. We used an expected value analysis of the complications of chlamydia and gonorrhoea to estimate the costs of infection (Chapter 5 Appendix). Data from Australia and expert opinion on the frequency and treatment of disease (and complications including arthritis, epididymitis and infertility) are used to estimate a cost per chlamydia infection of AU$57 and cost per gonorrhoea infection of AU$82. We did not calculate the cost associated with complications of syphilis infection because of a lack of data and uncertainty.

Utility of Disease

We estimated a loss of 7.5 QALYs from the time of HIV infection, discounted at 3%, as used in an recent systematic review of economic evaluations of HIV interventions [41]. For the utility loss associated with complications of chlamydia and gonorrhoea in men, we used the

expected value analysis discussed above to calculate a utility loss of 0.0085 per infection over 12 months, undiscounted. We did not calculate a utility loss for syphilis.

Results

The implementation of current STI screening guidelines for 2000 female sex workers in Victoria costs over AU$3,750,000 per year at the current screening frequency of every 12 weeks for HIV and syphilis and every 4 weeks for chlamydia and gonorrhoea. The cost of screening for chlamydia and gonorrhoea is AU$1,490,000; the cost of screening for HIV is AU$400,400 (Fig. 1).

The expected number of STI transmissions from sex workers to male clients per year is low with less than 0.1 HIV cases, ~3.6 syphilis cases, ~16.4 chlamydia cases, and ~2.8 gonorrhoea cases (Fig. 1) even if the STI incidence rate to sex workers is conservatively high. This is because the population prevalence (and incidence) of STIs in sex workers is low and condom usage rates are very high.

If testing frequency was increased then screening costs would increase sharply. But not surprisingly, if the testing frequency was decreased then screening costs would decrease but the number of infections to clients would increase (Fig. 1). Even if testing frequency was decreased to just once per year, if the incidence rate to sex workers remained unchanged then less than 1 HIV transmission, ~16 syphilis transmissions, ~36 gonorrhoea transmissions, and ~210 chlamydia transmissions could be expected to male clients.

To ascertain the degree to which investment in frequent testing leads to the low incidence we calculated the cost outlaid (for screening) per infection averted in clients. In Figure 2a we

present the modelled relationship between the screening costs per infection averted and the number of weeks between tests for HIV, syphilis, chlamydia, and gonorrhoea. Under current testing rates, for example, it costs over AU$90,000 in screening costs for every chlamydia infection averted and over AU$4,000,000 for every HIV infection averted (Fig. 2a). To assess the value of this testing schedule we extended this relationship to estimate the cost per QALY saved (Fig. 2b). We calculated that under current testing rates, it costs almost AU$600,000 in screening costs for each QALY saved due to the burden of chlamydial infections and it costs over AU$10,000,000 in screening costs for each QALY saved from HIV infection.

Figure 1: Relationship between the annual cost of screening sex workers for STIs (solid curves) and the modelled expected number of STI transmissions from sex workers to clients (dashed curves) versus the duration of time between testing for **(a)** HIV, **(b)** syphilis, **(c)** chlamydia, **(d)** gonorrhoea. The grey lines and numbers indicate the screening cost and expected number of transmissions under the current testing frequency of once every 12 weeks for HIV and syphilis and once every 4 weeks for chlamydia and gonorrhoea. The expected number of transmissions is shown on a $\log_{10}$ scale.

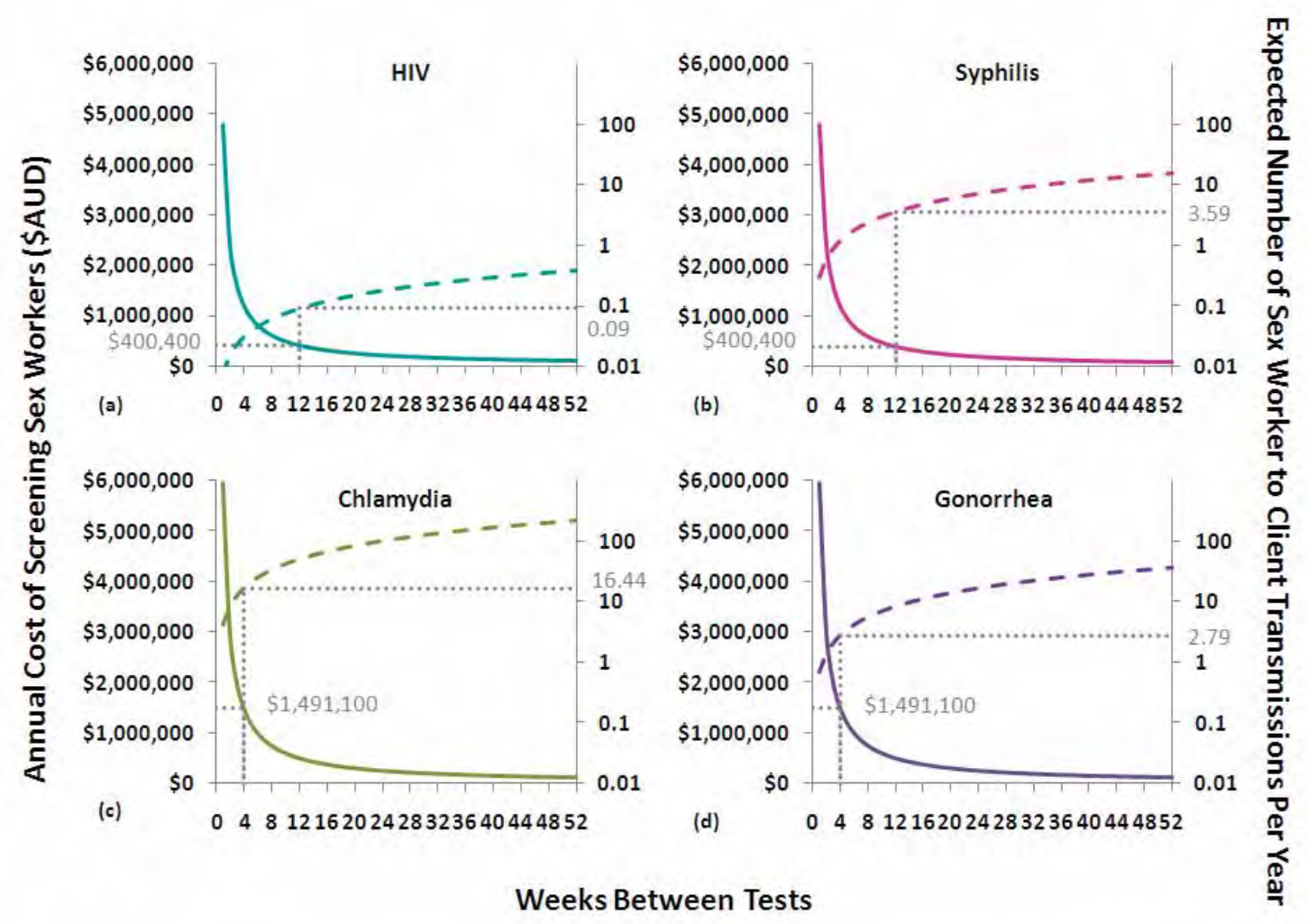


Figure 2: Modelled relationship between the **(a)** cost per infection averted and testing frequency, **(b)** cost per QALY saved and testing frequency, for HIV (blue-diamonds), syphilis (pink-triangles), chlamydia (green-circles), and gonorrhoea (purple-squares).

Figure 2a

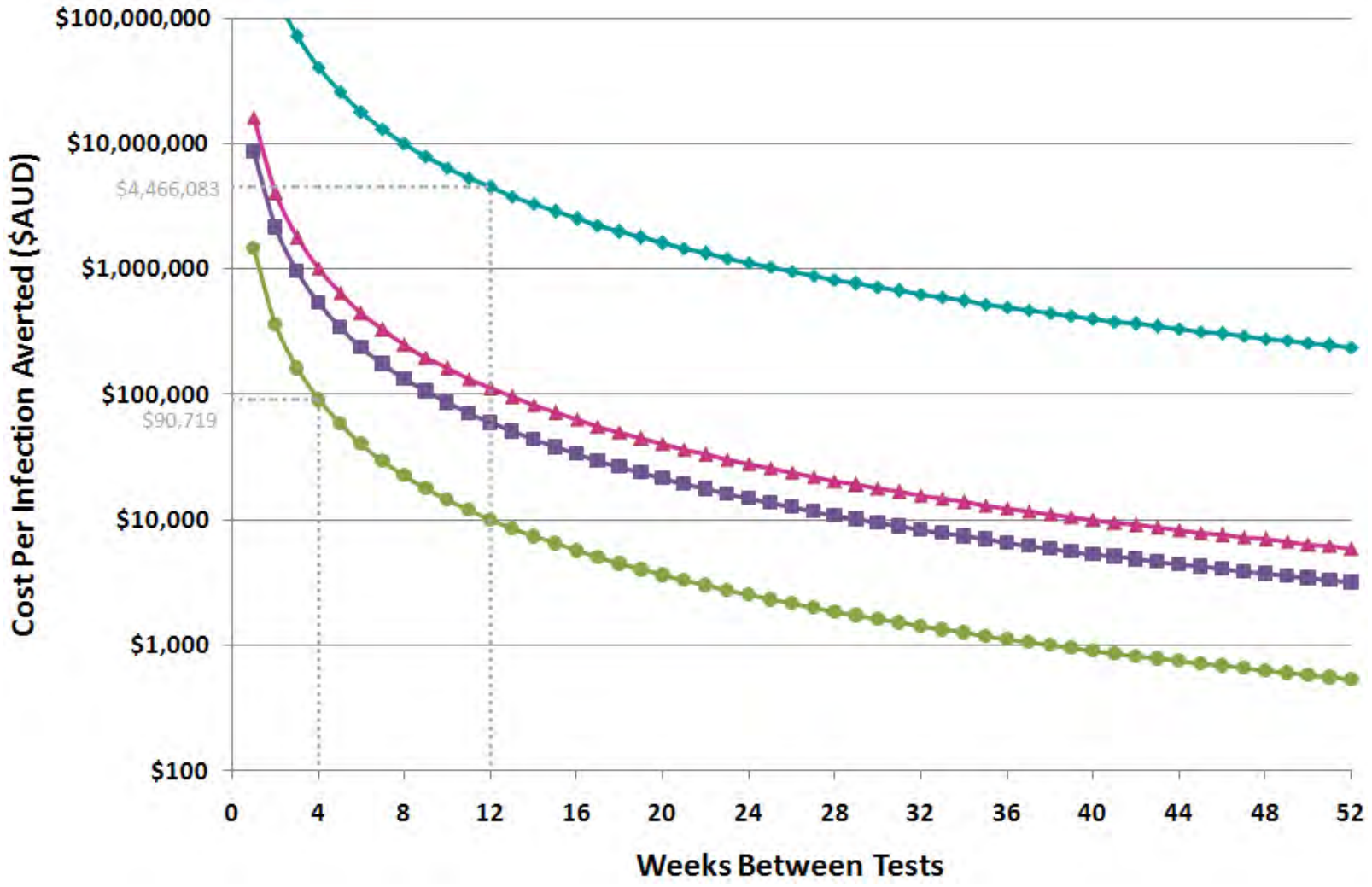
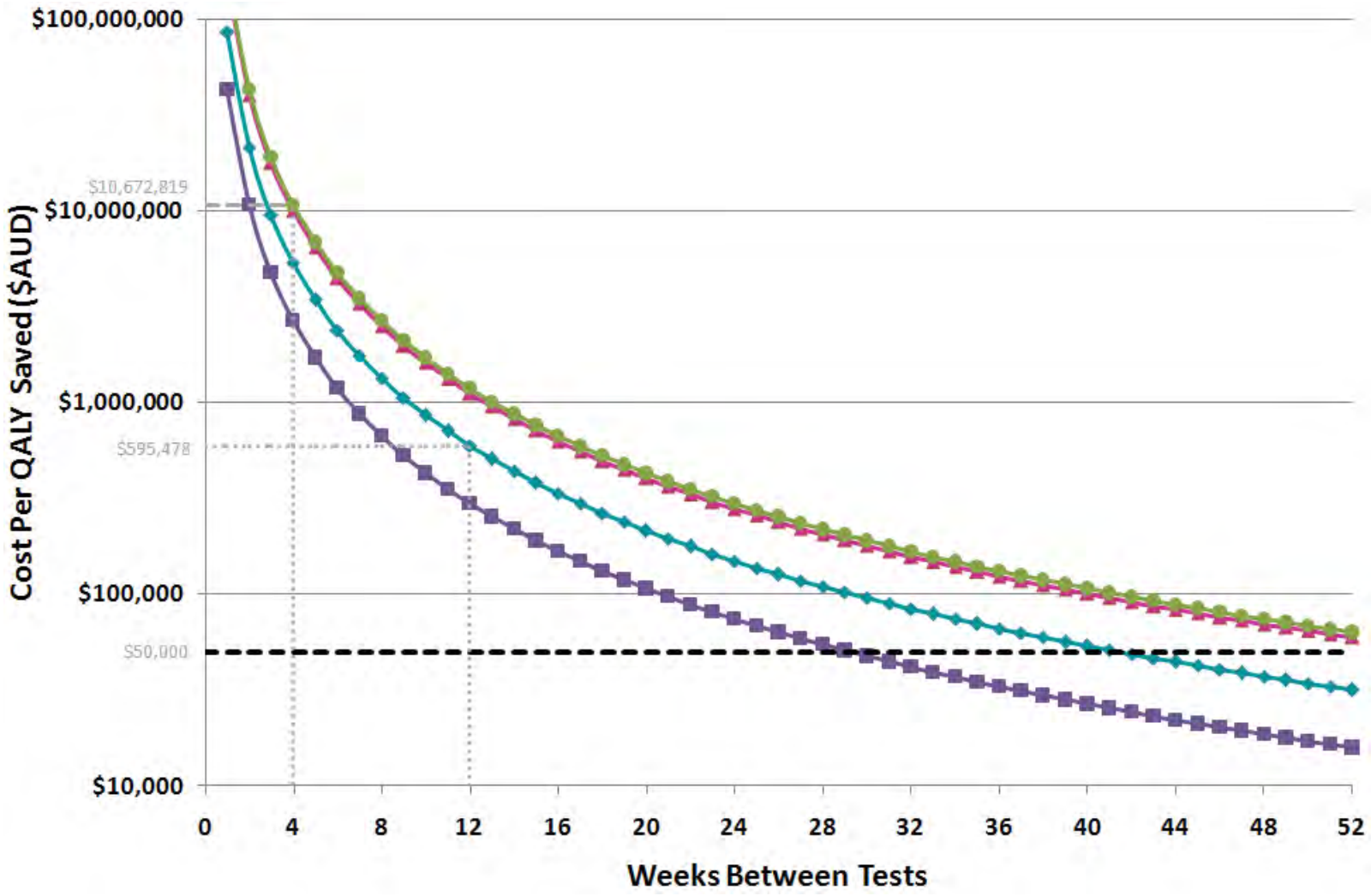


Figure 2b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$1,000,000
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$10,000
Cost Per QALY Saved ($AUD)
0
4
8
12
16
20
24
28
32
36
40
44
48
52
Weeks Between Tests

We determined the incidence levels that would be required in order for the current testing rates to become cost-effective. We found that current frequencies of STI testing would only be cost-effective if incidence increases substantially (Table 2). Incidence would need to increase by 12-fold for HIV, 67-fold for syphilis, 213-fold for chlamydia, and 53-fold for gonorrhoea from the conservatively high incidence already assumed.

Table 2: Comparison between current conditions and increased risk scenarios in order to satisfy cost effectiveness of no more than $50,000 per QALY saved.

		Current condom use (99%)	Decrease in condom use (to 90%)
Incidence rate required for current testing frequency to be cost-effective	HIV	1.2/100py	0.6/100py
	Syphilis	6.7/100py	3.3/100py
	Chlamydia	704.4/100py	351.5/100py
	Gonorrhoea	37.4/100py	18.7/100py
Minimum time between tests (weeks) for cost effectiveness (at current incidence)	HIV	41.41	29.25
	Syphilis	56.71	40.06
	Chlamydia	58.44	41.28
	Gonorrhoea	29.25	20.66
Minimum time between tests (weeks) for cost-effectiveness (if incidence increases 3-fold)	HIV	23.91	16.89
	Syphilis	32.74	23.13
	Chlamydia	33.74	23.83
	Gonorrhoea	16.89	11.93

We then determined the frequency of testing that would be cost-effective (cost per QALY saved less than $50,000) under conservative assumptions about the present and if condom use declines and/or STI incidence increases. In Table 2 we show the minimum time between tests that is cost-effective under current conditions and for the scenarios of condom use decreasing from 99% to 90% and/or incidence increases by 3-fold. Even under the extreme (and unrealistic) scenario of a substantial change in both condom use and incidence, the minimum time between tests that is cost-effective is over 16 weeks for HIV, approximately 24 weeks for syphilis and chlamydia, and almost 12 weeks for gonorrhoea. This is still markedly longer than current practice.

We also estimated the marginal (incremental) cost-effectiveness ratio of each screening frequency. Screening at the current recommended frequency costs over AU$500,000 per QALY saved for HIV, and over AU$10 million per QALY saved for Chlamydia (Fig. 3a). The Net Monetary Benefit (NMB) of screening at current frequencies is calculated using an assumed willingness to pay of AU$60,000 per QALY gained (or US$50,000 per QALY) [42]. The NMB was a loss of AU$356,000 per year for HIV and a loss of almost AU$1.5 million for chlamydia (Fig. 3b); that is, none are cost-effective at current screening frequencies. Based on our model analysis, HIV testing should not be conducted less than approximately every 40 weeks for the cost per QALY saved to be less than AU$50,000 and the frequency of chlamydia testing should not be less than approximately once per year. Indeed, just in terms of financial aspects, screening costs are almost AU$1,500,000 more expensive than the treatment costs saved by preventing chlamydia infections and screening costs are over AU$350,000 more expensive than the treatment costs saved by preventing HIV infections (Fig. 3). In order to break-even financially, such that the cost of screening is not less than the costs saved on treatment (when the curves on Fig. 3 cross zero), based on our model we calculated that testing should not be less than every 36 weeks for HIV, 295 weeks for syphilis, 160 weeks for chlamydia, and 446 weeks for gonorrhoea. These

estimates are independent of the number of sex workers. Thus, if the incidence of STIs in sex workers remains low then there is a strong argument for relaxing regulations to less frequent testing, if not abandoning mandatory testing entirely. Notably, among representative population-based samples of female sex workers, more of the women in the voluntary testing environment in Sydney (53%) attended public sexual health clinics than in the mandatory testing environment in Melbourne (29%, $p<0.001$)) [43].

Figure 3: Modelled relationship between **(a)** the marginal cost effectiveness ratio and testing frequency **(b)** the net monetary benefit (costs saved on treatment minus costs spent on screening) for HIV (blue-diamonds), syphilis (pink-triangles), chlamydia (green-circles), and gonorrhoea (purple-squares); note that the total savings curve appears the same for chlamydia and gonorrhoea.

Figure 3a

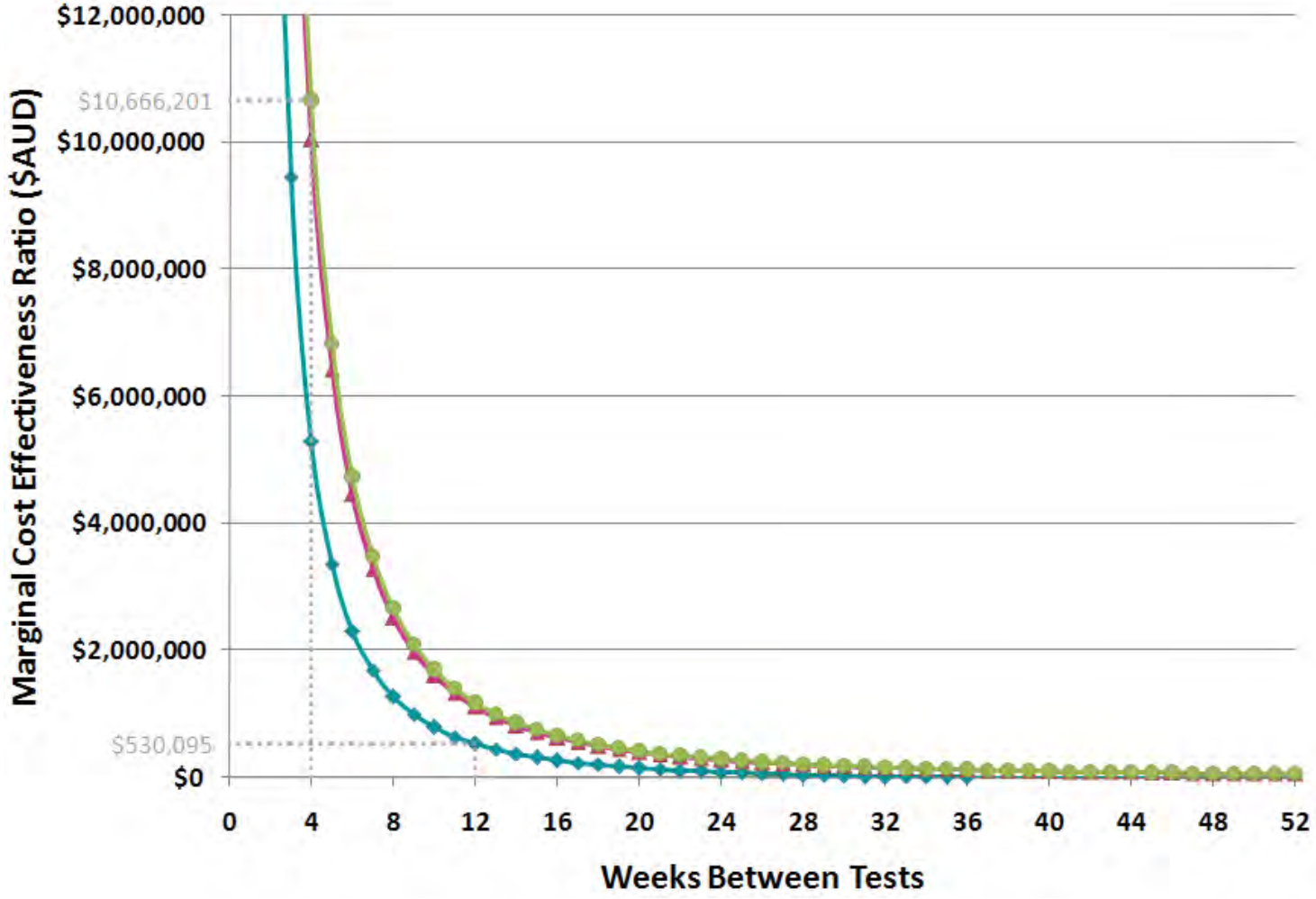
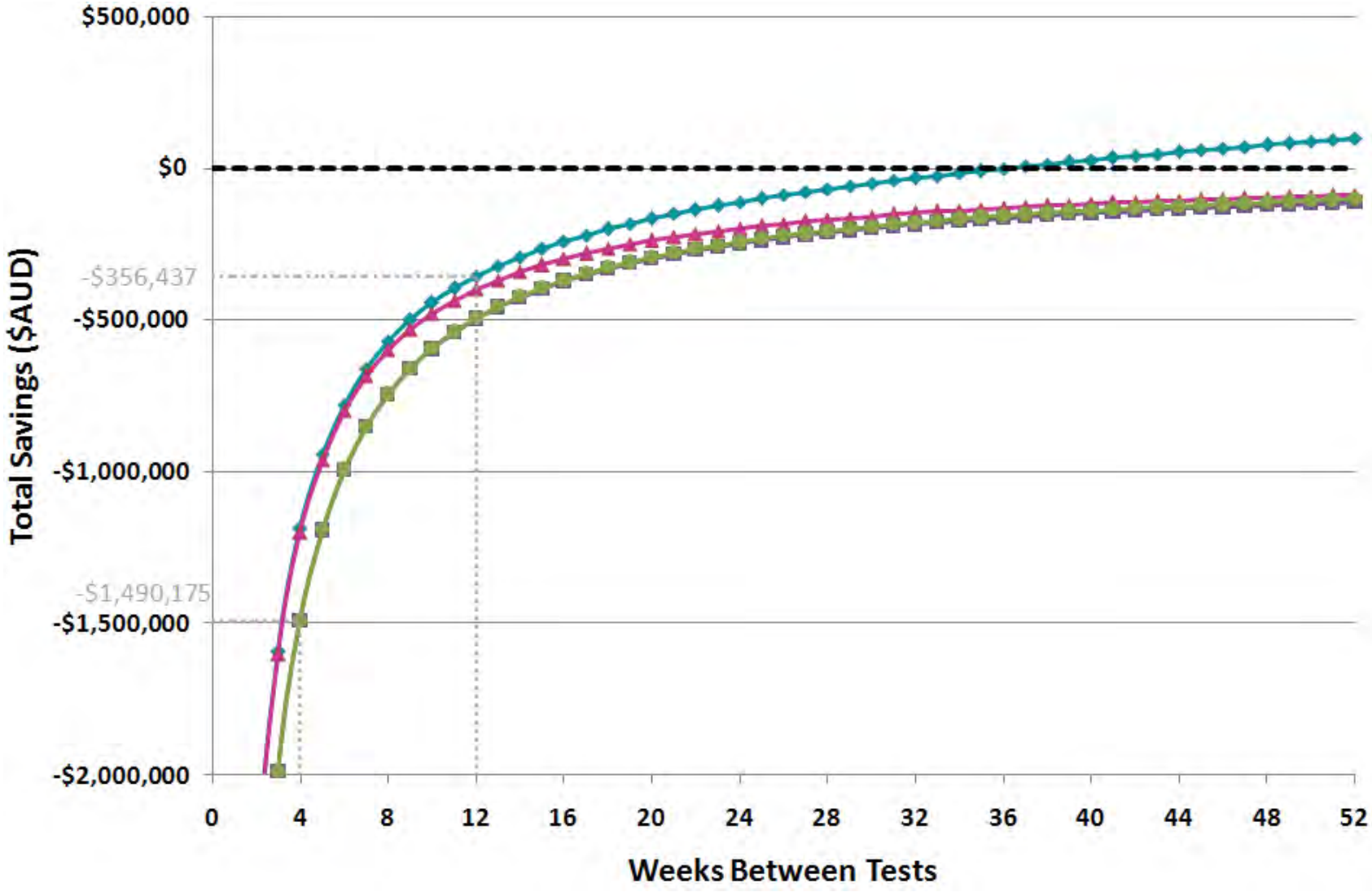


Figure 3b


$500,000
$0
-$356,437
-$500,000
-$1,000,000
-$1,490,175
-$1,500,000
-$2,000,000
Total Savings ($AUD)
0
4
8
12
16
20
24
28
32
36
40
44
48
52
Weeks Between Tests

Discussion

Some previous studies have attempted to estimate the costs averted by STI prevention programs in various settings (e.g. [2, 44, 45]). Our study used a novel mathematical transmission model and conservative parameters, linked to a cost-effectiveness analysis, to examine current testing rates among commercial sex workers in Victoria. We show, for the first time, that the current testing rates are not cost-effective. Mandatory screening of sex workers as legislated in Victoria is not cost-effective for the prevention of disease in their male clients at current test frequencies. If screening occurs much less frequently it may be cost-effective although the benefit is still very limited. Expenditure on screening at the current frequency could be spent on more effective and cost-effective prevention programs to produce more benefit for individuals and the health sector. Female sex workers have one of the lowest prevalences of HIV (and other STIs) in Australia, compared with levels in other groups of the general sexually active population [2, 46, 47]. Legal climates and STI testing regulations for sex workers varies across Australian jurisdictions. Despite much more frequent testing of the women in Victoria, STI (gonorrhoea, chlamydia, trichomoniasis, and Mycoplasma genitalium infection) prevalences have been found to be uniformly low (0%-3.6%) in representative samples of sex workers tested in brothels in Melbourne, Sydney, and Perth [43]. In Sydney and Perth, STI screening is voluntary and the appropriate screening interval is negotiated between the woman and her clinician on an individual basis. This also suggests that relaxing STI screening requirements in Victoria may not result in a noticeable change in STI transmission rates. Since STI screening varies between jurisdictions but epidemiology of STIs and client behaviour is relatively similar, change in policy in Victoria could have little change in social perceptions or spread of STIs but could save considerable financial and time resources. Our study suggests that the current laws mandating regular

screening in Victoria may be using valuable resources in ways that are not cost-effective and should be reviewed.

Mandatory testing was introduced when the sex industry was decriminalised in Victoria in 1984 in the context of a general fear of the emerging AIDS epidemic and limited knowledge about transmission. However, sex workers have significant personal incentives to avoid the acquisition of STIs so consistent condom use has been an industry norm since the 1980s. The majority of STIs that are transmitted to sex workers are now from their regular non-commercial partners and not from their commercial sexual partners [2].

There are also legal and ethical dimensions of STI screening of sex workers that require consideration. Regulation is carried out in other industries of goods and services in order to protect the public (e.g., food/restaurants, medical devices, consumer products, health status of healthcare personnel etc.). There may be obligations and responsibilities for the government to ensure that sex workers do not have STIs. If clients acquire STIs from sex workers and then infect their regular partners, marital disruption (and attendant costs) could be significant. The acquisition of infections may produce psychological problems and cause other harm. Such outcomes could be grounds for awarding punitive damages in legal cases. Reviewing current regulations for screening in Victoria should consider the potential for such legal and ethical liabilities (and corresponding financial liabilities) as well as screening practices in similar settings where frequent testing is not mandatory.

Our study has a number of limitations. First, we only considered the health sector costs and outcomes related to mandatory screening for STIs. One could argue that there is a value related to reassurance for sex workers, clients and the wider community in regular STI testing. It is not clear whether or not the decision by a client to visit a sex worker is affected by knowledge that the sex worker has been screened for STIs in the last 4 weeks. Second, we

used costs and outcomes of infections that were derived from the literature and an expected value analysis. This approach allows comparisons between our results and the cost-effectiveness of other interventions for HIV prevention such as antenatal testing of pregnant women. Third, we only included the infections occurring in the commercial sexual partners of sex workers, but not infections in the sex workers themselves or their non-commercial partners. However, such infections are personal health issues unrelated to the women's occupation. Similarly, secondary infections from clients to non-commercial partners are not considered. As incidence and prevalence of STIs in the general female population is much higher than that of sex workers, there is no evidence to focus on this particular group. Fourth, our model simply investigated infections that remain between testing periods and did not consider other dynamic features associated with disease transmission such as possible clearance of bacterial infections due to the host immune response or background antibiotic use. Our simple static model does not take into account onward transmission in the population. This method is appropriate for analysis of low incidence settings but if the methods were to be applied elsewhere to a location of high incidence then this simple transmission model would underestimate the contribution to control, and therefore overestimate the cost per case averted. However, this model would be appropriate for other settings of relatively low incidence. Fifth, there may be some sex workers that are not tested as frequently as required by law, or not test at all. These women may have greater levels of infection which is not accounted for in our analysis. However, the number of such women is believed to be small. Lastly, we did not carry out a detailed multivariate sensitivity analysis, although we did explore the impact of changes in STI incidence and condom use (Table 2). We also determined that the most important factor in the model is the average time between tests. The influence of this parameter on the annual cost of screening, cost per infection averted, cost per QALY saved, marginal cost-effectiveness ratio, and total savings was shown

in Figures 1-3. It is also important to note that if the screening program were removed or if there were long intervals between testing then it may be difficult to ascertain whether STI incidence changes. If there were outbreaks or local epidemics then the cost-benefit estimates could also change substantially. Such changes may go undetected without a frequent screening program; however, it is also possible that screening less frequently allows more sex workers to be screened.

However, our simple model has been useful to provide insight into the magnitude of the expenditure and effectiveness in preventing infections in male clients with respect to the frequency of testing for STIs in female sex workers. In conclusion, we show that mandatory regular screening of sex workers for STIs and HIV is not cost-effective. We propose that resources could be better spent on more cost-effective interventions instead. Furthermore, screening intervals for sex workers in any jurisdiction around the world should be based on local STI epidemiology. Specifically, the cost-effectiveness of screening for STIs in any setting is highly dependent on the incidence of the infections which are likely to be geographically specific and the behaviour of sex workers in that setting.

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Key messages

- Commercial sex is licensed in Victoria, Australia such that sex workers are required to test regularly for STIs despite very low incidence and prevalence.
- It was determined that mandatory screening of sex workers at current frequencies is not cost-effective and costs are well-beyond normal willingness to pay thresholds.
- Screening intervals for sex workers should be based on local STI epidemiology and not locked by legislation.

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Chapter 6: Serosorting in men who have sex with men

Research Article

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Author Contributions: DPW developed the model framework, conducted literature surveys, supervised the project, and wrote the manuscript. KJH assisted in construction of model, carried out all analyses and produced results and figures, and assisted in writing of the manuscript. DGR was involved in conceptualization, literature surveys, and manuscript editing. FJ, GP and AG provided expert advice on model formulation, provided data, contributed to the writing of the paper and overseeing its message.

Research Letter

Kelly-Jean Heymer and David P. Wilson

Published Citation: Heymer KJ, Wilson DP. *Available evidence does not support serosorting as an HIV risk reduction strategy*. AIDS, 2010, 24 (6), pp:935-936.

Author Contributions: KJH conducted literature reviews and wrote the manuscript. DPW assisted in the writing of the manuscript.

Abstract

Background: Serosorting, the practice of seeking to engage in unprotected anal intercourse with partners of the same HIV status as oneself, has been increasing among men who have sex with men (MSM). However, the effectiveness of serosorting as a strategy to reduce HIV risk is unclear, especially since it depends on the frequency of HIV testing.

Methods: We estimated the relative risk of HIV acquisition associated with serosorting compared with not serosorting by using a mathematical model, informed by detailed behavioral data from a highly studied cohort of gay men.

Results: We demonstrate that serosorting is unlikely to be highly beneficial in many populations of MSM, especially where the prevalence of undiagnosed HIV infections is relatively high. We find that serosorting is only beneficial in reducing the relative risk of HIV transmission if the prevalence of undiagnosed HIV infections is less than ~20% and ~40%, in populations of high (70%) and low (20%) treatment rates, respectively, even though treatment reduces the absolute risk of HIV transmission. Serosorting can be expected to lead to increased risk of HIV acquisition in many settings. In settings with low HIV testing rates serosorting can more than double the risk of HIV acquisition.

Conclusions: Therefore caution should be taken before endorsing the practice of serosorting. It is very important to continue promotion of frequent HIV testing and condom use, particularly among people at high risk.

Summary: In this paper we calculated the relative risk of acquiring HIV associated with

serosorting and determine that serosorting is only beneficial in settings with very high testing rates.

Introduction

Serosorting is the practice of choosing sexual partners thought to be of concordant HIV serostatus in order to reduce the risk of HIV transmission during unprotected intercourse [1-3]. There is strong evidence to suggest that in various populations of men who have sex with men (MSM) around the world the formation of casual sexual partnerships and behavior within such partnerships has been increasingly influenced by the disclosure of HIV serostatus [1, 4-9]. But the extent to which the practice of serosorting protects HIV-uninfected MSM from acquiring HIV is unclear. In this study we aim to quantify the relative effectiveness of serosorting across a wide spectrum of contexts related to the prevalence of undiagnosed infections. The effectiveness of serosorting for reducing the risk of HIV acquisition is highly dependent on other population-specific parameters, in particular, the coverage and frequency of HIV testing. Serosorting may in fact lead to increased risk [10] if a partner's HIV serostatus is unintentionally misreported because it is unknown. Consequently, the proportion of the sexually active population that is HIV-infected but undiagnosed is a crucial determinant of the effectiveness of serosorting. In the ideal scenario of 100% accurate knowledge and no misreporting of serostatus, serosorting is 100% effective at preventing HIV acquisition by HIV-negative people who practice it. Conversely, serosorting may result in substantially increased risk of HIV acquisition if a large proportion of the HIV-infected population is undiagnosed and serosorting thereby leads to the formation of discordant partnerships and more unprotected sex. Here we present the results of a mathematical

modeling analysis that demonstrate the importance of context, especially the prevalence of undiagnosed HIV infection, in determining the effectiveness of serosorting in reducing the risk of HIV acquisition. We estimate thresholds for the prevalence of undiagnosed HIV infections in a population for which serosorting increases risk.

Methods

We developed a mathematical model to investigate the relationship between the proportion of the HIV-infected population that is undiagnosed and the relative risk of serosorting, which refers to the risk of HIV acquisition for MSM who practice serosorting relative to the risk of HIV acquisition for those who do not practice serosorting. A full description of the mathematical formulation of the model is given in the Appendix. Briefly, the relative risk of serosorting is determined by calculating the probability that a casual partnership is serodiscordant (a prerequisite for HIV transmission) when serosorting does and does not occur, and the probability that HIV transmission will occur in both cases. The probability of any casual partnership being serodiscordant will, be dependent on the proportion of the population that has undiagnosed infection and the prevalence of HIV in the population. The probability of transmission in a serodiscordant partnership is taken to be dependent on the proportion of acts that are insertive, receptive with withdrawal and receptive with ejaculation, and the proportion of partners with diagnosed HIV infection that are on antiretroviral treatment (ART). We assume different rates of transmission from cases on ART than from cases not on ART but we did not consider heterogeneity in transmission rates throughout the natural course of infection. We use detailed behavioral data from the Health in Men (HIM) cohort [11, 12], a highly studied cohort of gay men, to inform the expected proportion of acts

that are insertive, receptive with withdrawal or receptive with ejaculation based on knowledge of the partner's HIV status (see Figure A1 in the Appendix). The modeled formulation yields theoretical maximum and minimum relative risks of serosorting of: ~2.15 when all HIV-infected people are undiagnosed, and 0 when everyone knows their true HIV serostatus, respectively.

To evaluate the relative risk of serosorting in specific settings we chose parameters from 5 representative locations. (1) In Sydney, Australia, the percentage of HIV infections that are undiagnosed has been estimated from a modeling study to be ~10% [13] and this is consistent with data from a community-based study that recruited gay men [14]. In Australia, ~70% of diagnosed cases are on ART [15]. (2) It is widely cited that in the United States ~48% of all infections are undiagnosed [16]. However, there is very large heterogeneity between cities and other demographic variables, particularly age and ethnicity. (3) Other estimates suggest that ~25% of HIV infections in the United States are undiagnosed [17-19]. We assume treatment rates are between 50% and 70% among diagnosed cases in the United States. (4) It has been estimated that ~44% of HIV infections in London, England are yet to be diagnosed [20]. We also assume that treatment rates are around 50% of all diagnosed infections in this population [21]. (5) We assume that in many sub-Saharan countries ~80-90% of all HIV infections are undiagnosed and HIV treatment rates are low (20%).

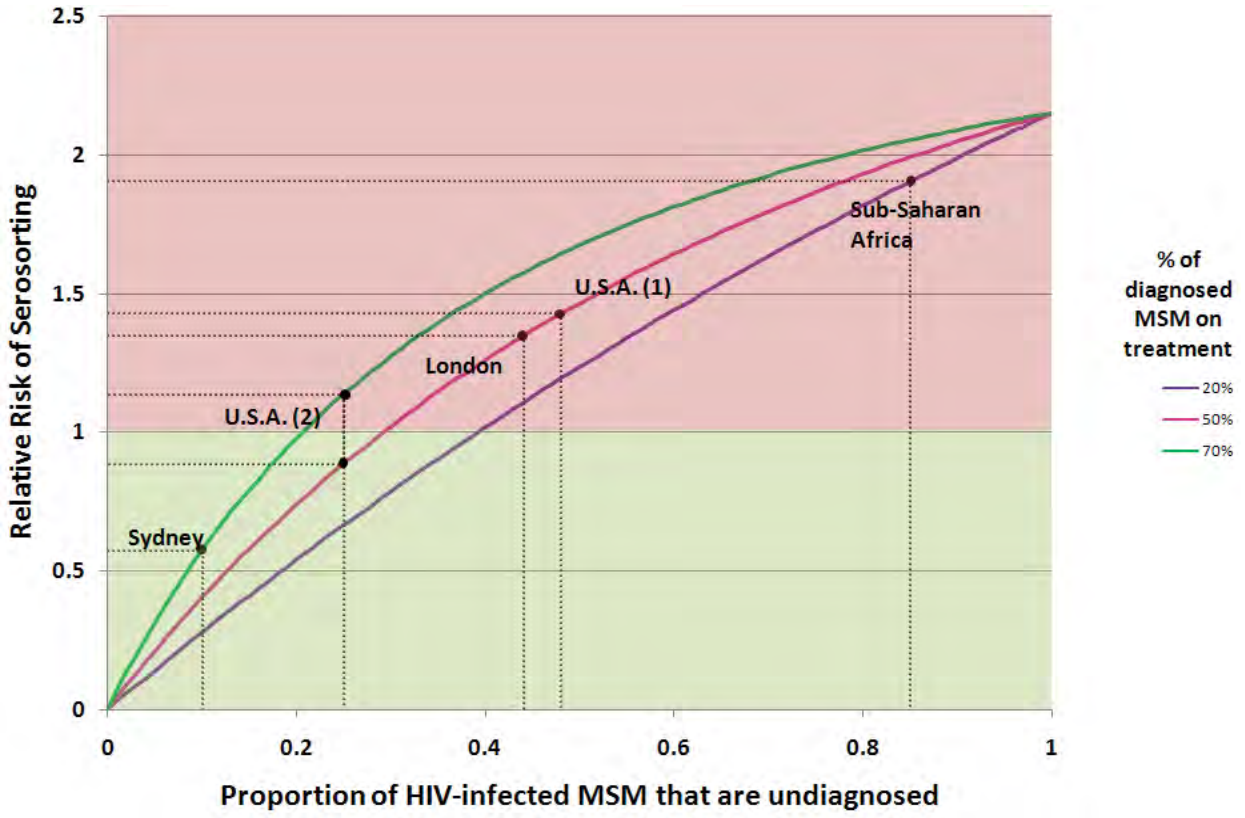
Results

In Figure 1 we present the modeled relationship between the relative risk of HIV acquisition due to serosorting compared with not serosorting, versus the proportion of the HIV-infected MSM population that are undiagnosed, for various treatment rates. As the proportion of undiagnosed infections increases there is a corresponding increase in the risk associated with serosorting. Whilst it is theoretically possible for serosorting to achieve 100% effectiveness (if everyone knows and discloses their true serostatus), in a worst case scenario the relative risk of practicing serosorting is more than double the risk of not serosorting (Fig. 1); this value is informed by the average proportion of acts that are insertive or receptive with or without withdrawal and the average transmission rates for each type of sex act (see Chapter 6 Appendix). The relative risk of serosorting was not found to be highly sensitive to HIV prevalence but it was moderately sensitive to HIV treatment rates. We estimate that serosorting is only of any benefit at all for reducing HIV risk when the proportion of men with HIV who are undiagnosed is less than ~20% in the case of high treatment rates (70%) and less than ~40% for low treatment rates (20%)(Fig. 1), assuming treatment reduces transmission rates by 95%.

In resource-rich countries where there are often high rates of testing for HIV amongst MSM, serosorting *may* be an effective means of reducing the incidence of HIV infections. For example, we estimate that the relative risk of serosorting in Sydney, Australia (where approximately 10% of HIV infections are undiagnosed) is ~0.57 (i.e., 43% effectiveness)(Fig. 1). Using commonly cited estimates of the percentage of undiagnosed infections in the United States (of 48%), our model indicates that practicing serosorting in the United States is likely

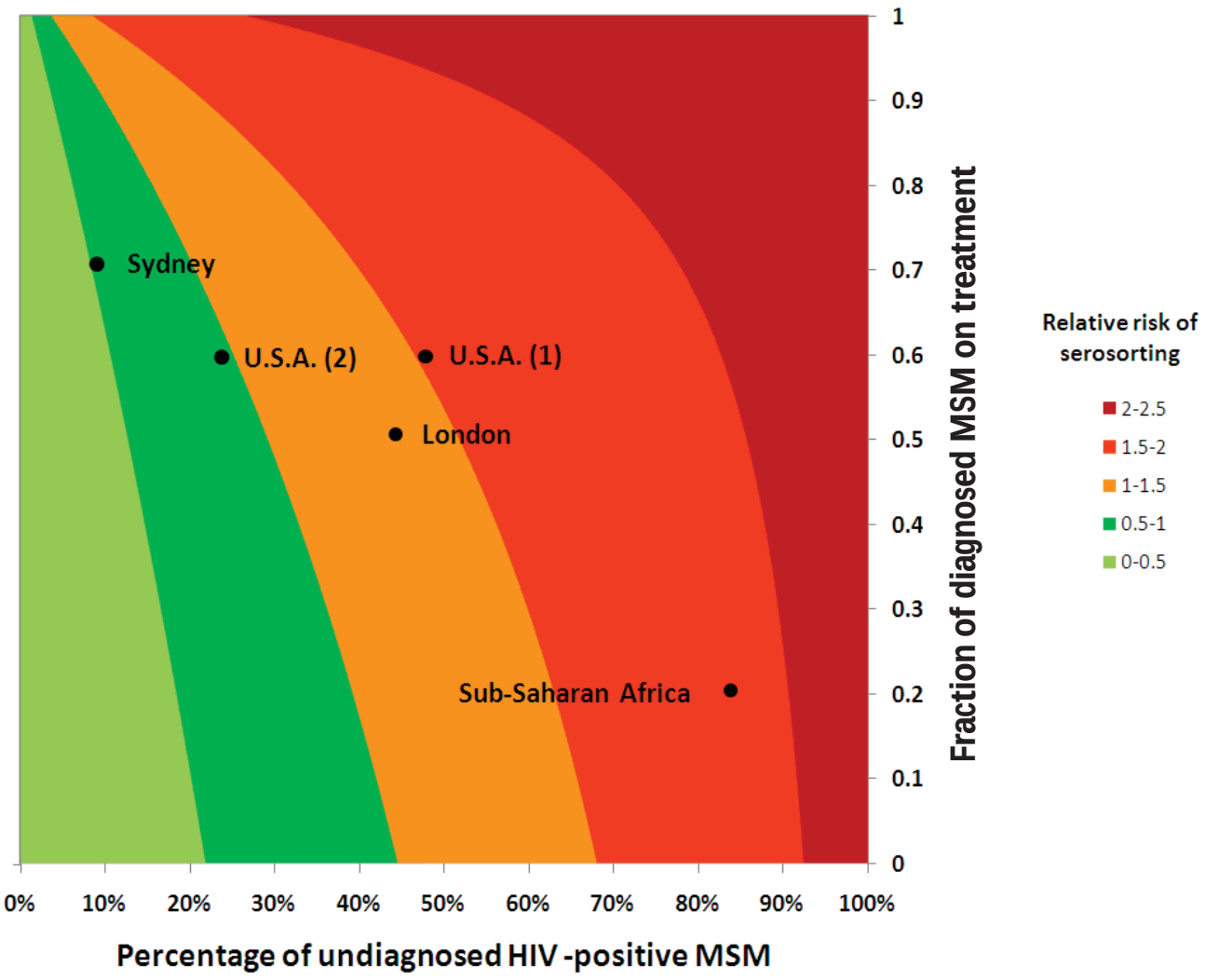
to increase risk by almost 50% (Fig. 1). If just 25% of HIV infections in the United States were undiagnosed then it is unclear whether practicing serosorting would increase or decrease the risk of HIV acquisition (Fig. 1). We estimate that practicing serosorting in London (44% undiagnosed) is likely to increase the risk of acquiring HIV by over 30%. In comparison, in resource-constrained countries where the prevalence of undiagnosed infections is high, serosorting would not be effective even at low treatment rates and could increase HIV risk by ~90% (Fig. 1). However, these thresholds would be altered if sexual positioning preferences among gay men were considerably different in other settings than they are for gay men in Sydney.

Figure 1: Modeled relationship between the relative risk of serosorting and the proportion of HIV-infected MSM who have not been diagnosed with their infection, for varying treatment rates.



In Figure 2 we present the relative risk of serosorting for different combinations of treatment rates and prevalence of undiagnosed HIV infections. It can be seen that if treatment rates increase then the relative risk associated with serosorting worsens. This finding may seem counter-intuitive but it is important to note that the absolute risk of HIV transmission in the population decreases with increases in treatment rates. But the effectiveness of serosorting is calculated by the ratio of the chance of transmission when serosorting to the chance of transmission when not serosorting in a particular setting. Treatment rates do not influence the risk of acquiring HIV when serosorting and only choosing partners who are thought to be HIV-negative. However, when serosorting does not take place sexual partners of any serostatus could be chosen and could include partners who are HIV-positive and on ART. Consequently, the relative risk of serosorting compared with not serosorting is calculated using a term that is independent of treatment divided by a term that decreases with increasing treatment rates; the result is a relative risk statistic that increases with treatment rates. Therefore, high treatment rates in a population are likely to decrease overall incidence levels, however, serosorting has a reduced relative benefit compared with not serosorting because the risks of transmissions are less. Serosorting can still be of additional value in high-treatment settings if there are significant increases in testing rates which reduce the prevalence of undiagnosed infections. For example, in London the prevalence of undiagnosed HIV infections would need to decrease from 44% to ~30% for serosorting not to increase risk. But if treatment rates increased from 50% to 70% then the prevalence of undiagnosed infections would need to decrease to ~20% for the practice of serosorting to have the same risk as not serosorting.

Figure 2 Contour plot of the relative risk of serosorting versus the percentage of diagnosed cases on treatment and the prevalence of undiagnosed infections. Bands of color represent intervals of relative risk: 0-0.5 (light green), 0.5-1 (green), 1-1.5 (orange), 1.5-2(light red), 2-2.5 (dark red).



Discussion

Serosorting is unlikely to be highly beneficial in many populations of MSM, especially when the proportion of undiagnosed HIV infections is relatively high. Indeed serosorting with casual partners will likely increase HIV risk in settings where the percentage of infections that are undiagnosed is greater than approximately 40%. This percentage is likely to be exceeded in most resource-constrained countries and also in many resource-rich settings. However, our calculations suggest that serosorting can lead to effective reduction in risk in those locations where the proportion of undiagnosed HIV infections is relatively low.

Our mathematical modeling analysis of HIV transmission incorporates detailed data of sexual positioning and risk reduction strategies in MSM. A limitation of our analysis is that it is based on behavioral data of gay men in Sydney, Australia and this may not be representative of practices of MSM in other locations. However, similar trends in serosorting and strategic positioning have been observed in MSM throughout the industrialized world [1, 5, 6, 9]. Another limitation is that we used average transmission levels across all stages of HIV infection. We assumed that ART reduces transmission by 95%, however, the actual reduction in transmission rates due to ART is not yet well established.

The effectiveness of serosorting depends on accurate disclosure of HIV serostatus. Some HIV-infected people may mistakenly believe that they are not infected and thus disclose as HIV-negative to sexual partners [22]. Disclosure of HIV status in sexual partnerships may also lead to other strategies to reduce the risk of HIV transmission, such as strategic

positioning and negotiated safety [23-26]. But disclosing HIV status may be associated with substantial stigma, so that even if a man knows he is HIV-infected, he may not disclose his HIV status or may even disclose false information (although this is thought to be relatively rare). However, even if truthful disclosure always occurs, serosorting is a potentially risky strategy and its effectiveness for an individual uninfected man also depends on the frequency of testing of his sexual partner and the partner's previous risk exposure. At a population level, the effectiveness of serosorting is specific to each context because it depends on the average HIV testing coverage and frequency in the population, and the rate of treatment. Different testing and treatment patterns exist between different populations.

Serosorting is safer than having unprotected anal intercourse with a serodiscordant partner but our model-based estimates suggest that it is not as safe as consistent condom use. Here, we only considered unprotected sex and not sex where a condom is used. If condoms are only used with partners of known discordant status, then it is imperative to know the true HIV status of partners. Our analysis suggests that unless the surrounding population has a small proportion of undiagnosed infections, serosorting is likely to increase the risk of HIV acquisition in practice. Therefore, it is not appropriate to suggest that serosorting may offer partial protection from HIV. The available evidence suggests that HIV-uninfected men who serosort remain at risk of acquiring HIV infection, and quite possibly at significantly increased risk compared with not serosorting.

Encouraging frequent testing for HIV, particularly among people at high risk, is a very important public health strategy. In addition to greater accuracy in serosorting, the benefits of undiagnosed HIV-infected individuals becoming aware of their serostatus include the

tendency for sexual behavior to decrease and treatment can be sought. Both of these lower the risk of HIV transmission. Various behavioral studies provide evidence that risky sexual behavior decreases after HIV diagnosis [27-35]. Increasing HIV diagnoses requires educating susceptible populations to seek HIV testing on the basis of indicators such as a known exposure to HIV or early recognition of symptoms. The practice of serosorting is increasing among MSM in various settings. In order for this practice to be beneficial, public health campaigns must continue to promote frequent HIV testing among groups at high risk. This message is of even greater importance in regions where current testing rates are relatively low.

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Available evidence does not support serosorting as an HIV risk reduction strategy

Serosorting is an increasingly common practice among gay men whereby the selection of sexual partners is based on concordance of HIV serostatus [1-3]. Serosorting occurs in order to facilitate unprotected anal intercourse without risk of HIV transmission. Evidence suggests that disclosure of HIV serostatus is increasingly influential not only on the formation of casual partnerships among gay men (serosorting) but also on the sexual position that each man is likely to take in a coital act (known as strategic positioning) and the likelihood of using a condom (known as negotiated safety) [3-9]. Although these inter-related strategies appear to be sophisticated measures for reducing risk, in some circumstances they may lead to increased risk of HIV transmission in a population [10, 11]. Serosorting, when coupled with actual positioning and condom behavior, may result in increased risk of HIV acquisition if a moderate proportion of the HIV-infected population is undiagnosed. This undiagnosed proportion may lead to the formation of partnerships that are thought to be concordant but are actually discordant. In partnerships that are thought to be concordant, HIV-negative men are more likely to take a receptive role (which is more risky in a discordant partnership) and less likely to use condoms.

Cassels et al. developed a detailed compartmental mathematical transmission model in order to demonstrate that ‘under realistic scenarios of sexual behavior and testing for men who have sex with men (MSM) in the United States, serosorting can be an effective harm reduction strategy’ [12]. However, they failed to consider how strategic positioning and negotiated safety behaviors change with or without disclosure of HIV status and therefore

their assertions about the benefits of serosorting are overstated. Additionally, they assumed that all men test for HIV 1-2 times per year. This is much greater than the best available data on actual testing rates in the United States [13]. It is estimated that between 25% [14-16] and 48% [17] of all HIV infections in the United States are undiagnosed which implies that testing rates are considerably lower than 1-2 times per year for all men. If Cassel's et al. used more conservative testing rates in line with rates that are consistent with levels of undiagnosed infections then based on their model-derived Figure 4, serosorting would have been shown to result in higher equilibrium prevalence. The authors also state that with serosorting, 22% of contacts are apparently serodiscordant, and 50% without. With a prevalence of 16% their model would require partner acquisition rates among HIV-positive men to be much greater than among HIV-negative men. Lastly, we question the relevance of using equilibrium prevalence (that is, no epidemiological or behavioral change) to gain insight into the effect of a recent phenomenon on an epidemic where there is increasing incidence.

Using more realistic assumptions the model of Cassel et al. would yield very different conclusions, such that serosorting is not likely to reduce risk of HIV acquisition among gay men in the United States but in fact is likely to increase risk in most contexts. Serosorting, strategic positioning and negotiated safety cannot be decoupled. It has been demonstrated that accounting for behavior change is integral, as the risk reduction strategies adopted by negative men vary with the level of knowledge of their partner's serostatus [11, 18]. There is not sufficient evidence to measure the true effectiveness of serosorting as a harm-reduction strategy. Modeling can be useful to inform our understanding when realistic behavioral inputs are used. The benefit of serosorting is highly context specific and depends upon the frequency of testing, accurate disclosure of serostatus and behavior. Our position, based on

this study and others in the literature, is that serosorting has a real potential to increase risk and should not be promoted as a public health strategy.

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Conclusion

In Chapter 1, the Cambodian HIV Epidemic Model (CHEM) was presented. The accompanying software to the model has been designed so that users can define and assess different targeted scenario combinations of past and future epidemic patterns and programs. Results from our model demonstrate that past public health programs in Cambodia were effective in reducing HIV incidence. The 100% Condom Use Program (100% CUP) was an intervention promoting 100% condom use for transactional sex in direct sex workers. For the years 2000 -2010, using the CHEM it was estimated that the 100% CUP intervention averted almost 70% of HIV infections in female sex workers that would have otherwise been expected had it not been put into place. As an added benefit, the flow on effect of this program was such that it also averted approximately 40% of infections in their male clients and led to a 5-10% reduction in the overall incidence of HIV in Cambodia. The introduction of antiretroviral therapy was of even greater benefit to the overall population. Overall, the implementation of access to ART was estimated to avert 10-15% of infections with a reduction in incidence across all population groups.

In order to mitigate future epidemic trends, combinations of interventions should cover all populations at risk of HIV infection. In addition to those with high-risk behaviours, such as female sex workers and men who have sex with men, it is important to ensure any future public health policy include strategies which protect those who have lower-risk behaviours but remain at risk of infection due to their relationship type. Interventions such as increasing testing rates, scaling-up the provision of ART and promoting condom use in combination provide the most benefit for the majority of people at risk of HIV, including women who are spouses of men who participate in transactional sex and injecting drug users. Results from the model predict that in comparison to projections under current conditions, that almost one-

third of infections expected in 2011-2020 could be averted with a health policy that results in: 10% condom use in heterosexual non-transactional sex; a testing rate of 20% in the general lower-risk population; and a reduction in the rate of needle sharing for injecting drug users to 30%. This combination of interventions is thought to be feasible in the Cambodian context and this study showed that it would have a substantial impact on the HIV epidemic in Cambodia.

The impact of the Global Economic Crisis on HIV epidemics in Papua New Guinea and Cambodia was assessed in Chapter 2. The GEC likely had a greater effect in PNG than in Cambodia. Increases of up to 17% in HIV incidence and 11% in diagnoses could be expected in PNG over the following 3 years. It was found that for Cambodia, due to existing funding, infrastructure, and surveillance systems, it would not be expected for the total number of diagnoses to be largely effected. Due to possible behaviour changes however, an estimated increase in incident cases of HIV of up to 10% may not be observed under the surveillance system currently in place. The number of AIDS-related deaths could be increased by a reduction in antiretroviral therapy. In terms of epidemic mitigation, a decrease in education programs and voluntary counseling and testing services are the key areas of concern for both settings. These findings are consistent with the findings from CHEM in Chapter 1.

A model exploring the expected epidemiological impact of adopting a strategy that increases HIV testing and initiates earlier use of antiretroviral therapy as a method of reducing HIV transmission was presented in Chapter 3. The rationale for this study is the large international movement towards treatment as prevention for HIV and it was important to assess whether this strategy may be of benefit in a local concentrated epidemic. This study focused on the population of men who have sex with men in South Australia, a group to which HIV transmission in that location is predominantly confined. What made this model unique is the classification of MSM into two behavioural groups, men that are socially engaged with the

gay community and those whom are not. This division of MSM is unique to the location, and those who do not identify as socially-engaged are also more likely to participate in heterosexual intercourse. The mathematical model used in the study found that in a population that already has high testing rates, a further increase in testing rates alone is unlikely to have a substantial impact upon expected future incidence. However, if a strategy combines increases in treatment coverage and testing rates, a 60-70% reduction in incidence over the next 5 years could be expected. The model found that the majority of potential reductions in incidence were achieved by targeting men who are socially engaged. As this population is easier to reach through the use of gay community networks, investing in such a strategy would be highly effective in reducing the incidence in that population. Due to the stratification of behavioural groups, any reduction in HIV transmission in those who do not identify as socially-engaged could have a positive carry-on effect to the greater community as it would reduce risk for their heterosexual partners also.

Also in the setting of South Australia, an argument for the provision of free antiretroviral medication is given in Chapter 4. The concern that financial constraints could be providing a barrier to accessing ART motivated the analysis of the cost-effectiveness of removing the co-payment requirement by the Australian government. By calculating the expected number of new HIV transmissions caused by persons who are currently on ART compared with those who are not on ART, it is possible to determine the extra financial investment required to cover the co-payments to prevent an HIV infection. The cost of this investment was then compared to the costs saved by not requiring provision of treatment for the HIV infections averted. The model found that one HIV infection is averted for approximately every 31.4 persons who receive treatment. In terms of removing the co-payment requirement, the cost to the government to prevent an infection is less than how much would cost in order to treat the person for their HIV infection. Facilitating access and adherence to treatment can have

numerous beneficial outcomes in addition to a reduction in transmissions. Community viral load is decreased, as the number of infected persons delaying or ceasing treatment due to financial constraints is reduced. Improved adherence reduces the likelihood of resistance to antiretrovirals. The improved health outcomes for HIV-infected individuals also reduce the burden on public health resources. Via this simple health economic analysis, we find that covering co-payments for HIV antiretroviral drugs is cost-effective from a governmental perspective. This study has been presented to South Australia Health and has been recommended for implementation.

In Chapter 5 a cost-effectiveness analysis was conducted of the financial cost of the sexual health screening policy on female sex workers in Victoria. The cost of regular testing of licensed commercial sex workers in Victoria were compared with health benefits gained in averting transmission of HIV, syphilis, chlamydia, and gonorrhoea to clients. Results from the transmission model found that each year the expected number of transmissions from sex workers to clients of HIV, syphilis, chlamydia and gonorrhoea would be extremely low, due mainly to their low STI prevalence level and almost 100% condom use. Licensed workers are required to test for Chlamydia and gonorrhoea every 4 weeks and every 12 weeks for HIV and syphilis. With current incidence rates, in order to make testing cost-effective, it would be required to reduce the minimum time between tests for HIV, syphilis, chlamydia, and gonorrhoea to 41.4, 56.7, 58.4 and 29.3 weeks respectively. This study highlights that whilst female sex workers are traditionally a high-risk group for HIV transmission, it is location dependant and that it should not be assumed that they are a driver behind an epidemic. It is important to ensure that when public-health interventions are implemented that they are epidemiologically appropriate, as the impact they may have may not be effective in terms of reducing infections or financially. This study was presented to the Health Department of the

Victorian government and has been a key piece of evidence in the controversial debate about revising current policy.

The practice of serosorting and its impact on the likelihood of HIV transmission is presented in Chapter 6. Serosorting is a risk-reduction strategy growing in the gay male community that is not based on promotion or education from health or governmental authorities. Evidence presented in Chapter 6 suggests that especially where the prevalence of undiagnosed HIV infections is relatively high, serosorting is unlikely to be highly beneficial in many populations of men who have sex with men. The benefit of serosorting depends upon the frequency of testing, accurate disclosure of serostatus and behaviour and is therefore highly context-specific. In settings with low HIV testing rates we found serosorting can more than double the risk of HIV acquisition and in general can be expected to lead to increased risk in most settings even with high treatment rates. This modelling exercise highlights the importance of education and regular HIV testing. The crucial factor in safety of this practice is the accurate disclosure of serostatus. Whilst this may intuitively seem to be a good practice, based on our findings, serosorting has a real potential to increase risk and should not be promoted as a public health strategy.

In this thesis mathematical modelling is used in a number of different ways. Modelling was used to measure how effective the implementation of a public health policy was in mitigating the HIV epidemic in Cambodia in the past (Chapter 1). We then used modelling to project possible epidemic trajectories and calculate risk in two very different settings: Cambodia, a low income country where the majority of infections occur due to heterosexual intercourse and Australia, a high-income country with an epidemic predominantly based in the MSM population (Chapters 1, 2, 3 & 6). What can be learned from both settings is: the importance of ensuring that any intervention put into place is contextually appropriate; sentinel and behavioural surveillance are conducted routinely, are maintained and any deficiencies

identified and addressed; and educating those who are at risk about how they are at risk and how to minimise that risk through behaviour change is important.

Mathematical modelling was then used as an economic tool to evaluate the cost-effectiveness of potential changes to public health strategies (Chapters 4 & 5). What was learnt in these studies is that again, it is important to ensure that any intervention is appropriate for the setting for where it is to be implemented. In the case of Victoria, whilst some sub-populations, such as female sex workers, may often display higher-risk behaviour and be a crucial part of the driving force behind an epidemic, this cannot be assumed to be always true. The high-frequency testing policy was implemented at great cost to the government with negligible return fiscally or epidemiologically. It also results in substantial amounts of time wasted by clinicians, which diverts attention from other people in need of services. Through the study in South Australia, we learned that a policy of spending money to remove obstacles for infected persons to benefit from existing interventions in place can avert infections and save money in the long term.

All of the studies presented in this thesis utilised behavioural data in addition to other, more easily quantifiable inputs such as viral load, length of infection, etc. What has been learned from this work is that there is a need for modellers to interact with social researchers in the design of surveys, such that the outputs are directly aligned for modelling and other quantitative evaluation. Number, gender split and frequency of encounters with sexual and injecting partners, condom use at last – sex, and frequency of role taken in homosexual sex are examples of quantities that are crucial to the examination of the spread of STIs. Whilst this data is sometimes collected by social researchers, it is often grouped: for example sexual partners could be 0, 1 -5, 6-10, 11+. For condom use, it is often reported as “rarely”, “sometimes”, “often”, “always” – which is subjective to the interviewee and is difficult to translate to percentages. Small changes in survey design achieved by collaboration with

social researchers could only improve model outcomes. Additionally, the impact of modelled interventions could be more easily globally compared and communicated if outcomes are aligned with UNGASS /UNAIDS indicators.

Since the Global Economic Crisis, a reduction in HIV spending has been seen not just in the developing and middle-income countries discussed in Chapter 2, but universally. The optimum allocation of scarce resources is topical and relevant in various funding environments: be it the assessment of the most effective intervention strategies in resources limited countries in South-East Asia, the economic arguments for the provision of free access to ART, and how best to implement test and treat strategies in both generalised and localised epidemics. As social contexts change it pertinent to ensure that resource allocation adapts to the epidemic faced to remain relevant and maximally beneficial.

Currently, there is no viable vaccine or cure for HIV. Overall, the recurring theme throughout our studies was testing and treatment, and showed time and again the positive outcomes such a scheme provides. Diagnosis benefits the person infected with HIV, in allowing him/her to access support and treatment. The community is benefited with the behavioural changes made by those diagnosed in order to minimise the risk of further transmissions and the reduced community viral load achieved through treatment. For those countries that cannot afford it, it is crucial that they receive the funding to put the required infrastructure into place and for those who can afford scaling up treatment, it is important to remove any barriers to access for those who require it.

Appendix

Acronyms

100% CUP	100% Condom Use Program
AEM	Asian Epidemic Model
AIDS	Acquired Immune Deficiency Syndrome
ART	Antiretroviral Therapy
CHEM	Cambodian HIV Epidemic Model
DALY	Disability Adjusted Life Year
DSW	Direct Sex Worker (Brothel- Based)
EPP	Estimation and Projection Packahe
FSW	Female Sex Worker
GEC	Global Economic Crisis
HAART	Highly Active Antiretroviral Therapy
HIV	Human Immunodeficiency Virus
IDU	Injecting Drug User
IQR	Inter-Quartile Range
ISW	Indirect Sex Worker
MSM	Men who have Sex with Men
MSMW	Men who have Sex with Men and Women
NMB	Net Monetary Benefit
NSP	Needle and Syringe Program
ODE	Ordinary Differential Equation
PBS	Pharmaceutical Benefits Scheme
PPT	Periodic Presumptive Treatment
PRCC	Partial Rank Correlation Coefficients
QALY	Quality Adjusted Life Year
RNA	Ribonucleic Acid
STD	Sexually Transmitted Disease
STI	Sexually Transmitted Infection
VCCT	Voluntary Confidential Counselling and Testing
WTP	Willingness To Pay

Appendix for Chapter 3

The mathematical transmission model is described by a series of ordinary differential equations (ODES), one for each compartment/disease stage for each population group. The model ODEs are as follows:

$$\frac{dS^{SE}}{dt} = \pi^{SE} - S^{SE}\left(\mu + \lambda^{SE}\right) \quad (1)$$

$$\frac{dU^{SE}_{>500}}{dt} = \lambda^{SE} S^{SE} - U^{SE}_{>500}\left(\mu + \gamma^{SE}_{>500} + \omega_{>500} + \delta_{>500}\right) \quad (2)$$

$$\frac{dU^{SE}_{500-350}}{dt} = \omega_{>500} U^{SE}_{>500} - U^{SE}_{500-350}\left(\mu + \gamma^{SE}_{500-350} + \omega_{500-350} + \delta_{500-350}\right) \quad (3)$$

$$\frac{dU^{SE}_{350-200}}{dt} = \omega_{500-350} U^{SE}_{500-350} - U^{SE}_{350-200}\left(\mu + \gamma^{SE}_{350-200} + \omega_{350-200} + \delta_{350-200}\right) \quad (4)$$

$$\frac{dU^{SE}_{<200}}{dt} = \omega_{350-200} U^{SE}_{350-200} - U^{SE}_{<200}\left(\mu + \gamma^{SE}_{<200} + \omega_{<200} + \delta_{<200}\right) \quad (5)$$

$$\frac{dS^{OM}}{dt} = \pi^{OM} - S^{OM}\left(\mu + \lambda^{OM}\right) \quad (6)$$

$$\frac{dU^{OM}_{>500}}{dt} = \lambda^{OM} S^{OM} - U^{OM}_{>500}\left(\mu + \gamma^{OM}_{>500} + \omega_{>500} + \delta_{>500}\right) \quad (7)$$

$$\frac{dU^{OM}_{500-350}}{dt} = \omega_{>500} U^{OM}_{>500} - U^{OM}_{500-350}\left(\mu + \gamma^{OM}_{500-350} + \omega_{500-350} + \delta_{500-350}\right) \quad (8)$$

$$\frac{dU^{OM}_{350-200}}{dt} = \omega_{500-350} U^{OM}_{500-350} - U^{OM}_{350-200}\left(\mu + \gamma^{OM}_{350-200} + \omega_{350-200} + \delta_{350-200}\right) \quad (9)$$

$$\frac{dU^{OM}_{<200}}{dt} = \omega_{350-200} U^{OM}_{350-200} - U^{OM}_{<200}\left(\mu + \gamma^{OM}_{<200} + \omega_{<200} + \delta_{<200}\right) \quad (10)$$

$$\frac{dD_{>500}}{dt} = \gamma^{SE}_{>500} U^{SE}_{>500} + \gamma^{OM}_{>500} U^{OM}_{>500} - D_{>500}\left(\mu + \omega_{>500} + \eta_{>500} + \delta_{>500}\right) \quad (11)$$

$$\frac{dD_{500-350}}{dt} = \gamma^{SE}_{500-350} U^{SE}_{500-350} + \gamma^{OM}_{500-350} U^{OM}_{500-350} + \omega_{>500} D_{>500} - D_{500-350}\left(\mu + \omega_{500-350} + \eta_{500-350} + \delta_{500-350}\right) \quad (12)$$

$$\frac{dD_{350-200}}{dt} = \gamma^{SE}_{350-200} U^{SE}_{350-200} + \gamma^{OM}_{350-200} U^{OM}_{350-200} + \omega_{500-350} D_{500-350} - D_{350-200}\left(\mu + \omega_{350-200} + \eta_{350-200} + \delta_{350-200}\right) \quad (13)$$

$$\frac{dD_{<200}}{dt} = \gamma^{SE}_{<200} U^{SE}_{<200} + \gamma^{OM}_{<200} U^{OM}_{<200} + \omega_{350-200} D_{350-200} - D_{<200}\left(\mu + \omega_{<200} + \eta_{<200} + \delta_{<200}\right) \quad (14)$$

$$\frac{dT}{dt} = \eta_{>500} D_{>500} + \eta_{500-350} D_{500-350} + \eta_{350-200} D_{350-200} + \eta_{<200} D_{<200} - T\left(\mu + \nu + \delta_T\right) \quad (15)$$

$$\frac{dF}{dt} = \nu T - F\left(\mu + \delta_{TF}\right) \quad (16)$$

Here, the force of infection for socially engaged MSM is given by

$$\lambda^{SE} = \lambda_1 + \lambda_2 + \lambda_3 + \lambda_4 + \lambda_5 + \lambda_6 + \lambda_7 + \lambda_8$$

where

$$
\begin{aligned}
\lambda_1 &= \frac{c_{reg}^{SE}}{\grave{N}^{SE}}\left(\beta_{>500}^{SE_{reg}}U_{>500}^{SE}+\beta_{500-350}^{SE_{reg}}U_{500-350}^{SE}+\beta_{350-200}^{SE_{reg}}U_{350-200}^{SE}+g\beta_{<200}^{SE_{reg}}U_{<200}^{SE}\right)\\
\lambda_2 &= \frac{c_{reg}^{SE}f}{K_{SE}}\left(\beta_{>500}^{SE_{reg}}D_{>500}+\beta_{500-350}^{SE_{reg}}D_{500-350}+\beta_{350-200}^{SE_{reg}}D_{350-200}+g\beta_{<200}^{SE_{reg}}D_{<200}+\beta_{treat}^{SE_{reg}}T+\beta_{fail}^{SE_{reg}}F\right)\\
\lambda_3 &= \frac{(1-SE_{mix})SE_{pop}}{SE_{pop}+OM_{pop}}\frac{c_{cas}^{SE}}{\grave{N}^{SE}}\left(\beta_{>500}^{SE_{cas}}U_{>500}^{SE}+\beta_{500-350}^{SE_{cas}}U_{500-350}^{SE}+\beta_{350-200}^{SE_{cas}}U_{350-200}^{SE}+g\beta_{<200}^{SE_{cas}}U_{<200}^{SE}\right)\\
\lambda_4 &= \frac{(1-SE_{mix})SE_{pop}}{SE_{pop}+OM_{pop}}\frac{c_{cas}^{SE}f}{K_{SE}}\left(\beta_{>500}^{SE_{cas}}D_{>500}+\beta_{500-350}^{SE_{cas}}D_{500-350}+\beta_{350-200}^{SE_{cas}}D_{350-200}+g\beta_{<200}^{SE_{cas}}D_{<200}+\beta_{treat}^{SE_{cas}}T+\beta_{fail}^{SE_{cas}}F\right)\\
\lambda_5 &= \frac{c_{reg}^{OM}}{\grave{N}^{OM}}\left(\beta_{>500}^{OM_{reg}}U_{>500}^{OM}+\beta_{500-350}^{OM_{reg}}U_{500-350}^{OM}+\beta_{350-200}^{OM_{reg}}U_{350-200}^{OM}+g\beta_{<200}^{OM_{reg}}U_{<200}^{OM}\right)\\
\lambda_6 &= \frac{c_{reg}^{OM}f}{K_{OM}}\left(\beta_{>500}^{OM_{reg}}D_{>500}+\beta_{500-350}^{OM_{reg}}D_{500-350}+\beta_{350-200}^{OM_{reg}}D_{350-200}+g\beta_{<200}^{OM_{reg}}D_{<200}+\beta_{treat}^{OM_{reg}}T+\beta_{fail}^{OM_{reg}}F\right)\\
\lambda_7 &= \frac{(1-OM_{mix})OM_{pop}}{SE_{pop}+OM_{pop}}\frac{c_{cas}^{OM}}{\grave{N}^{OM}}\left(\beta_{>500}^{OM_{cas}}U_{>500}^{OM}+\beta_{500-350}^{OM_{cas}}U_{500-350}^{OM}+\beta_{350-200}^{OM_{cas}}U_{350-200}^{OM}+g\beta_{<200}^{OM_{cas}}U_{<200}^{OM}\right)\\
\lambda_8 &= \frac{(1-OM_{mix})OM_{pop}}{SE_{pop}+OM_{pop}}\frac{c_{cas}^{OM}f}{K_{OM}}\left(\beta_{>500}^{OM_{cas}}D_{>500}+\beta_{500-350}^{OM_{cas}}D_{500-350}+\beta_{350-200}^{OM_{cas}}D_{350-200}+g\beta_{<200}^{OM_{cas}}D_{<200}+\beta_{treat}^{OM_{cas}}T+\beta_{fail}^{OM_{cas}}F\right)
\end{aligned}
$$

An equivalent mathematical construct for the force of infection applies to non-socially engaged MSM.

The population sizes in each disease state are defined by:

$$
\begin{aligned}
SE_{pop} &= S^{SE}+U_{>500}^{SE}+U_{500-350}^{SE}+U_{350-200}^{SE}+U_{<200}^{SE}\\
OM_{pop} &= S^{OM}+U_{>500}^{OM}+U_{500-350}^{OM}+U_{350-200}^{OM}+U_{<200}^{OM}\\
\grave{N}^{SE} &= S^{SE}+U_{>500}^{SE}+U_{500-350}^{SE}+U_{350-200}^{SE}+gU_{<200}^{SE}\\
\grave{N}^{OM} &= S^{OM}+U_{>500}^{OM}+U_{500-350}^{OM}+U_{350-200}^{OM}+gU_{<200}^{OM}\\
N_{all} &= \grave{N}^{SE}+\grave{N}^{OM}\\
K_{SE} &= \grave{N}^{SE}+f\left(D_{>500}+D_{500-350}+D_{350-200}+g\left(D_{<200}+T+F\right)\right)\\
K_{OM} &= \grave{N}^{OM}+f\left(D_{>500}+D_{500-350}+D_{350-200}+g\left(D_{<200}+T+F\right)\right)\\
K_{all} &= \grave{N}^{SE}+\grave{N}^{OM}+f\left(D_{>500}+D_{500-350}+D_{350-200}+g\left(D_{<200}+T+F\right)\right)
\end{aligned}
$$

The per-partnership and per-act transmission probabilities are mathematically described by the following equations, which are terms in the force of infection expression:

$$
\begin{aligned}
\beta_{>500}^{SE_{reg}} &= 1-(1-\beta_{>500})^{\left(n_{reg}^{SE}\left(1-r_{reg}^{SE}\right)\right)}\left(1-(1-\epsilon)\,\beta_{>500}\right)^{\left(n_{reg}^{SE}r_{reg}^{SE}\right)}\\
\beta_{500-350}^{SE_{reg}} &= 1-(1-\beta_{500-350})^{\left(n_{reg}^{SE}\left(1-r_{reg}^{SE}\right)\right)}\left(1-(1-\epsilon)\,\beta_{500-350}\right)^{\left(n_{reg}^{SE}r_{reg}^{SE}\right)}\\
\beta_{350-200}^{SE_{reg}} &= 1-(1-\beta_{350-200})^{\left(n_{reg}^{SE}\left(1-r_{reg}^{SE}\right)\right)}\left(1-(1-\epsilon)\,\beta_{350-200}\right)^{\left(n_{reg}^{SE}r_{reg}^{SE}\right)}\\
\beta_{<200}^{SE_{reg}} &= 1-(1-\beta_{<200})^{\left(n_{reg}^{SE}\left(1-r_{reg}^{SE}\right)\right)}\left(1-(1-\epsilon)\,\beta_{<200}\right)^{\left(n_{reg}^{SE}r_{reg}^{SE}\right)}\\
\beta_{treat}^{SE_{reg}} &= 1-(1-\beta_{treat})^{\left(n_{reg}^{SE}\left(1-r_{reg}^{SE}\right)\right)}\left(1-(1-\epsilon)\,\beta_{treat}\right)^{\left(n_{reg}^{SE}r_{reg}^{SE}\right)}\\
\beta_{fail}^{SE_{reg}} &= \beta_{500-350}^{SE_{reg}}
\end{aligned}
$$

$$
\begin{aligned}
\beta_{>500}^{SE_{cas}} &= 1-(1-\beta_{>500})^{\left(n_{cas}^{SE}\left(1-r_{cas}^{SE}\right)\right)}\left(1-(1-\epsilon)\,\beta_{>500}\right)^{\left(n_{cas}^{SE}r_{cas}^{SE}\right)}\\
\beta_{500-350}^{SE_{cas}} &= 1-(1-\beta_{500-350})^{\left(n_{cas}^{SE}\left(1-r_{cas}^{SE}\right)\right)}\left(1-(1-\epsilon)\,\beta_{500-350}\right)^{\left(n_{cas}^{SE}r_{cas}^{SE}\right)}\\
\beta_{350-200}^{SE_{cas}} &= 1-(1-\beta_{350-200})^{\left(n_{cas}^{SE}\left(1-r_{cas}^{SE}\right)\right)}\left(1-(1-\epsilon)\,\beta_{350-200}\right)^{\left(n_{cas}^{SE}r_{cas}^{SE}\right)}\\
\beta_{<200}^{SE_{cas}} &= 1-(1-\beta_{<200})^{\left(n_{cas}^{SE}\left(1-r_{cas}^{SE}\right)\right)}\left(1-(1-\epsilon)\,\beta_{<200}\right)^{\left(n_{cas}^{SE}r_{cas}^{SE}\right)}\\
\beta_{treat}^{SE_{cas}} &= 1-(1-\beta_{treat})^{\left(n_{cas}^{SE}\left(1-r_{cas}^{SE}\right)\right)}\left(1-(1-\epsilon)\,\beta_{treat}\right)^{\left(n_{cas}^{SE}r_{cas}^{SE}\right)}\\
\beta_{fail}^{SE_{cas}} &= \beta_{500-350}^{SE_{cas}}
\end{aligned}
$$

$$
\begin{aligned}
\beta_{>500}^{OM_{cas}} &= 1-(1-\beta_{>500})^{\left(n_{cas}^{OM}\left(1-r_{cas}^{OM}\right)\right)}\left(1-(1-\epsilon)\,\beta_{>500}\right)^{\left(n_{cas}^{OM}r_{cas}^{OM}\right)}\\
\beta_{500-350}^{OM_{cas}} &= 1-(1-\beta_{500-350})^{\left(n_{cas}^{OM}\left(1-r_{cas}^{OM}\right)\right)}\left(1-(1-\epsilon)\,\beta_{500-350}\right)^{\left(n_{cas}^{OM}r_{cas}^{OM}\right)}\\
\beta_{350-200}^{OM_{cas}} &= 1-(1-\beta_{350-200})^{\left(n_{cas}^{OM}\left(1-r_{cas}^{OM}\right)\right)}\left(1-(1-\epsilon)\,\beta_{350-200}\right)^{\left(n_{cas}^{OM}r_{cas}^{OM}\right)}\\
\beta_{<200}^{OM_{cas}} &= 1-(1-\beta_{<200})^{\left(n_{cas}^{OM}\left(1-r_{cas}^{OM}\right)\right)}\left(1-(1-\epsilon)\,\beta_{<200}\right)^{\left(n_{cas}^{OM}r_{cas}^{OM}\right)}\\
\beta_{treat}^{OM_{cas}} &= 1-(1-\beta_{treat})^{\left(n_{cas}^{OM}\left(1-r_{cas}^{OM}\right)\right)}\left(1-(1-\epsilon)\,\beta_{treat}\right)^{\left(n_{cas}^{OM}r_{cas}^{OM}\right)}\\
\beta_{fail}^{OM_{cas}} &= \beta_{500-350}^{OM_{cas}}
\end{aligned}
$$

$$
\begin{aligned}
\beta_{>500}^{all_{cas}} &= 1-(1-\beta_{>500})^{\left(n_{cas}^{all}\left(1-r_{cas}^{all}\right)\right)}\left(1-(1-\epsilon)\,\beta_{>500}\right)^{\left(n_{cas}^{all}r_{cas}^{all}\right)}\\
\beta_{500-350}^{all_{cas}} &= 1-(1-\beta_{500-350})^{\left(n_{cas}^{all}\left(1-r_{cas}^{all}\right)\right)}\left(1-(1-\epsilon)\,\beta_{500-350}\right)^{\left(n_{cas}^{all}r_{cas}^{all}\right)}\\
\beta_{350-200}^{all_{cas}} &= 1-(1-\beta_{350-200})^{\left(n_{cas}^{all}\left(1-r_{cas}^{all}\right)\right)}\left(1-(1-\epsilon)\,\beta_{350-200}\right)^{\left(n_{cas}^{all}r_{cas}^{all}\right)}\\
\beta_{<200}^{all_{cas}} &= 1-(1-\beta_{<200})^{\left(n_{cas}^{all}\left(1-r_{cas}^{all}\right)\right)}\left(1-(1-\epsilon)\,\beta_{<200}\right)^{\left(n_{cas}^{all}r_{cas}^{all}\right)}\\
\beta_{treat}^{all_{cas}} &= 1-(1-\beta_{treat})^{\left(n_{cas}^{all}\left(1-r_{cas}^{all}\right)\right)}\left(1-(1-\epsilon)\,\beta_{treat}\right)^{\left(n_{cas}^{all}r_{cas}^{all}\right)}\\
\beta_{fail}^{all_{cas}} &= \beta_{500-350}^{all_{cas}}
\end{aligned}
$$

$$
\beta_{UAI}^{C}=\frac{\alpha}{I}\left(d^{+}\rho^{+}Dx+d^{-}\rho^{-}UnDx+\rho^{?}\left(\left(1-d^{+}\right)Dx+\left(1-d^{-}\right)UnDx\right)\right)
$$

Final report

Evaluation of HIV in South Australia

2010

National Centre in HIV Epidemiology and Clinical Research
197
UNSW THE UNIVERSITY OF NEW SOUTH WALES

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Contents

Executive summary

Background

Over the period 1985-2008, 1155 HIV infections were detected in South Australia and over 300 of these people have died from AIDS or HIV-related illnesses. Historically, after following a typical infectious disease epidemic trajectory until 1999 there has since been a moderate but important increase in the number of HIV diagnoses, reflecting what is believed to be a rise in underlying incidence. From 2004 to 2008, 93.1% of South Australian HIV diagnoses were attributed to three predominant routes of exposure: intercourse between men who have sex with men (MSM, 60%), heterosexual sex (25.3%) and transmission via injecting drug use (IDU, 7.8 %). Approximately 76% of the diagnosed cases are receiving antiretroviral therapy[1]. HIV-infected men who have sex with men (MSM) in South Australia have also disproportionately been affected by the emergence of a syphilis epidemic over the last decade.

This report evaluated the patterns of HIV infections among MSM in South Australia in order to determine the key drivers of past trends, evaluate past and present programs, and to forecast epidemic trajectories in the future according to current conditions or due to implementation of public health interventions. The primary method for investigation was the development and analysis of a mathematical transmission model. The deterministic compartmental model used behavioural, clinical and biological data to track the number of MSM in South Australia over time that are in each state of HIV disease stage and HIV transmission to MSM who are socially engaged with the gay community or to other MSM. The model was calibrated to reflect the past and present epidemiology of HIV in South Australia.

Evaluating the past

The rate of HIV diagnoses in South Australia has increased significantly over the past decade but over the past few years it has stabilised or even started to decline. Over the same period of increased HIV diagnoses there has been reported decrease in condom use, first declining among regular partners (from around 2003) and then with casual partners (from around 2005). A rise in unprotected anal intercourse with casual partners has been attributed as the major reason for the rise in HIV diagnoses in other Australian jurisdictions; however, it is not clear to what extent the change in condom use contributed to the rise in diagnoses in South Australia since reported changes in rates of unprotected anal intercourse occurred after the observed increase in HIV cases.

Changes in conditions and implementation of public health interventions were analysed. According to the South Australian HIV model for MSM:

- If the 2008 Testing-Testing-123 campaign was not implemented and testing rates continued on the previous trend then there would have been 0.18 extra HIV infections in the following year; that is, one infection would be averted for every five years of implementation of this campaign.
- Without the increase in testing reported over the past decade, an additional 2.87 HIV infections would have occurred in South Australia.
- Had condom use not declined in recent years there would have been 12.46 less HIV infections.
- If rates of disclosure of HIV serostatus to casual partners over this period had remained the same there would have been 0.48 less HIV infections
- Without the increase in effectiveness of ART over this period, an additional 2.20 HIV infections would have occurred.

In addition, an estimated 122 HIV infections were averted due to Clean Needle Programs in South Australia over the decade, 1999-2009.

Epidemic projections

The South Australian HIV model for MSM was used to forecast epidemic trajectories according to a number of different scenarios. The model suggests that if conditions do not change, incidence should decline moderately from about 30 cases per year to about 24 cases per year by 2015. However, if conditions change there would be a different number of observed HIV cases over the next 5 years (2010-2015):

- An intervention that results in halving the number of sexual partners for a period of one year would result in a median reduction of 2.63 (2%) HIV infections.
- If condom use was increased to 100% with all casual partners for a period of one year there would be a median reduction of 3.84 (3%) infections.
- By increasing HIV testing rates among men socially engaged with the gay community to 80% testing each year a median of 1.17 (1%) infections would be averted.
- If 70% or 80% of all MSM receive an annual test for HIV this would result in median reductions of 0.72 (0.6%) and 1.86 (1.5%) infections respectively.
- An intervention that results in twice yearly testing among 70% of MSM who are socially engaged with the gay community or 70% of all MSM testing result in median reductions of 4.53 (3.6%) and 4.77 (3.8%) infections.
- ‘Test and treat’ strategies could potentially lead to substantial decreases in the number of HIV infections. If 70% of MSM are tested each year and all HIV-diagnosed men receive antiretroviral therapies then there would be a median reduction of 76.24 (61%) infections. If twice-yearly testing was carried out and all diagnosed cases

receive antiretroviral therapies then the median infections averted would raise to 85.35 (68%).

- If only HIV-diagnosed cases with a CD4 count less than 500 cells per µl receive treatment upon diagnosis, and 70% of all MSM are tested each year, then 33.84 (27%) of infections would be averted.

Summary

South Australia has responded successfully to contain and minimise the spread of HIV such that the prevalence of infection among all South Australians has remained at or below 0.1%. The success of South Australia's past response to HIV is in part due to the coordination of HIV prevention programs and partnership approach between government, NGOs, researchers, clinicians and community representatives. However, the rate of HIV diagnoses in South Australia has increased significantly over the past decade particularly among MSM. If preventative changes in risk-related behaviour could be sustained for the long-term then it is likely to substantially reduce the number of new infections but if only short-term changes are feasible then there will be very modest impacts. Promotion of testing among MSM in South Australia has been successful to lead to very high rates. Whilst testing is a cornerstone of HIV prevention and is highly important, it is unlikely that further increases in testing rates will have a substantial impact on HIV trajectories, but if testing rates decrease then incidence could be expected to increase. However, if early treatment was commenced for diagnosed individuals then it could have a substantial public health impact by reducing community-level viral load and average infectiousness of HIV-infected people. Implementation of wide-scale 'test and treat' campaigns may be worth considering. Eliminating barriers to accessing treatment, such as removing the requirement of patients to cover financial co-payments, would be cost-effective for reducing HIV transmissions and benefit people living with HIV.

Introduction

Australia's response to HIV has generally been very effective in minimising the spread of HIV such that the prevalence of infection among all Australians has remained at or below 0.1%. Despite this, the burden of HIV is high for the people infected with this virus and certain population groups are at particularly high risk of acquiring HIV. South Australia has had similar, if not even better, success compared with the rest of Australia with regards to containing the spread of HIV. South Australia has a strong and successful commitment to the partnership approach to HIV/AIDS with shared responsibility and cooperation between the Federal and State governments, affected communities, non-government organisations, medical professionals and research bodies. Stemming from this partnership, and led by the South Australian Department of Health, an HIV Action Plan 2009-2012 was developed and it was launched in 2009 [2]. It describes strategies and activities to:

- Reshape the prevention response to stem rises in new infections of HIV;
- Improve the coordination of care for people with HIV;
- Connect people isolated from HIV education, prevention and care services to appropriate supports.

The plan identifies new key priority actions to be accomplished by 2012 in South Australia's response to HIV/AIDS.

The current report supports the HIV Action Plan by evaluating past responses, determining the key drivers of change in trends and numbers of new infections, examining the current epidemiological patterns of HIV infection, and projecting the future HIV trajectories according to scenarios whereby there is no change in behaviour or practice or according to effective implementation of a host of potential intervention strategies. Therefore, this report specifically supports the reshaping of the prevention response to HIV.

Epidemiology of HIV in South Australia

Over the period 1985-2008, 1155 HIV infections were detected in South Australia and over 300 of these people have died from AIDS or HIV-related illnesses. The epidemic curve in South Australia of numbers of HIV diagnoses followed a typical pattern of infectious disease epidemic trajectories until around 1999 (Figure 1). From

the year 2000 there has been a moderate but important increase in the number of HIV cases detected in South Australia (Figure 1).

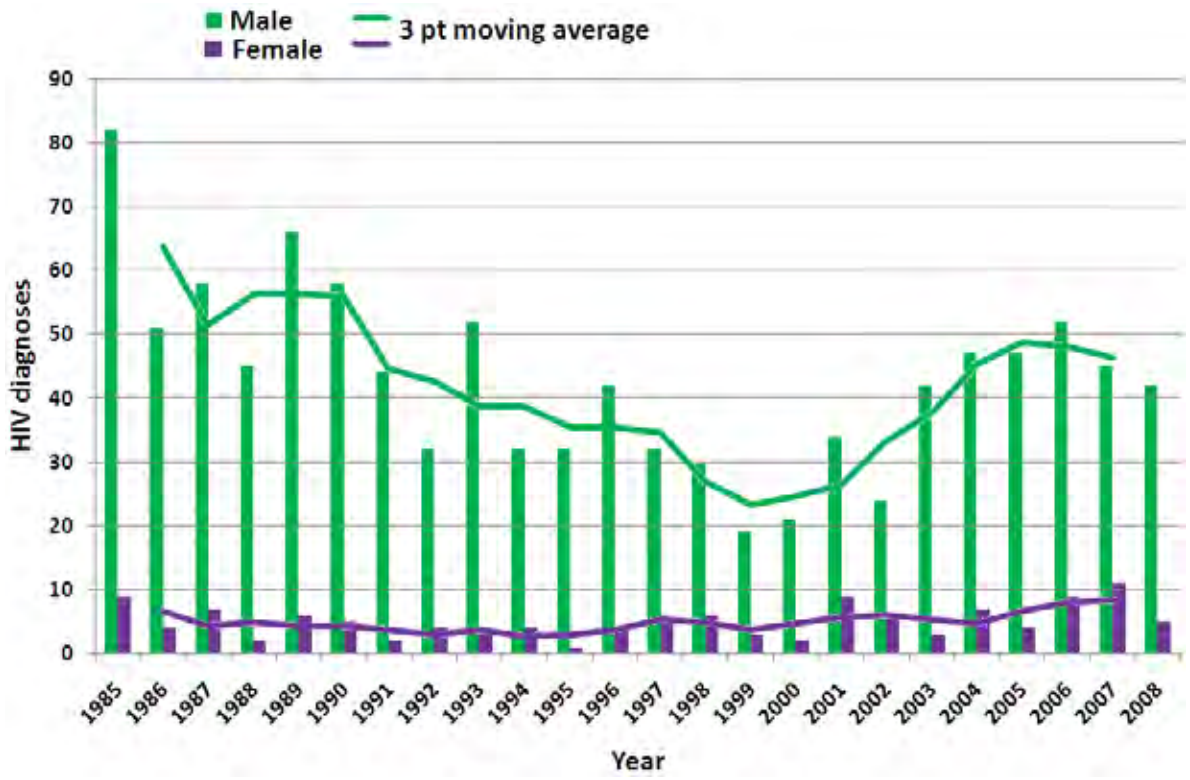


Figure 1: HIV diagnoses in South Australia, 1985-2008, by gender and year of diagnosis (three-year moving averages included)

It is evident from the HIV epidemic curve (Figure 1) that HIV has disproportionately affected males compared to females. This is due to HIV infection predominantly contained within the population of men who have sex with men (MSM) (Figure 2, 3); in the five-year period 2004-2008 162, or 60%, of the 269 new diagnoses were among MSM. A significant number of newly infected people (68 people, 25%) reported acquiring HIV through heterosexual contact. Women represent approximately 10% of all HIV cases in South Australia and 13% of the notifications in 2004-2008. In South Australia from 2004 to 2008, 93.1% of HIV diagnoses were attributed to three predominant routes of exposure: intercourse between men who have sex with men (MSM, 60%), heterosexual sex (25.3%) and transmission via injecting drug use (IDU, 7.8 %). The increase in HIV diagnoses since 2000 has largely been due to male homosexual sex (Figure 3), but there has also been an increase in reported heterosexual transmission of HIV.

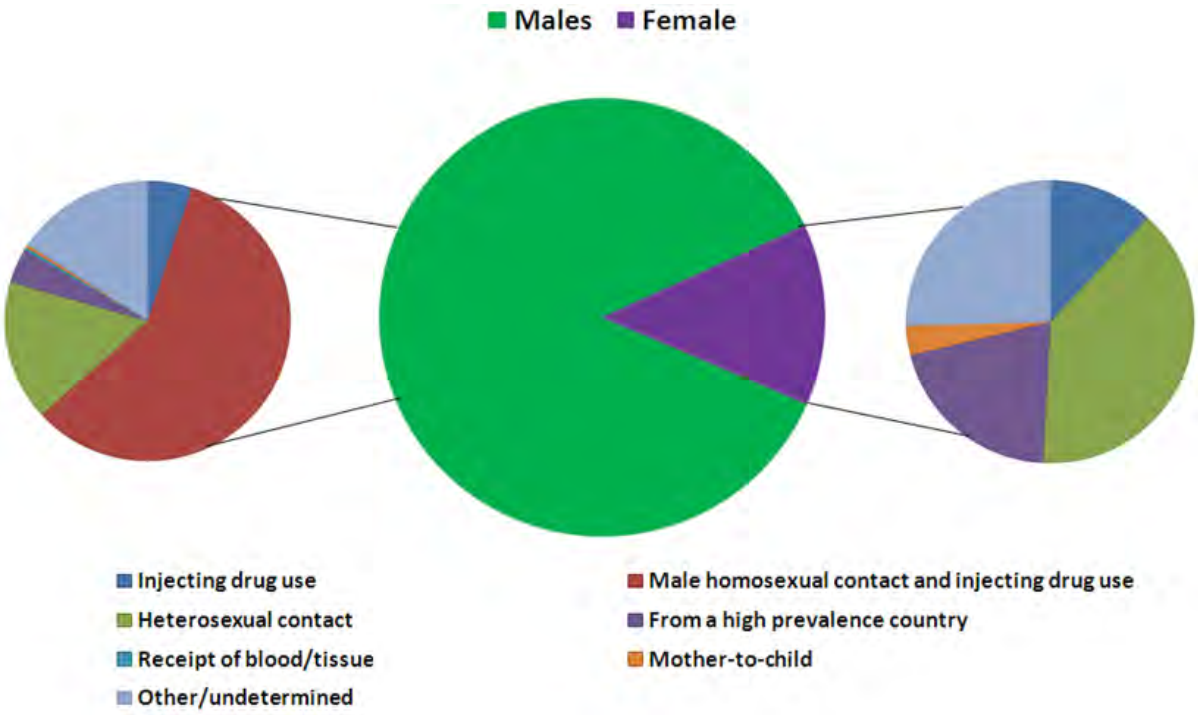


Figure 2: HIV diagnoses in South Australia over the five-year period, 2004-2008, by gender and route of exposure

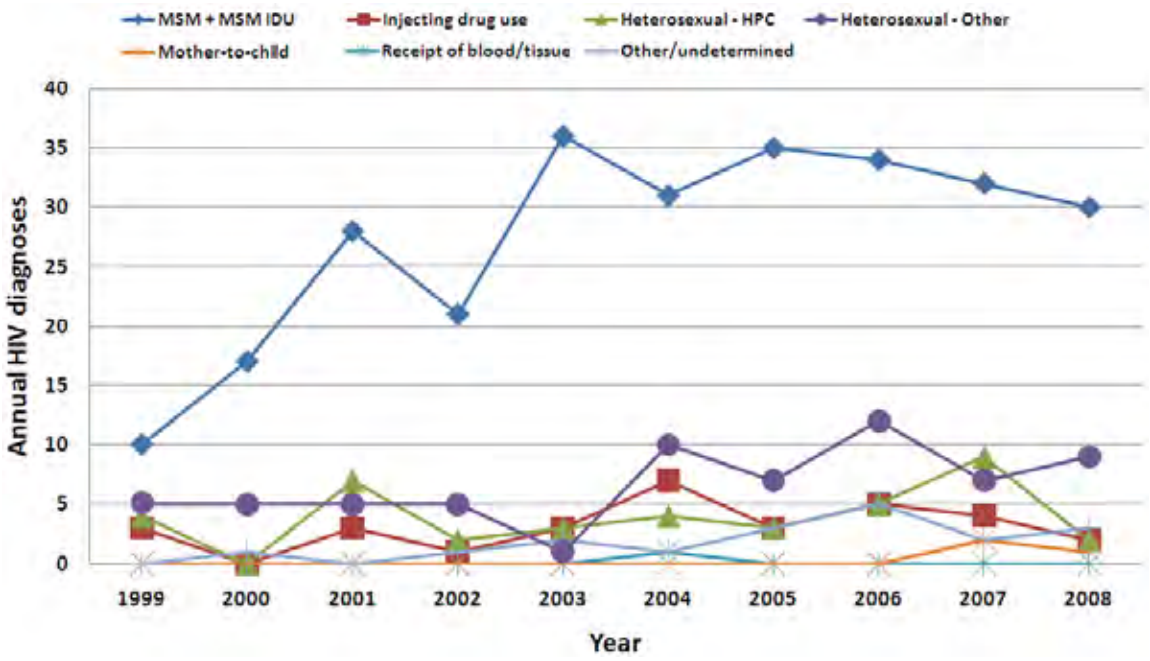


Figure 3: Trend in HIV diagnoses in South Australia, 1999-2008, by route of exposure

The overall per-capita rate of HIV diagnosis in South Australia has increased significantly over the past decade (Figure 4). The rate of HIV diagnoses is roughly at a median level when compared with other Australian States and Territories (Figure 4).

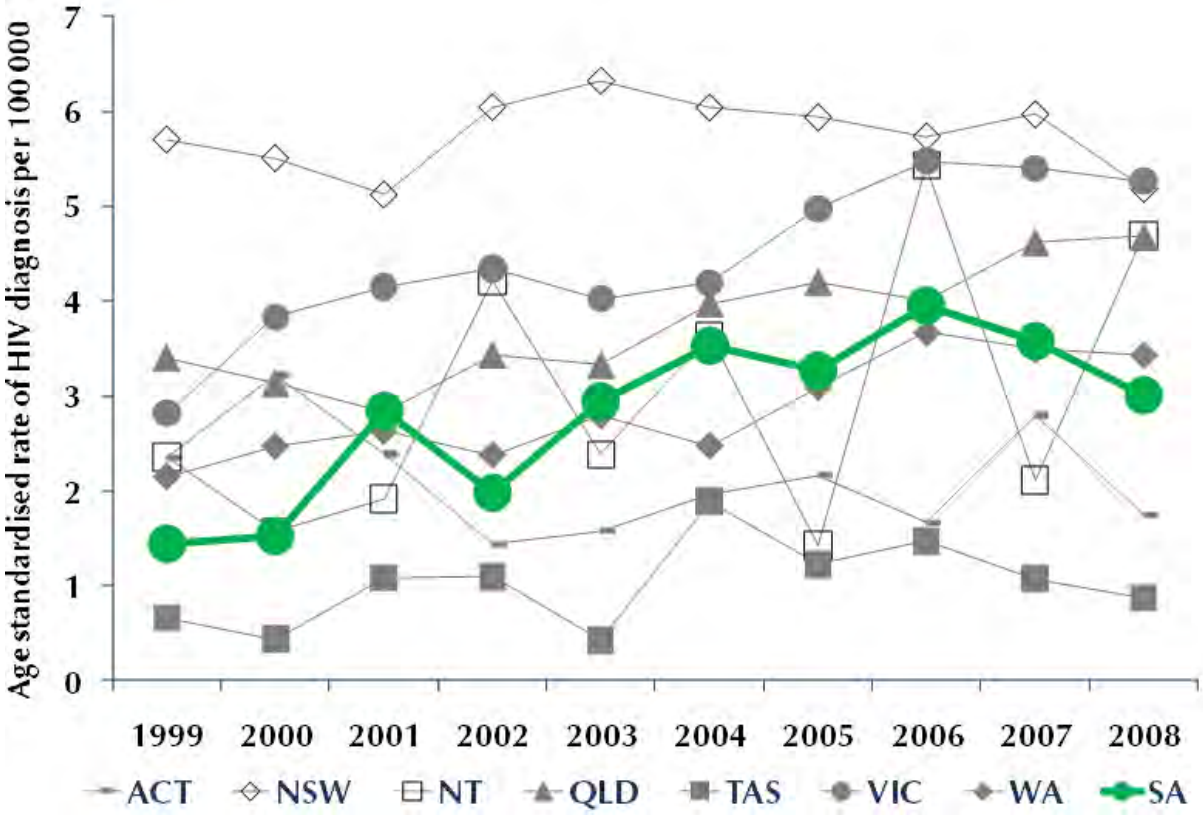


Figure 4: Age standardised rate of HIV diagnosis, 1999-2008, by jurisdiction

Priority populations

Based on the epidemiology of HIV in South Australia the HIV Action Plan [2] identified four populations of South Australians to receive the highest priority for education, prevention and health promotion initiatives:

- Gay and other men who have sex with men;
- People living with HIV/AIDS;
- Aboriginal and Torres Strait Islander people;
- People with diverse cultural and linguistic backgrounds who are from countries in which HIV/AIDS is highly prevalent.

Other priority populations include:

- People who inject drugs;
- People in custodial settings;
- Sex workers.

Gay and other men who have sex with men (MSM)

Clearly gay and other men who have sex with men are the priority group most affected by HIV in South Australia. Since the beginning of the HIV epidemic in the early 1980s men who have sex with men account for approximately 70% of all HIV diagnoses in South Australia. Of all HIV diagnoses among these men, 86% can be attributed solely to male homosexual sex, 6% of reported cases indicated injecting drug use and 8% of reported cases indicated sex with both men and women. Over

the past five years these proportions have changed slightly to 76%, 15%, and 9%, respectively, suggesting that although male homosexual exposure remains the most dominant route of transmission, the epidemic has become moderately more generalised.

Based on the Australian Study of Health and Relationships and Australian Census data, it is estimated that there are approximately 12,000 homosexual and bisexual men in South Australia [3]. This suggests that the prevalence of HIV among gay and other men who have sex with men is approximately 5%; this is considerably lower than HIV prevalence levels in the Eastern States of Australia [3]. However, the prevalence of HIV among men who have sex with men is substantially higher than in the rest of the population in South Australia (where it is about 0.1%).

The population of men who have sex with men is not homogeneous in behaviour or in the burden of HIV. For example, some men attach themselves to the gay community whilst others do not. According to the e-male survey in South Australia, approximately 47% of men who have sex with men are gay socially engaged (as determined by whether men know other gay men and can be reached through gay male networks)[4]. Further, 76.5% of respondents in South Australia identified as gay/homosexual/queer, 20.8% as bisexual, 1.5% as heterosexual/straight, and 1.2% as other [4]. In comparison, the respective proportions of participants of the 2007 Adelaide Gay Community Periodic Survey self-reporting each sexual identity were 86.4%, 9.5%, 2.6%, and 1.6% [5].

People living with HIV/AIDS

In South Australia around 750-800 people are currently living with HIV and diagnosed with their infection [6]. It is likely that there is a further 80-140 people (10-15%) who are currently infected with HIV and undiagnosed with their infection based on testing rates and estimated diagnosis levels in other Australian jurisdictions [7-8]. Approximately 76% of the diagnosed cases are receiving antiretroviral therapy [1].

Aboriginal and Torres Strait Islander people

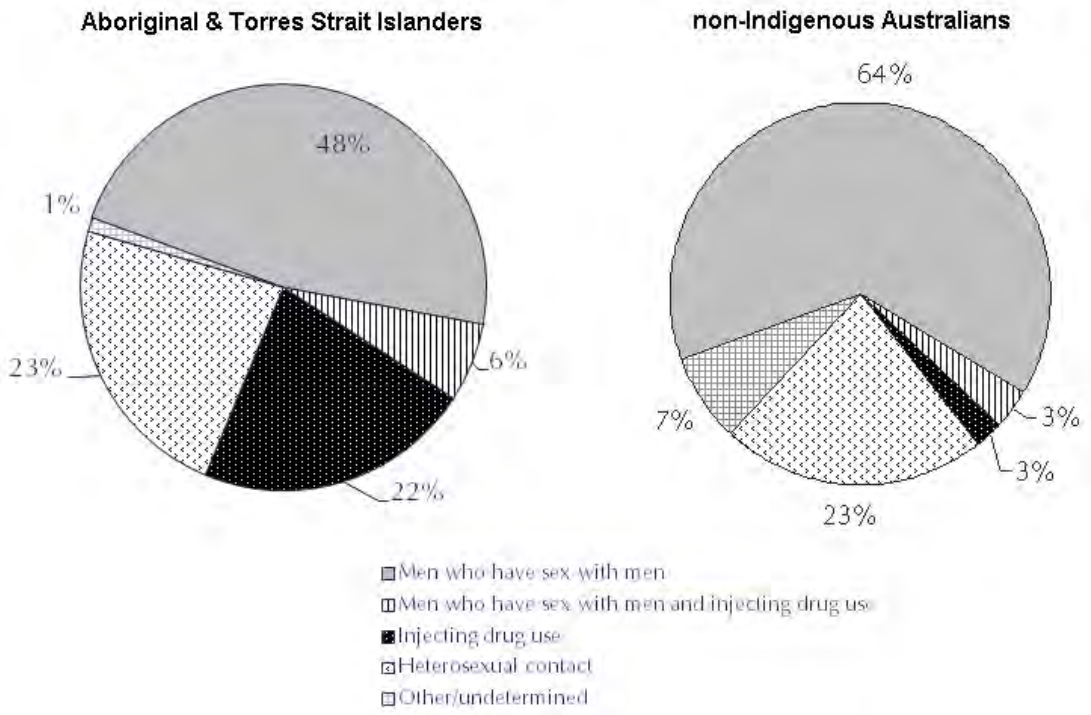


Figure 5: HIV diagnoses by route of exposure across all Australian jurisdictions, 2004-2008, among Aboriginal and Torres Strait Islanders and non-Indigenous Australians

The number of Aboriginal people diagnosed with HIV in South Australia is small (28 notifications by the end of 2008) but the risk of increasing infections among this population remains unless prevention efforts continue. Given the higher rate of HIV transmission due to injecting drug use in this population compared with the non-Indigenous population (Figure 5) and the link between some sexually transmissible infections (STIs) and the transmission of HIV as well as the national upward trend in STI infections in the Aboriginal population, prevention work with Aboriginal organisations and communities is highly important.

Location/travel associated with HIV including people from overseas

The majority of HIV diagnoses in South Australia were likely due to transmissions that occurred in South Australia. However, data on the new diagnoses in the five-year period 2004-2008 indicate that 26% of new notifications in South Australia were likely to have been acquired overseas; of these, approximately 28% of cases were known to be HIV-positive before entering Australia. HIV was likely acquired interstate for 7.5% of cases.

Heterosexually acquired HIV has been increasing in importance in recent years (Figure 3). Over the past 10 years, 1999-2008, 39/105 (37%) of reported heterosexually acquired cases were in people from a high prevalence country with approximately equal numbers of males and females (Figure 6); 40% were reportedly female-to-male heterosexually acquired and 23% male-to-female heterosexually acquired. The increased reported number of female-to-male transmissions compared

with male-to-female, with relative rate of 1.74, suggests that some cases may be homosexually acquired but reported as heterosexual exposure.

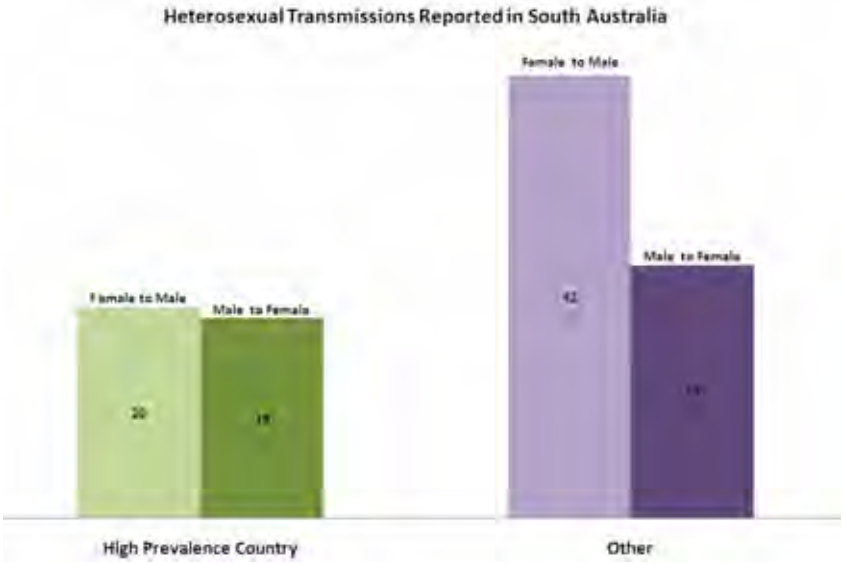


Figure 6: Reported heterosexually acquired diagnoses in South Australia, 1999-2008

People who inject drugs

It is well established that injecting drug use has been a major driver of the spread of HIV in Asia whereby epidemics have typically followed a chain of transmission starting from spread among injecting drug users to the rest of the general population [9]. Thus, it is always important that people who inject drugs are a priority population to ensure effective prevention measures are in place. In South Australia HIV has largely been contained outside of the population of injecting drug users, primarily due to needle and syringe programs (see evaluation of the past section). The number of injecting drug users in South Australia is estimated to be approximately 15,000 people [10] (Figure 7). Over the 10-year period, 1999-2008, 31 HIV diagnoses in South Australia were attributed solely to injecting drug use, accounting for 5.8% of diagnoses. The prevalence of HIV among people who inject drugs in South Australia is estimated to be 0.86% [10].

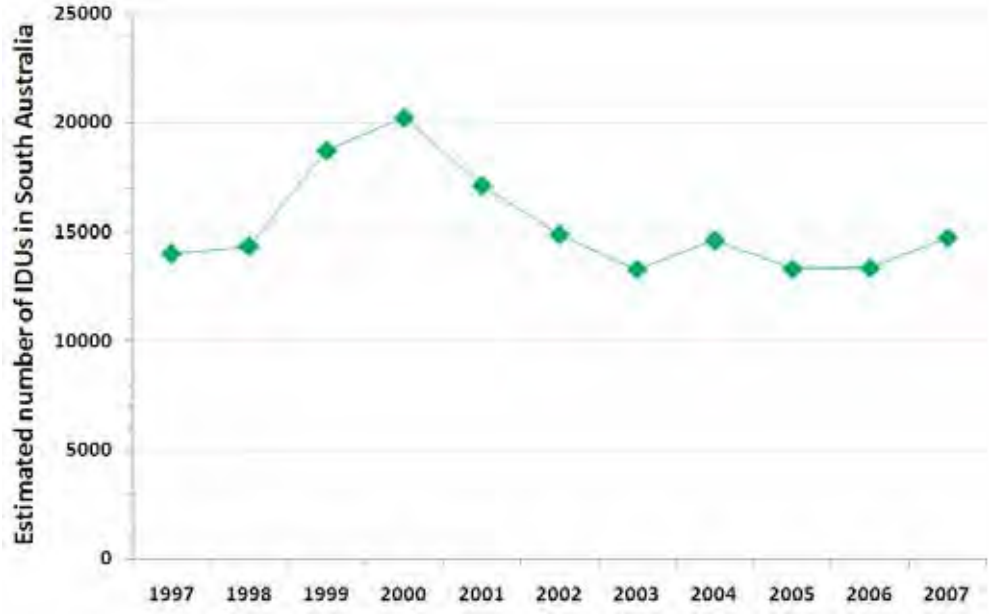


Figure 7: Estimated number of injecting drug users in South Australia **[10]**

Despite the availability of needle and syringe programs in South Australia, sharing of injecting equipment is still relatively common (Figure 8); coupled with relatively high frequencies of injecting (Figure 9) suggests that populations of people who inject drugs should remain a priority population for HIV in South Australia.

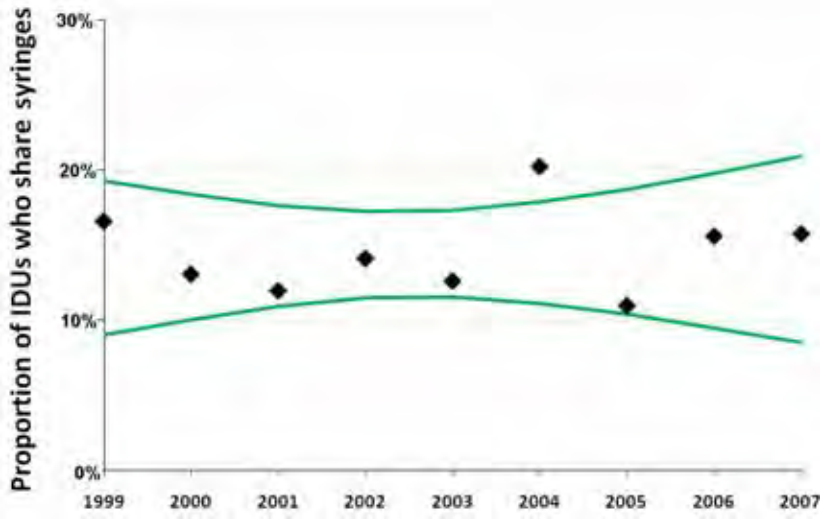


Figure 8: Proportion of injecting drug users in South Australia participating in the Australian Needle and Syringe Program Survey to report sharing syringes in the last month **[11]**

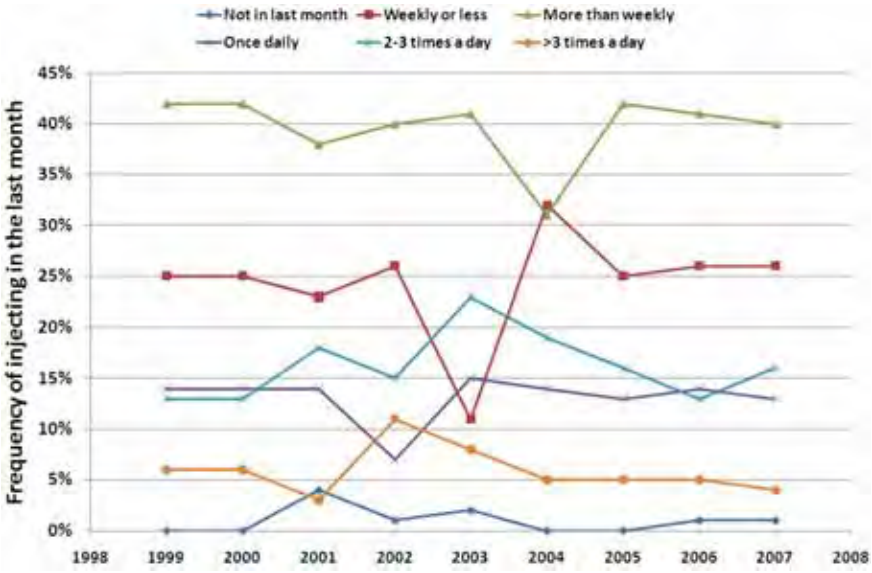


Figure 9: Frequency of injecting by participants of the Australian Needle and Syringe Program Survey in South Australia **[11]**

People in custodial settings

Over the five-year period, 2004-2008, 17,716 people were received into South Australian prisons [12]. Of these people, 26.4% were tested for HIV antibody. Twenty cases were found to be HIV-positive, representing 0.4% prevalence [12].

Sex workers

Sex workers are generally population groups of priority due to the large number of exposure events and high potential for the acquisition and spread of HIV and other sexually transmissible infections. Sex work is prohibited in South Australia (like in Western Australia and the Northern Territory). There are limited data on sex workers in South Australia. However, all surveillance activities, primarily through Adelaide's Clinic 275, have not documented any case of HIV among sex workers in South Australia [12]. This is likely due to almost universal condom usage [13]. Furthermore, South Australian men are the least frequent consumers of commercial sex services in Australia [14].

Testing rates and CD4 counts

South Australia has consistently collected CD4+ T cell counts of HIV-infected individuals at diagnosis and completion rates are greater than in any other Australian jurisdiction, at over 90%. However, HIV cases in South Australia (and the Northern Territory) have a significantly greater likelihood of presenting with infection with advanced disease (CD4 count < 200 cells per µl) compared with all other Australian jurisdictions. Late presentation is associated with exposure other than male homosexual sex and increasing age (based on multivariate logistic regression

analysis). CD4 counts at diagnosis have generally increased over time in South Australia (Figure 10a). As expected, CD4 count at diagnosis is strongly associated with the frequency of testing (Figure 10b).

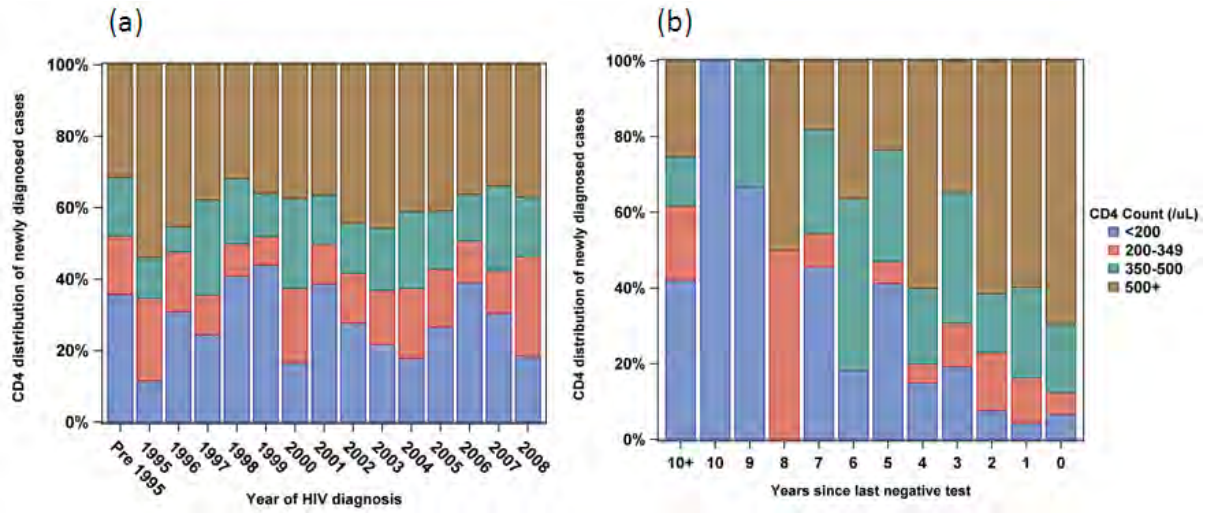


Figure 10: CD4 distribution at HIV diagnosis for cases detected in South Australia (a) by calendar year, (b) by years since last HIV-negative test

The degree of HIV disease progression from the time of infection until diagnosis among cases in South Australia is shown by comparison of CD4 distributions in Figure 11. There is clearly a large distribution in disease progression by the time of diagnosis, with reductions from a mean of approximately 900 CD4 cells per µl in uninfected people to a bimodal distribution with peaks at approximately 500 and 100 CD4 cells per µl. Testing rates are crucial for detecting earlier infection.

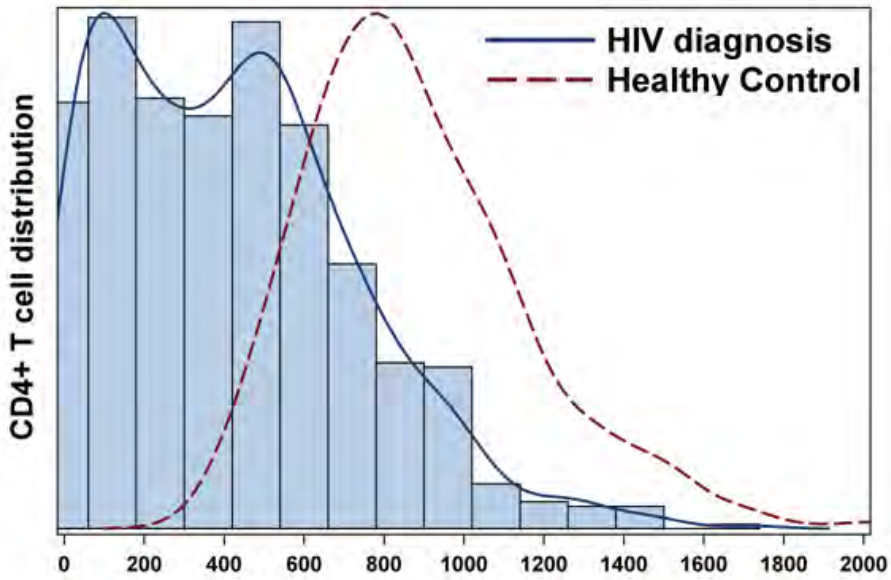


Figure 11: CD4 distribution at HIV diagnosis in South Australia compared with uninfected controls

HIV testing among the priority group of men who have sex with men is relatively high. Among men recruited to the Adelaide Gay Community Periodic Survey in 2007, 8.7% did not know their HIV status and 10.4% had not been tested for HIV [5]. This is comparable to the 7% of men in the e-male survey who report being gay socially engaged but have not had an HIV test [4]. However, 32% of men living in South Australia who are not socially engaged with gay networks in South Australia did not know their HIV status. Men who have received an HIV test generally test for HIV relatively frequently (Figure 12) [4-5]. Testing rates have also been increasing (Figure 13).

HIV testing among MSM is relatively high, but it may be important to improve access to mechanisms that facilitate HIV screening for non-MSM populations in South Australia.

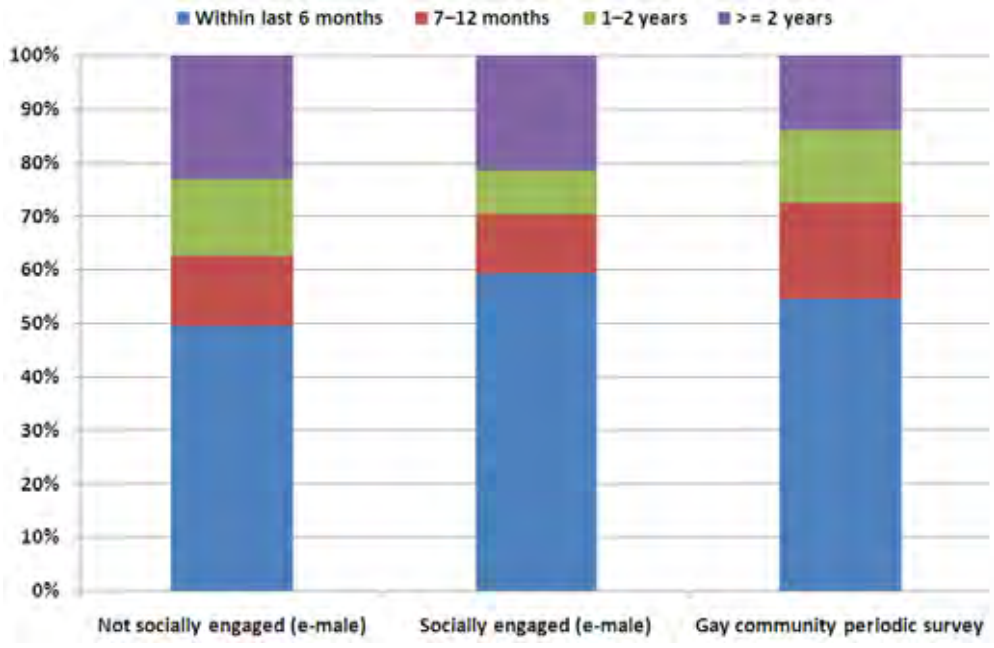


Figure 12: HIV testing rates among MSM in South Australia who have received an HIV test

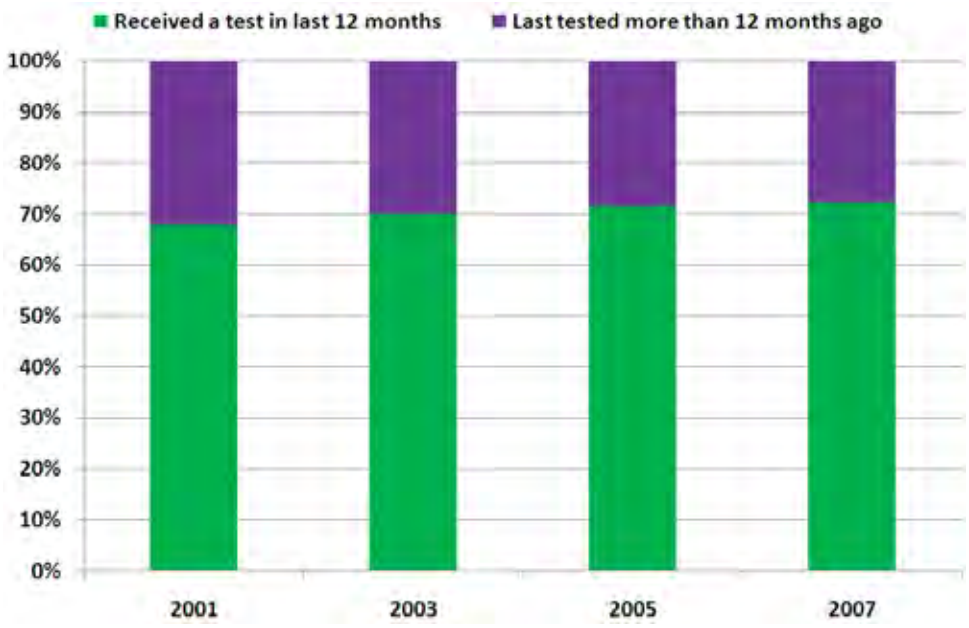


Figure 13: HIV testing rates among gay men recruited to the Gay Community Periodic Surveys in South Australia (excluding those recruited from sexual health clinics) who have received an HIV test

Association between HIV and syphilis

Over the last decade syphilis has re-emerged in numerous industrialized countries including Australia [15-19], particularly among gay men [20-23]. Infectious syphilis diagnoses in Australian men have increased from approximately 1 per 100,000 in the year 2000 to 10-15 per 100,000 in 2008, with increasing trends in diagnoses of infectious syphilis occurring in each Australian state and territory including South Australia. Among gay and other homosexually active men, rates of sexually transmissible infections (STIs), and particularly syphilis have increased significantly in all major Australian cities since the late 1990s, with at least half the cases being among HIV-positive gay men. These epidemics are concerning since syphilis infections are accompanied by significant health burdens as untreated cases may progress to tertiary syphilis [24-25], and the presence of syphilis lesions facilitate HIV transmission [26].

South Australia has experienced a relatively unique switch in the pattern of syphilis infections. During the 1990s syphilis infections were predominantly (91.7%) affecting Aboriginal and Torres Strait Islander populations, with roughly equal diagnoses among males and females (Figure 14). The number of syphilis cases declined over the 1990s. There was a re-emergence of syphilis in the 2000s. However, the epidemic shifted to predominantly affect non-Indigenous males (Figure 14).

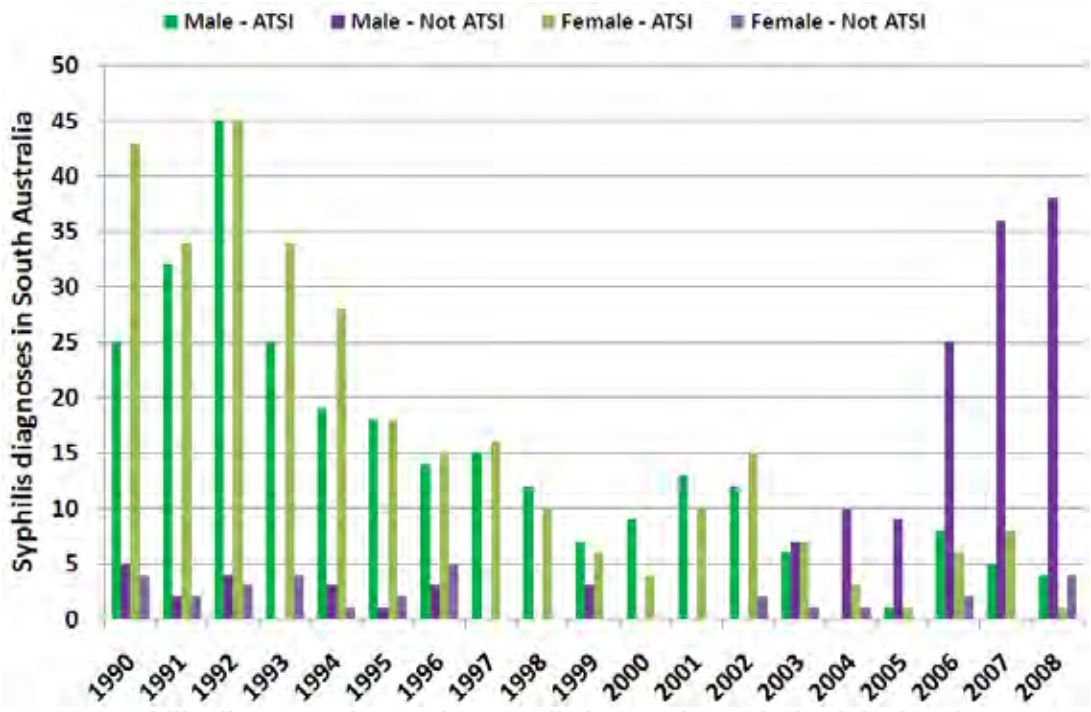


Figure 14: Syphilis diagnoses in South Australia by gender and Aboriginal and Torres Strait Islander status

In the five-year period, 2004-2008, there were 162 syphilis diagnoses in South Australia; 125 (77%) of which were among non-Indigenous Australians and 136 (84%) were among males. The emergent syphilis epidemic over the last decade has mainly affected gay and other men who have sex with men. More specifically,

syphilis has disproportionately affected HIV-positive gay men (Figure 15). In South Australia's surveillance mechanisms syphilis diagnoses have been linked to HIV status. During 2004-2008, 50% of all syphilis diagnoses were among HIV-positive men. The average age at syphilis diagnosis was 37.1 years. These summary statistics are not significantly different if data are limited to infectious syphilis (primary or secondary stages).

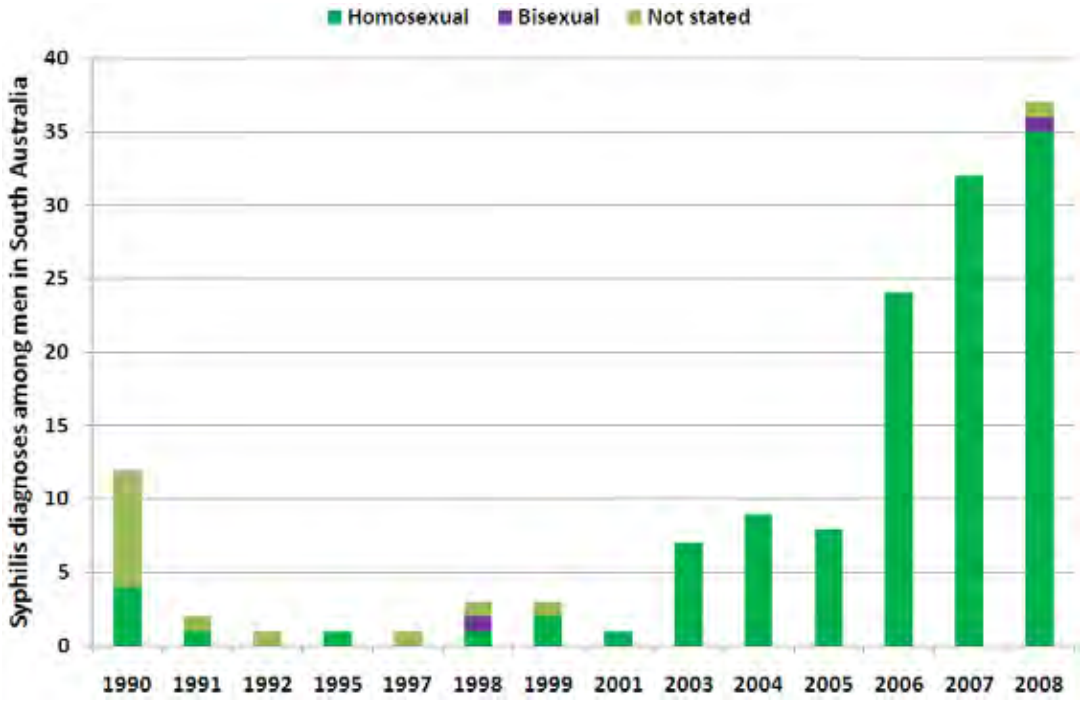


Figure 15: Syphilis diagnoses in South Australia among non-Indigenous males by reported sexual orientation

Health promotion activities across Australia have had little impact on the resurgence of syphilis among gay men and rates continue to rise [27-28]. During the period of late 2008 to end 2009, the National Gay Men's Syphilis Action Plan (NGMSAP) was developed [29]. This plan was initiated by the Blood Borne Virus and STIs Subcommittee (BBVSS) of the Australian Population Health Development Principal Committee and its development, along with underlying research, was carried out by the authors of the current report at the National Centre in HIV Epidemiology and Clinical Research [29]. The priorities of the NGMSAP are summarised as:

- **Priority 1**
  - Gay men are encouraged to test for syphilis as it pertains to their level of risk: The more sexually active the individual gay man then the more often he should be tested. For sexually-active gay men in general, testing for syphilis should be linked to other routine testing. ***Ongoing screening for syphilis should be routine with HIV management and testing*** (as opt-out strategies): Sexually-active HIV-infected men should be tested for syphilis during routine check-up, usually every 3 months; Screening for syphilis should also be conducted alongside every HIV test for

sexually-active gay men not previously diagnosed with HIV. In addition, as a minimum, ***men who have more than 20 partners per 6 months should be tested for syphilis at least twice per year***. Testing sexually active gay men who have never previously been tested is also important.

- **Priority 2**
  - ***Easier ways for notifying sexual partners discreetly*** should be created. The goal is to quantifiably observe an ***increase in the rate of partner notification***. To decrease stigma, ***increased education about syphilis*** is required. Mechanisms for partner notification should consider patient-led, clinician-led, and centralised notification models that use a variety of means and technologies.
- **Priority 3**
  - There is general agreement that the proposed syphilis chemoprophylaxis ('syphilaxis') trial should proceed as soon as is practical. It is recommended that ***possible Australian funding sources for the trial*** be investigated.
- **Supporting priority**
  - ***Promoting condom use to maintain current high usage levels remains critical***. Condom use and number of sexual partners are also important concepts in education for gay men in assessing their level of risk and relative need for, and frequency of, testing.
  - Consideration should be given to ***locating highly sexually active gay men***, who have greater than 20 partners per 6 months, for the purposes of targeting interventions. Care should be taken for protecting the confidentiality of the venues and men involved.

The priorities recommended in the NGMSAP are consistent with the priority action areas from the last National Sexually Transmissible Infections Strategy (2005-2008) and the next National Sexually Transmissible Infections Strategy to be released in 2010. Implementation of the NGMSAP priorities has commenced in 2010.

Modelling evaluation methods

Mathematical models can provide useful insights into the complex dynamics of disease transmission [30]. In this report a mathematical model is developed to describe the HIV epidemic among men who have sex with men (MSM) in South Australia. The model is informed by South Australian behavioural and clinical data along with biological data from the international literature and it is calibrated to reflect the past and present epidemiology of HIV in South Australia. The model is used to determine the key drivers of past trends, evaluate past and present programs, and to forecast epidemic trajectories in the future according to current conditions or due to implementation of public health interventions.

A deterministic compartmental model was constructed and formulated as a system of ordinary differential equations to track the number of MSM in South Australia over time that are in each state of HIV disease stage: whether uninfected with HIV or HIV-infected and undiagnosed, diagnosed, or on antiretroviral treatment. All MSM are classified according to whether they belong to a population that is socially engaged to the gay community or not. All HIV-infected individuals are classified according to their stage of HIV disease, based on CD4 count: CD4 count > 500 cells per µl; 350 cells per µl < CD4 count < 500 cells per µl; 200 cells per µl < CD4 count < 350 cells per µl; or CD4 count < 200 cells per µl. A schematic diagram of this natural history described in the model is presented in Figure 16. The ordinary differential equations used in the model are shown in Appendix A.

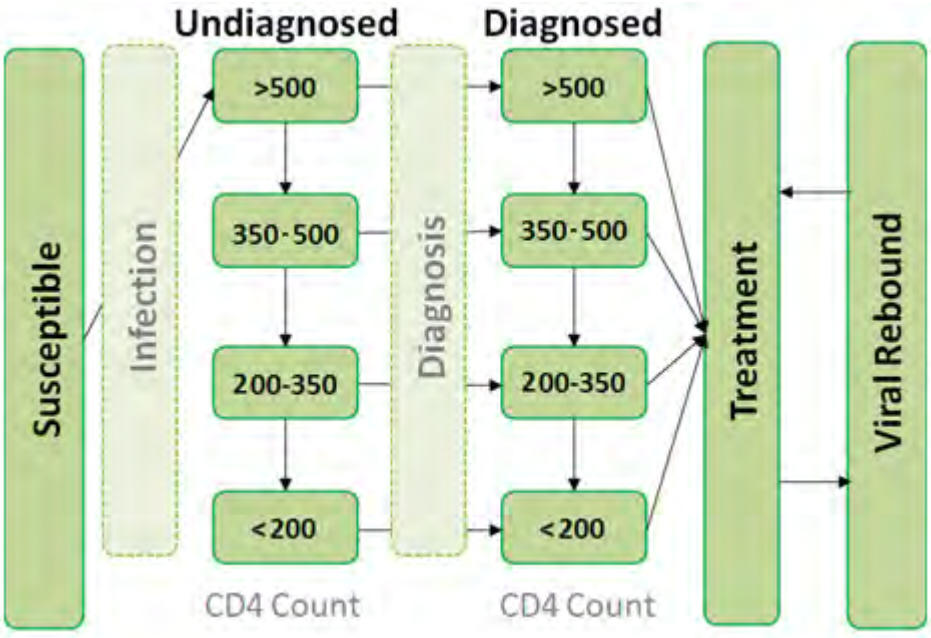


Figure 16: Schematic diagram of HIV natural history and structure of mathematical model

Force of infection

The force of infection is the dynamic rate at which susceptible individuals become infected with HIV. Typically the force of infection 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. Each of these factors will change continuously over time. A number of variables contribute to each of these components.

Number of sexual partners

The model incorporates the average numbers of casual sexual partners and the average numbers of regular partners MSM have each year. Stratified data of partner acquisition rates [4, 31-33] that demonstrate the heterogeneity in the population are used to obtain weighted average partner rates for the population; differences between men who identify as socially engaged to the gay community and men who are not socially engaged with the gay community are included. The degree of assortativity of partners (i.e., like with like – e.g., gay community attached men choosing only partners who are also attached to the gay community) [34] was determined by examination of the frequency distributions of the locations where community engaged and community non-engaged men report obtaining their sexual partners (Figure 17). These frequencies were balanced to determine the rate of mixing between the two population groups.

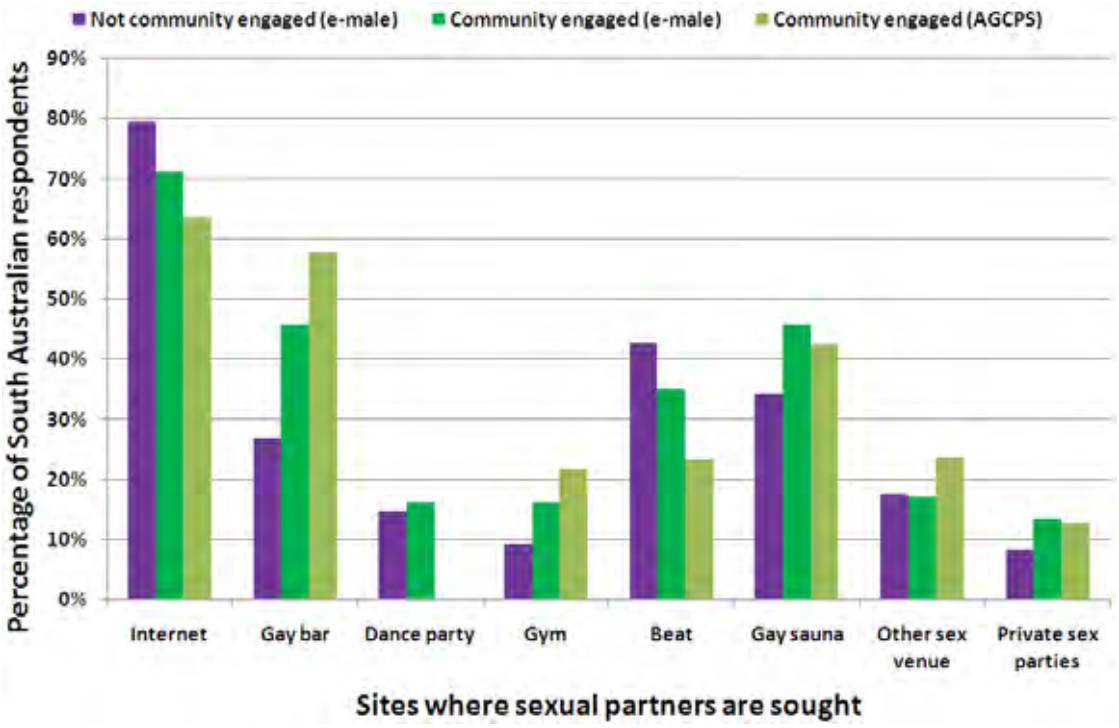


Figure 17: Locations where men who have sex with men, who participated in the e-male survey, reported looking for male sex partners in South Australia: (a) reported gay community engaged; (b) reported not gay community engaged.

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, then the probability that a new partner is HIV-positive is simply the ratio of the number of HIV-infected men to the total number of men in the population. There is evidence of change in behaviour upon diagnosis and men who have late-stage disease are likely to have reduced numbers of partners. Also, due to different assortative mixing rates (e.g. different groups of men acquire partners from different types of locations) the probability of new partners being HIV-positive must be calculated dynamically based on the prevalence of HIV in the pool of potential partners of the specific group of men. Furthermore, the probability of a discordant partnership depends on the rate of serosorting. Serosorting is the practice of choosing sexual partners thought to be of concordant HIV serostatus in order to reduce the risk of HIV transmission during unprotected intercourse [35-37]. There is strong evidence to suggest that in various populations of MSM around the world the formation of casual sexual partnerships and behaviour within such partnerships has been increasingly influenced by the disclosure of HIV serostatus [35, 38-43]. Serosorting is not as common in South Australia as in other locations in Australia [44] and is less common among HIV-negative MSM. However, serosorting has still been an increasing phenomenon in South Australia which has undoubtedly influenced the dynamics of partnership formation.

Probability of HIV transmission per discordant partnership per year

The probability of HIV transmission in a discordant partnership depends on the number and type of risk exposure events. Engaging in unprotected anal intercourse (UAI) is the most common risk-related event associated with HIV transmission among South Australian men. However, the actual per-exposure risk of acquiring HIV differs between insertive and receptive roles of penile-anal intercourse [45]. Further, transmission risk is less for receptive sex involving withdrawal compared with receptive sex involving ejaculation inside the rectum and transmission risk is less for circumcised men partaking in the insertive role [45]. According to knowledge of partners' serostatus an HIV-negative man may choose which sexual position they are willing to take (known as strategic positioning). It has been established that disclosure of HIV status influences sexual positioning of gay men in Australia [46]. If a condom is used during sex, then transmission risk decreases substantially. Also, if the HIV-infected partner is on effective antiretroviral therapy with suppressed viral load then transmission risk is also reduced [47]. The risk of transmission associated with each of these combinations differs and must be calculated to accurately estimate the risk per exposure event. Finally, the probability of transmission in a

discordant partnership must calculate the cumulative risk over all exposure events that occur over time (where there are likely to be numerous exposures to different types of risk events). The mathematical expression for the force of infection used in the mathematical model is presented in Appendix A.

Input data and assumptions

The model is based on available behavioural, clinical, biological and epidemiological data. All model inputs are presented in Table 1. The symbols correspond to rates used in the model equations presented in Appendix A.

Table 1: Inputs and assumptions for mathematical model

Parameter Symbol	Description		Value	Reference
c_{SE}^{reg}	Average number regular partners for socially engaged MSM (proportion of men with a regular sexual partner)		0.728	[48-50]
c_{OM}^{reg}	Average number regular partners for other MSM (proportion of men with a regular sexual partner)		0.518	[48, 50]
c_{SE}^{cas}	Average number casual partners per year for socially engaged MSM		11.504	[48, 50]
c_{OM}^{cas}	Average number casual partners per year for other MSM		8.736	[48, 50]
n_{SE}^{reg} n_{OM}^{reg}	Average number of anal intercourse acts per regular partnership per year		10-50	[48, 50]
n_{SE}^{cas} n_{OM}^{cas}	Average number of anal intercourse acts per casual partnership		1	
$condom_{reg}^{SE}$	Condom use with regular partners for socially engaged MSM	2001	69.09%	[48-50]
		2003	69.91%	
		2005	68.09%	
		2007	65.52%	
$condom_{reg}^{OM}$	Condom use with regular partners for other MSM	2001	0.69.22%	[48-50]
		2003	70.04%	
		2005	68.22%	
		2007	65.65%	
$condom_{cas}^{SE}$	Condom use with casual partners for socially engaged MSM	2001	88.83%	[48-50]
		2003	88.23%	
		2005	88.71%	
		2007	84.63%	
$condom_{cas}^{OM}$	Condom use with casual partners for other MSM	2001	80.17%	[48-50]
		2003	79.63%	
		2005	80.06%	
		2007	76.37%	
$disclose_{pos}$	Probability seropositive MSM will	2001	43.2%	[48-50]

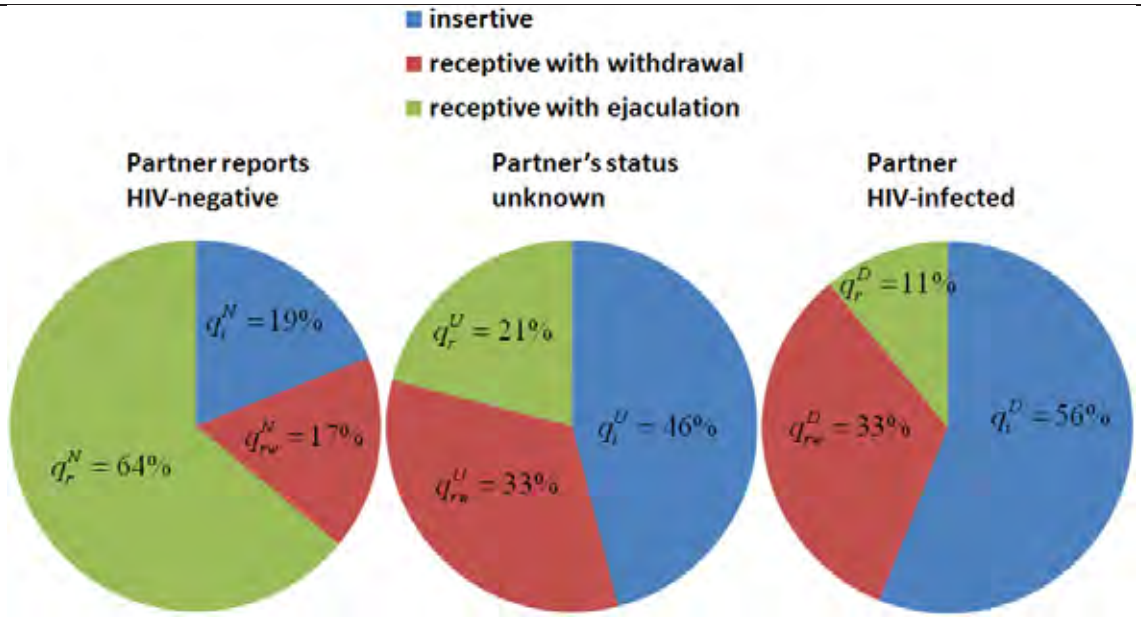
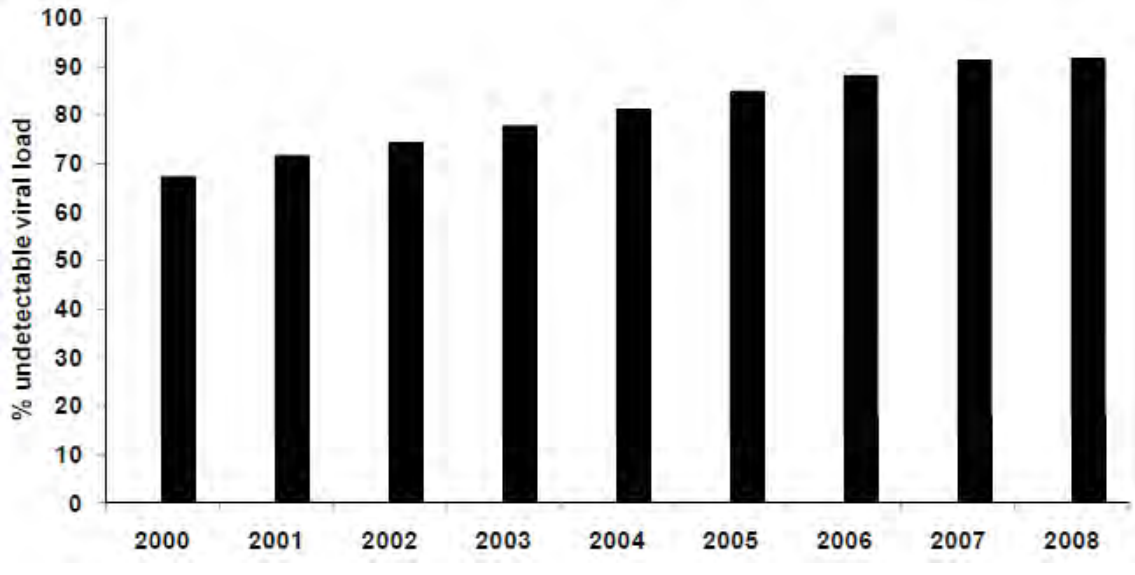
	disclose serostatus in casual act	2003	39.5%	
		2005	48.3%	
		2007	36.6%	
$disclose_{neg}$	Probability seronegative MSM will disclose serostatus in casual act	2001	0.3575	[48-50]
		2003	0.355	
		2005	0.378	
		2007	0.3205	
ε	Efficacy of condom protection per act		90-99%	[51-55]
c_{AIDS}	Multiplying factor for the reduction in number of sexual partners for men in AIDS stage disease		0.1 – 0.4	[56]
f	Multiplying factor for the change in number of sexual partners post diagnoses of HIV infection		0.4 – 0.9	[57-65]
μ_S	Average time for individuals to 'retire' out of sexually active population (no longer obtaining new partners)		30-70 years	[66]
γ_{SE}	Percentage of socially engaged MSM that test for HIV infection each year	2001	57%	[48-50]
		2003	61%	
		2005	60%	
		2007	65%	
γ_{OM}	Percentage of other MSM that test for HIV infection each year	2001	38%	[48-50]
		2003	41%	
		2005	40%	
		2007	43%	
$1/\gamma_{lt}^{200SE}$ $1/\gamma_{lt}^{200OM}$	Average time from the beginning of AIDS before individual is likely to be diagnosed with infection		2-4 months	[56]
$1/\omega^{500}$	Average time (without ART) for HIV-infected individuals to progress from CD4 count >500 to CD4 count 350-500		2.95 (1.79-4.42) years	[67] ^{a}
$1/\omega^{350–500}$	Average time (without ART) for HIV-infected individuals to progress from CD4 count of 350-500 to CD4 count of 200-350		1.96 (1.81-2.13) years	[67] ^{a}
$1/\omega^{200–350}$	Average time (without ART) for HIV-infected individuals to progress from CD4 count of 200-350 to CD4 count <200		1.96 (1.81-2.13) years	[67] ^{a}
δ^{500}	HIV-related death rate for patients with CD4 count >500 cells per μL and detectable viral load		0.051% (0.035-0.068%)	[68]
$\delta^{350–500}$	HIV-related death rate for patients with CD4 count 350-500 cells per μL and detectable viral load		0.128% (0.092-0.164%)	[68]
$\delta^{200–350}$	HIV-related death rate per 100 person-years for patients with CD4 count 200-350 cells per μL and detectable viral load		1.0% (0.2-2.0)%	[68-69]
δ^{200}	HIV-related death rate per 100 person-years for patients with CD4 count <200 cells per μL and detectable viral load		4.08 (0.30-7.86)%	[68-69]
δ^{T}	HIV-related death rate per 100 person-years for patients with CD4 count <200 cells per μL and detectable viral load		1.0% (0.2-2.0)%	Experimental variable

δ^{TF}	HIV-related death rate per 100 person-years for patients with CD4 count <200 cells per μL and detectable viral load	4.08 (0.30-7.86)%	Experimental variable
η^{500}	Proportion of individuals with CD4 count >500 that commence treatment for HIV each year	0.2	Experimental variable
$\eta^{350–500}$	Proportion of individuals with CD4 count 350-500 that commence treatment for HIV each year	0.5	Experimental variable
$\eta^{200–350}$	Proportion of individuals with CD4 count 200-350 that commence treatment for HIV each year	0.75-0.85	Experimental variable
η^{200}	Proportion of individuals with CD4 count <200 that commence treatment for HIV each year	0.85-0.95	Experimental variable
ν	Percentage of individuals on ART who cease therapy each year	1-5%	*b*
$posn$	The percentage of times a negative man will take each role in a sex act based on disclosure of partner's serostatus	See footnote *c*	[46]
β_r	Per-contact risk of transmission when negative partner takes receptive role	0.48-1.52%	[70]
β_w	Per-contact risk of transmission when negative partner takes receptive role with withdrawal prior to ejaculation	0.15-1.53%	[70]
β_i^{uncirc}	Per-contact risk of transmission when negative partner is uncircumcised and takes insertive role	0.07-1.68%	[70]
β_i^{circ}	Per-contact risk of transmission when negative partner is circumcised and takes insertive role	0.02-0.24%	[70]
pa_{mult}	Multiplicative factor for transmission probability for people in primary/acute infection or in AIDS stage infection (due to higher viral load)	14.7	[71-72]
t_{mult}	Relative reduction in HIV transmission probability for people on antiretroviral therapy	92%	[47]
ART_{eff}	Proportion of people on antiretroviral therapy with undetectable viral load	See footnote *d*	[73]
SE^{mix}	Average percentage of sex acts a socially engaged MSM will have with a non-socially engaged MSM	43%	[48, 50]
OM^{mix}	Average percentage of sex acts a non-socially engaged MSM will have with a socially engaged MSM	55%	[48, 50]

a A summary of the relation between HIV-1 RNA concentration and decline in $CD4^+$ count from the prospective study by Mellors et al. [67] is given below:

Plasma HIV-1 RNA concentration (*copies/mL*)	**Mean decrease in $CD4^+$ T cell count per year (*cells/μL*)**
≤ 500	-36.3 (-30.4,-42.3)
501-3,000	-44.8 (-39.1,-50.5)
3,001-10,000	-55.2 (-50.7,-59.8)
10,001-30,000	-64.8 (-59.6,-70.0)
> 30,000	-76.5 (-70.5,-82.9)

With this data, and assuming that the average viral load is ~$10^{4.87}$ copies per mL for people without treatment, the $CD4^+$ T cell count decreases by an average of 76.5 (70.5, 82.9) every year.

	To progress through the >500 CD4 cell category, we assume that the average CD4 count is 800 cells/μL after the 2-month acute phase of HIV infection and then declines at the constant rate of 76.5 (70.5, 82.9) cells/μL each year. Then the average time to progress through this compartment is 2/12 + 300/(76.5 (70.5, 82.9)) years; that is 4.09 (3.79, 4.42) years. To progress through the 350-500 and 200-350 CD4 cell categories, we assume an average loss of 150 CD4 cells. Then the average time to progress through this compartment is 150/(76.5 (70.5, 82.9)) years; that is 1.96 (1.81, 2.13) years.
b	15.4/100 person years is the average rate of stopping one regime due to toxicity but the vast majority usually start another regime [74]. Very few people who commence ART stop altogether (expert opinion). Therefore, we take the absolute rate of completely stopping therapy to range from 1-5% per year as an experimental variable.
c	
d	

The key time-dependent behavioural parameters used in the model are provided in Figures 18-21.

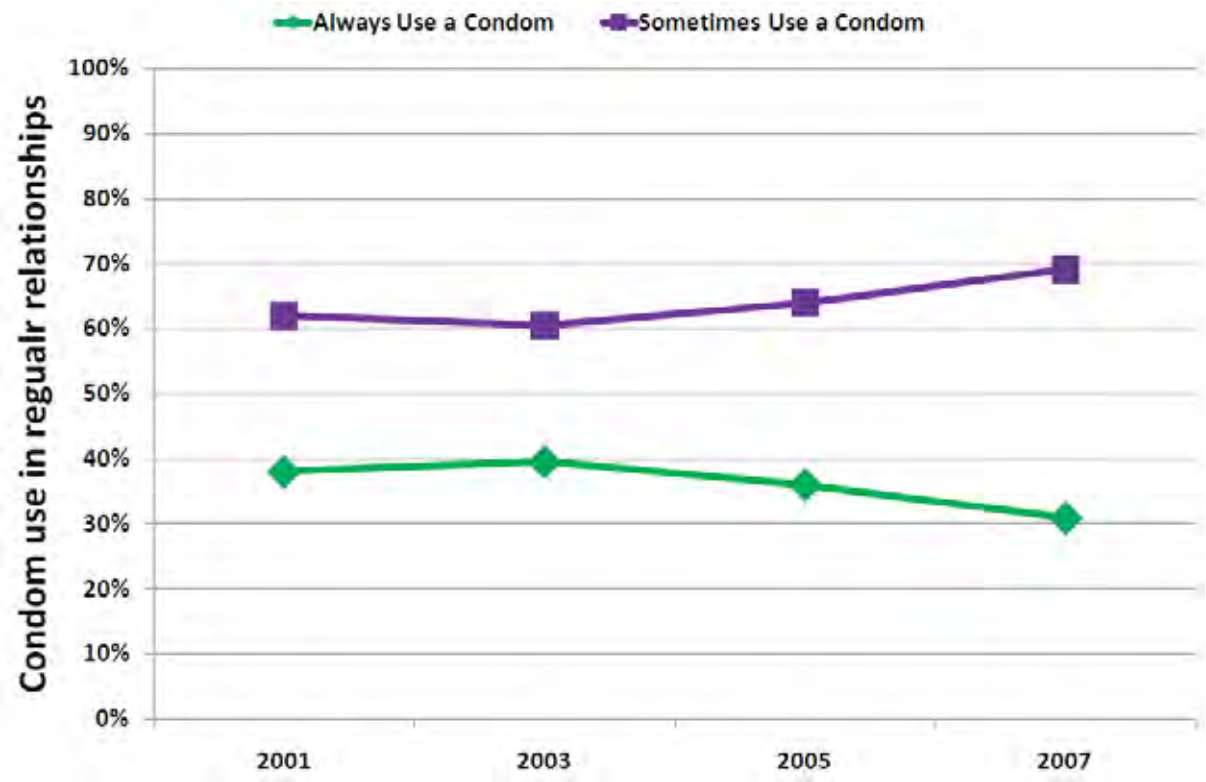


Figure 18: Reported condom usage in regular relationships from the Adelaide Gay Community Periodic Surveys

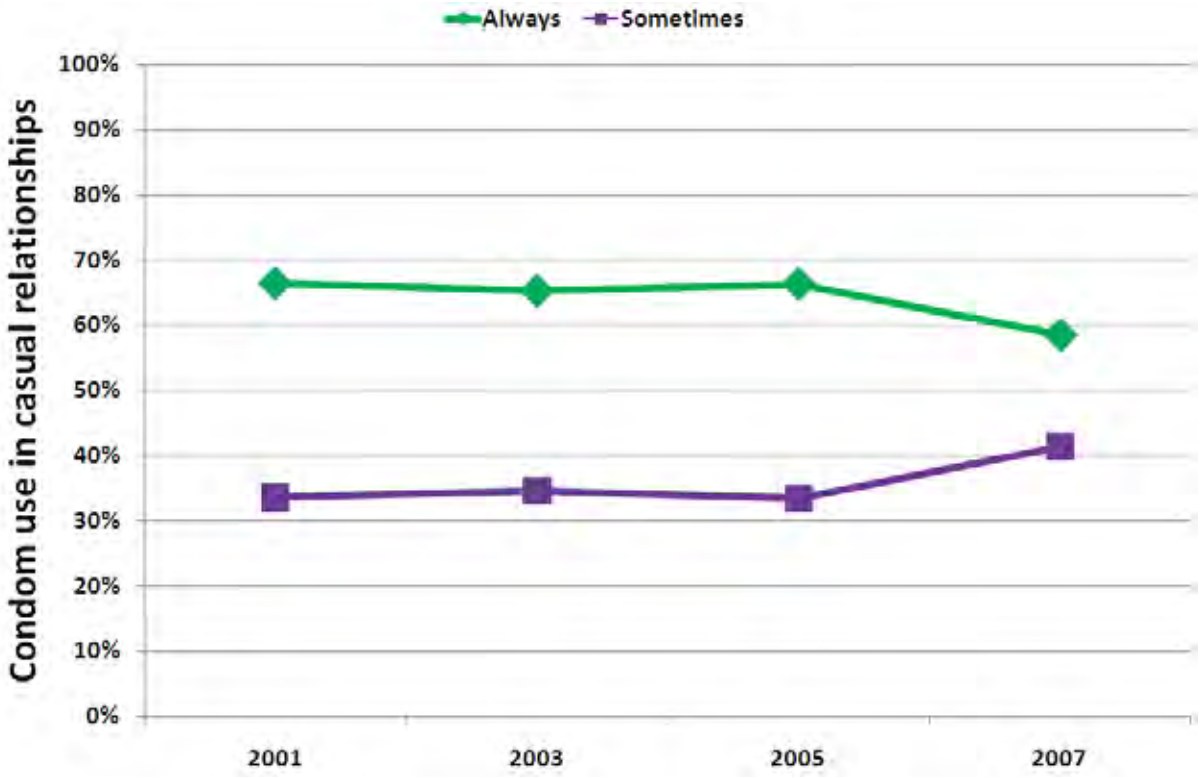


Figure 19: Reported condom usage in casual relationships from the Adelaide Gay Community Periodic Surveys

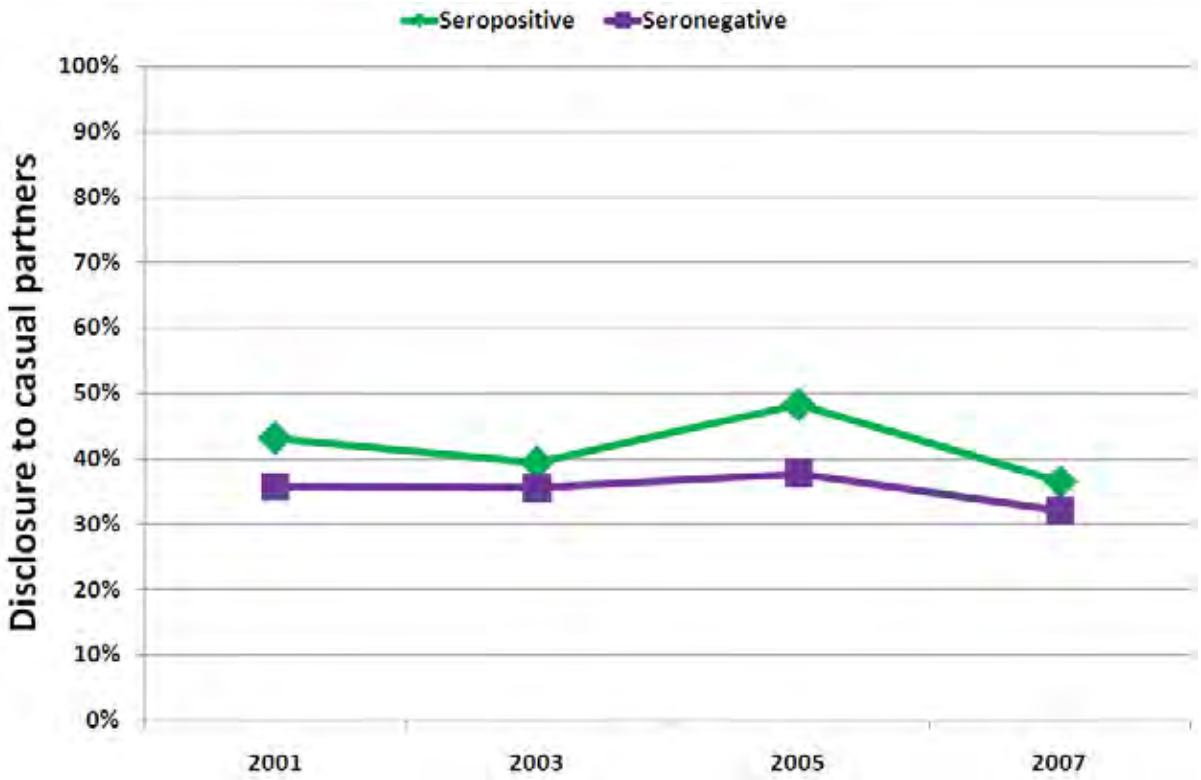


Figure 20: Reported disclosure of HIV status to casual partners from the Adelaide Gay Community Periodic Surveys

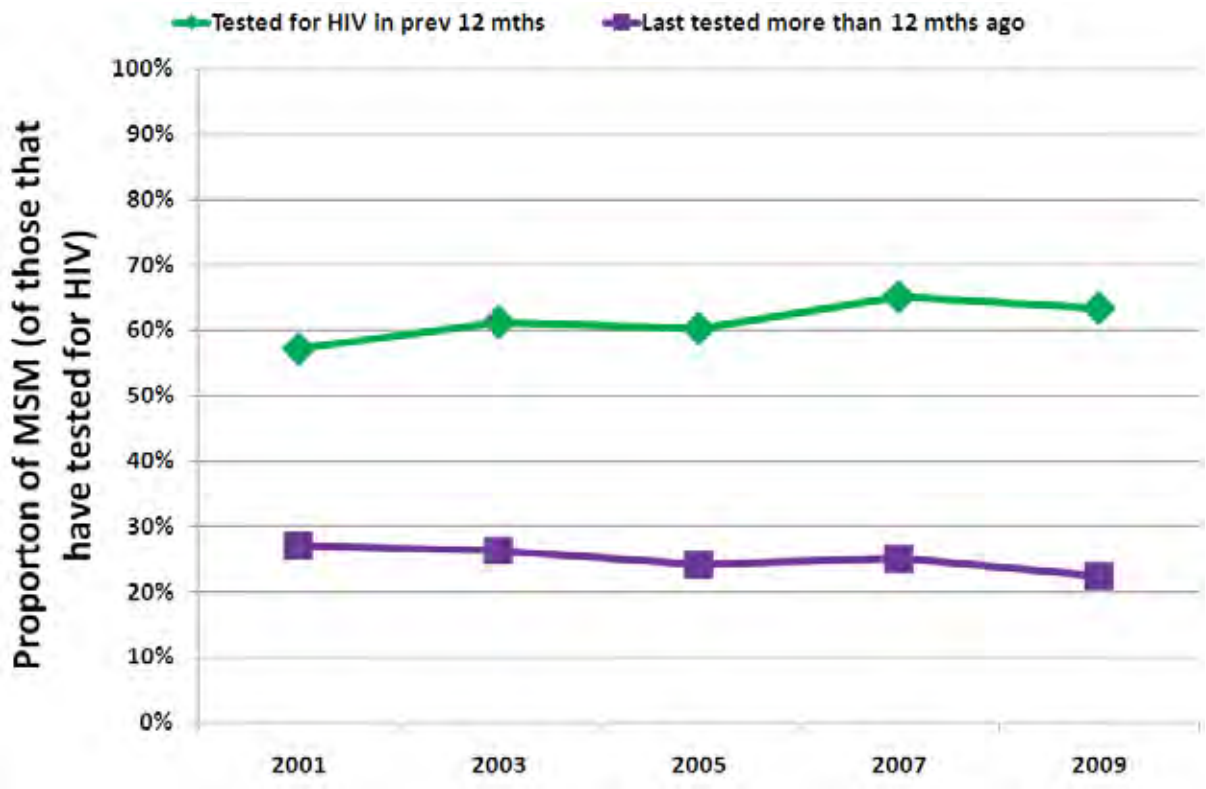


Figure 21: Reported HIV testing rates from the Adelaide Gay Community Periodic Surveys

Sampling and sensitivity analysis

Parameters used in the model were assigned a range of plausible values based on available data (Table 1). Latin Hypercube Sampling [75] generated 10,000 samples from each distribution. These parameter sets became input values for the mathematical model which was run 10,000 times. The sum of squares of the difference between the model simulated number of HIV diagnoses and the actual number of HIV diagnoses in South Australia over the period 2003-2008 was calculated for each simulation and Monte Carlo filtering was used to arrive at 100 parameter sets that best describe the past epidemiology. It was ensured that the model also accurately represents other epidemiological features in the population such as HIV prevalence, rates of undiagnosed infections, and antiretroviral treatment rates. Sensitivity analyses were performed to determine important factors associated with epidemic patterns. The SaSAT software package [76] was used to sample input parameters. The mathematical model was implemented in computer programming code using Matlab software.

Model fit to surveillance data

Using the established input data, the South Australian HIV mathematical model was run over the time period 2002 to 2008. In Figure 22 the model-generated simulated expected number of HIV diagnoses is plotted with the actual number of HIV diagnoses in South Australia. The model accurately reflected the epidemic trends in diagnoses (Figure 22). The model also estimated that 13.68% (median, 13.41-14.10% IQR) of HIV-infected people in South Australia are undiagnosed and 79.40% (median, 78.42-80.21% IQR) of diagnosed people are on antiretroviral treatment.

The model estimated the expected number of incident infections over the period 2002-2008 that must have occurred in order to lead to the observed number of diagnoses (Figure 23). This suggests that incidence was relatively high at the beginning of the last decade, giving rise to an emergence of HIV (as indicated in Figure 4). However, the number of incident cases very closely aligns with the number of diagnoses over the past 4-5 years (Figure 23). This is attributable to the high testing rates among MSM in South Australia. Furthermore, the number of diagnoses approximately mirrors the incident cases approximately 18 months earlier (distance between roughly parallel curves) (Figure 23).

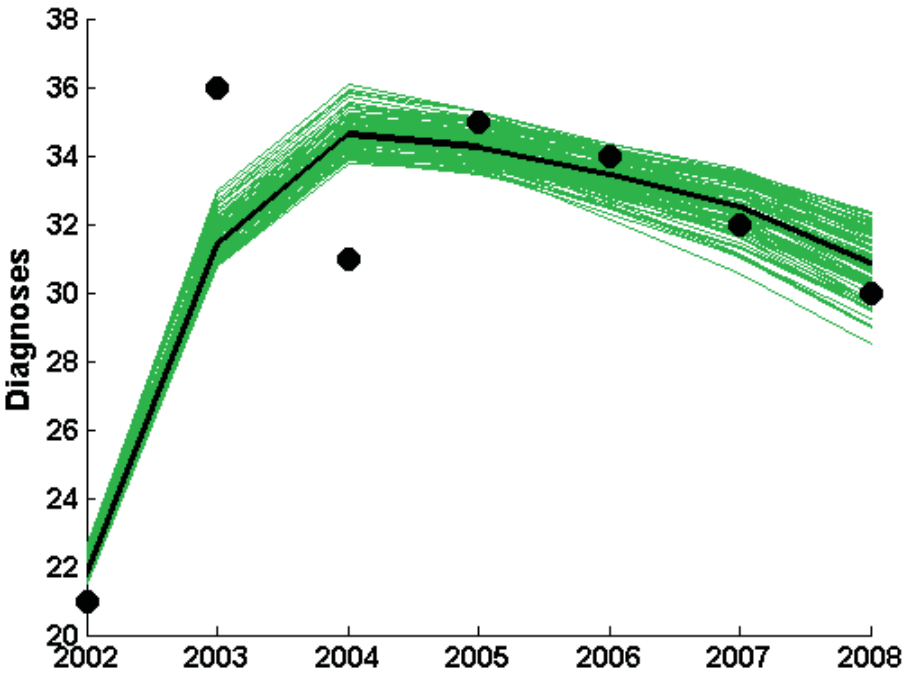


Figure 22: Model simulated number of HIV diagnoses over the period 2002- 2008 from 100 simulations (median in black); actual HIV diagnoses are also indicated

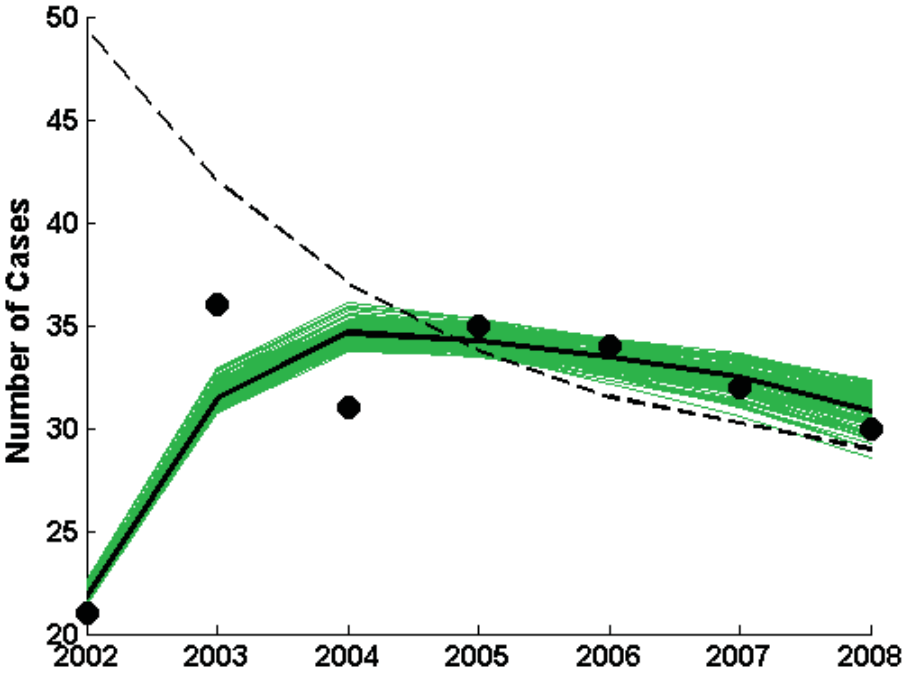


Figure 23: Model simulated number of HIV diagnoses over the period 2002- 2008 from 100 simulations (median is black solid curve) compared with simulated number of incident cases (dashed curve)

Evaluating the past

The rate of HIV diagnoses in South Australia has increased significantly over the past decade but over the past few years it has stabilised or even started to decline (Figure 4). Over the same period of increased HIV diagnoses there has been an increase in unprotected anal intercourse, as indicated by a reported decrease in condom use (Figures 18 and 19). As expected, condom use is higher among casual partners (Figure 19) than among regular partners (Figure 18). However, it was among regular partners that condom use appears to have declined first, from around 2003) and later followed by a decline in condom use among casual partners, from around 2005 (Figures 18 and 19). It is not clear to what extent the change in condom use contributed to the rise in HIV diagnoses in South Australia since the rise in HIV cases (Figure 4) occurred before the reported changes in condom use.

In most populations of MSM in Western countries, including in most Australian jurisdictions, disclosure of HIV serostatus between casual sexual partners has become increasingly common (in addition to commonly disclosing to regular partners) [35, 38-43]. Disclosure of HIV status facilitates decisions around partnership formation, sexual positioning within partnerships and negotiations around condom use. These risk reduction strategies based on knowledge of HIV status is becoming more common. However, in contrast to most settings, in South Australia disclosure of HIV status has not increased but remained relatively constant or even decreasing. Disclosure of HIV status occurs in approximately 40% of partnerships for both HIV-seronegative and HIV-seropositive gay men (Figure 20).

Testing rates among gay men in South Australia are relatively high and increasing (Figure 21). High rates of HIV testing are valuable for effective surveillance but more importantly high testing rates benefit the individuals at risk of HIV in order to provide appropriate clinical care, management and treatment but increasing testing rates is also beneficial at the population-level as a public health prevention strategy [77]. This is because HIV-infected people who are aware of their HIV status tend to change their behaviour in order to reduce secondary transmission to others.

TT123 campaign

The *Reducing Rising Rates of HIV Infection in South Australia* working party first met in mid May 2008. It was charged with the responsibility of developing a health promotion response to the rising rates of HIV infection amongst gay men and men who have sex with men in South Australia. Group membership comprised representatives of service organisations responsible for HIV prevention in South Australia. The Adelaide 2008 Feast Festival was identified as an opportunity in which to promote messages about HIV prevention to gay men. After considerable cross-sector collaboration the TESTING - TESTING - 1 - 2 – 3 campaign was developed. The campaign's aims and objectives were to:

- Make gay men aware of the rise in HIV infections in South Australia and to encourage behaviours that would assist to reduce the risk of HIV transmission;
- Make gay men aware of the rising rates of sexually transmitted infections such as Chlamydia, syphilis and gonorrhoea and their association with HIV transmission;
- Reduce levels of STIs in the gay community by encouraging men to test for STIs and HIV, and especially if they have had unprotected sex;
- Reduce HIV transmission by encouraging gay men to test for HIV and to know their HIV status.

The campaign's messages focussed on:

- The importance of testing regularly for HIV and for gay men to know their HIV status;
- The importance of testing regularly for STIs as one way for gay men to reduce their risk of getting or passing on HIV.

These key messages were placed on print press advertisements, posters, condoms, websites, and pride march placards. Other campaign activities also promoted the increase in testing.

Did the TT123 campaign influence testing rates?

Impact assessment of interventions attempts to translate investment into estimates of impact. The impact of a campaign can be measured by the degree of awareness of the interventions among the targeted groups in the public. But the primary impact of this campaign is in the measurement of HIV testing rates among gay men. The potential effectiveness of the intervention can then be estimated by comparing observed epidemiological outcomes with what would have been expected had the campaign not been implemented. In order to assess the impact of an intervention it is essential to compare data before and after it took place. The Adelaide Gay Community Periodic Surveys are serial cross-sectional surveys and the best source for independently measuring general trends in testing rates. Data on reported HIV testing rates from the Adelaide Gay Community Periodic Surveys are shown in Table 2.

Table 2: Proportion of non HIV positive men who reported to have had HIV test excluding men recruited from sexual health clinics (Note: before 2005, answer option did not include "never tested")

	1998 n (%)	1999 n (%)	2001 n (%)	2003 n (%)	2005 n (%)	2007 n (%)	2009 n (%)
Never tested	-	-	-	-	79 (14.2)	39 (9.11)	109 (14.2)
Less than 6 months	195 (46.4)	161 (44.2)	202 (45.3)	344 (49.5)	238 (43.3)	202 (47.2)	342 (44.6)
7 – 12 months	71 (16.9)	69 (19.0)	90 (20.2)	132 (19.0)	102 (18.3)	78 (18.2)	144 (18.8)
1 -2 years	77 (18.3)	65 (17.9)	59 (13.2)	102 (14.7)	62 (11.1)	56 (13.1)	70 (9.1)
More than 2 years	77 (18.3)	69 (19.0)	95 (21.3)	117 (16.8)	77 (13.8)	53 (12.4)	102 (13.3)
Total	420 (100)	364 (100)	446 (100)	695 (100)	558 (100)	428 (100)	767 (100)

To evaluate whether the TT123 campaign had a noticeable impact on testing rates, the data from 2009 should be compared with the trend in testing data from previous years. It should be noted, however, that because different samples of individuals participate in each survey sampling biases may exist. For example, the percentage of gay men who report never testing for HIV was 14.2% in 2005, 9.1% in 2007 and 14.2% in 2009 which is unlikely reflective of the actual changes in numbers of gay men who have not had an HIV test. When all testing data are included, the distribution of testing rates in 2009 appears to be almost identical to the reported data from 2005 (Figure 23). These data suggest that the TT123 did not have an impact on decreasing the proportion of gay men who have not received an HIV test. In order to assess potential changes in testing practices among gay men who have previously received an HIV test the non-testing respondents should be excluded. In Figure 24 it is shown that the proportion of gay men who have tested for HIV in the last 12 months has modestly increased over the last few years: from 71.79% in 2005, to 71.96% in 2007, to 73.89% in 2009. That is, there was a relative increase in

testing rates among gay men who have been tested of 0.22% from 2005 to 2007 but the relative increase in testing rates from 2007 to 2009 was 2.69%. Therefore, it is reasonable to infer that the TT123 campaign did marginally increase testing among gay men who had previously been tested.

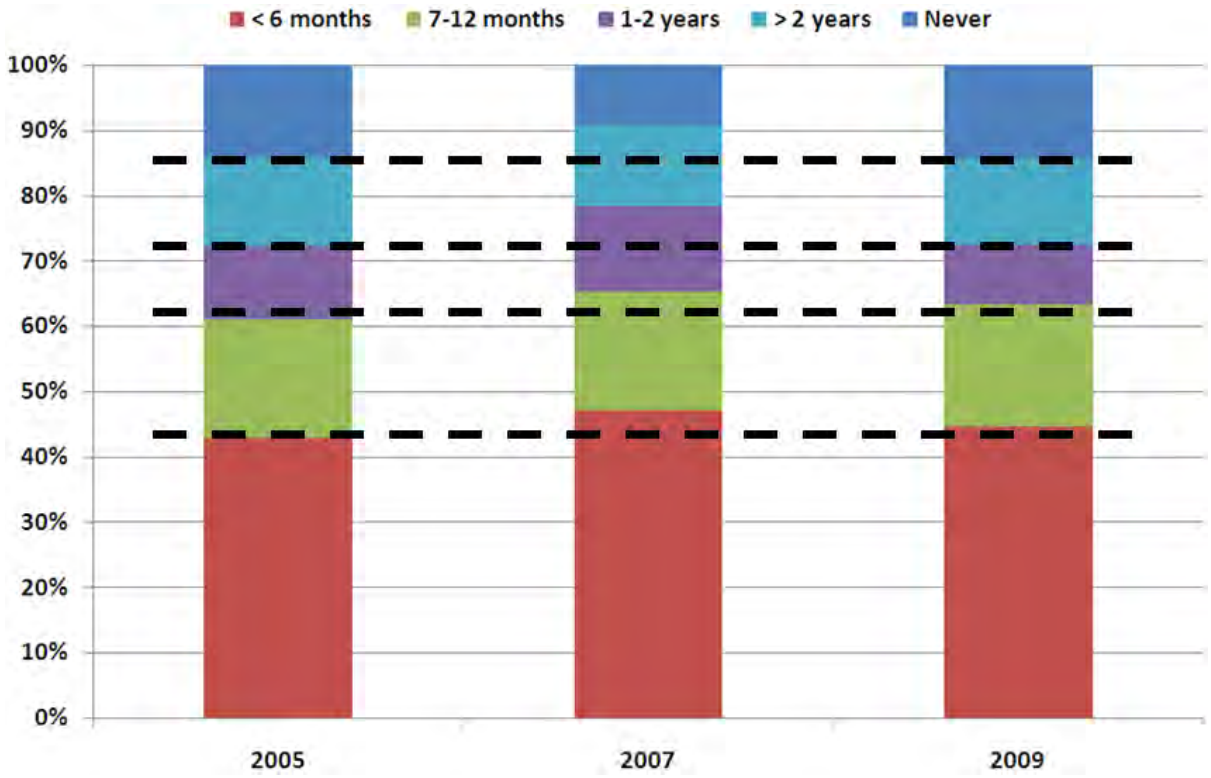


Figure 23: Reported HIV testing rates from the Adelaide Gay Community Periodic Surveys, 2005-2009

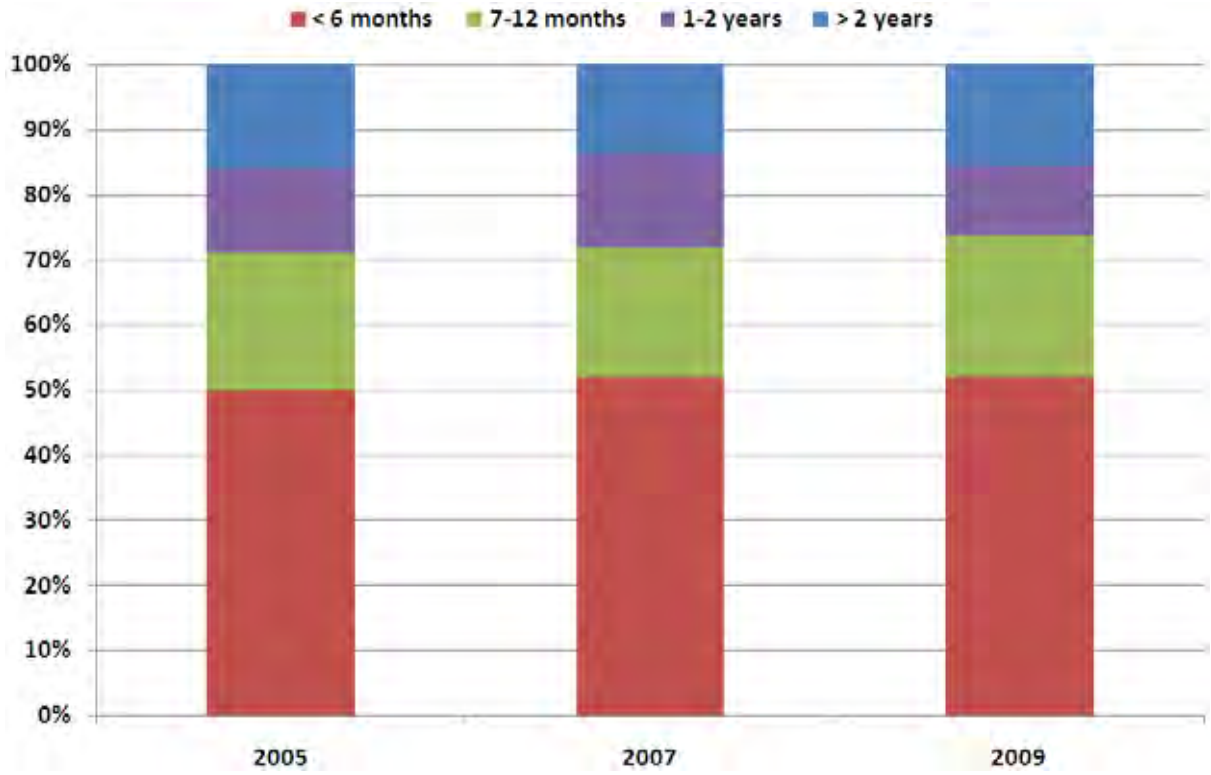


Figure 24: Reported HIV testing rates from the Adelaide Gay Community Periodic Surveys, 2005-2009, excluding men who report never testing for HIV

According to the South Australian HIV model, if the TT123 campaign was not implemented and testing rates continued on the previous trend then there would have been 0.18 (median, 0.14-0.22 IQR) extra HIV infections in the following year. That is, if the intervention was implemented every year for 10 years then approximately 2 infections could be expected to be averted that are directly attributable to TT123.

The influence of testing patterns

Over the last decade there has been a steady increase in the rate of testing for HIV among gay men in South Australia (Figure 21). If the increase in testing over this period had not occurred then, according to the model, an additional 2.87 (median, 0.99-1.81 IQR) HIV infections would have occurred among men who have sex with men in South Australia (Figure 25).

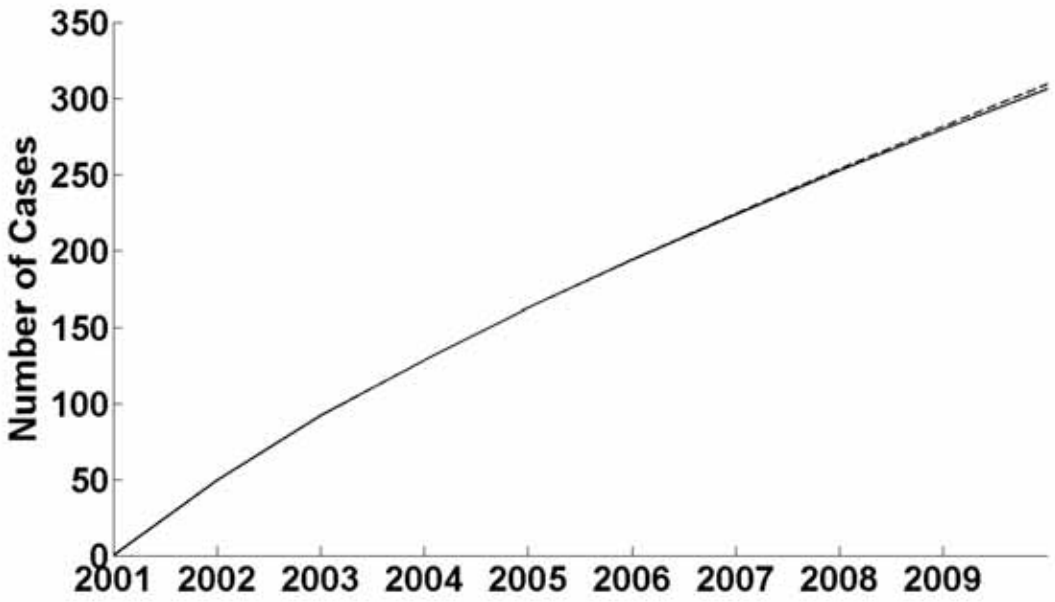


Figure 25: Cumulative number of HIV incident infections among men who have sex with men in South Australia (solid curve) compared with expected cumulative number of incident HIV infections if testing rates had not changed (dashed curve)

Epidemiological impact of changes in behaviour and treatment

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 [31] (Table A.1). Condom use has declined in recent years in South Australia (Figures 18, 19). If the change in condom use over this period had not occurred then, according to the model, there would have been 12.46 (median, 13.48-14.82 IQR) less HIV infections among men who have sex with men in South Australia (Figure 26).

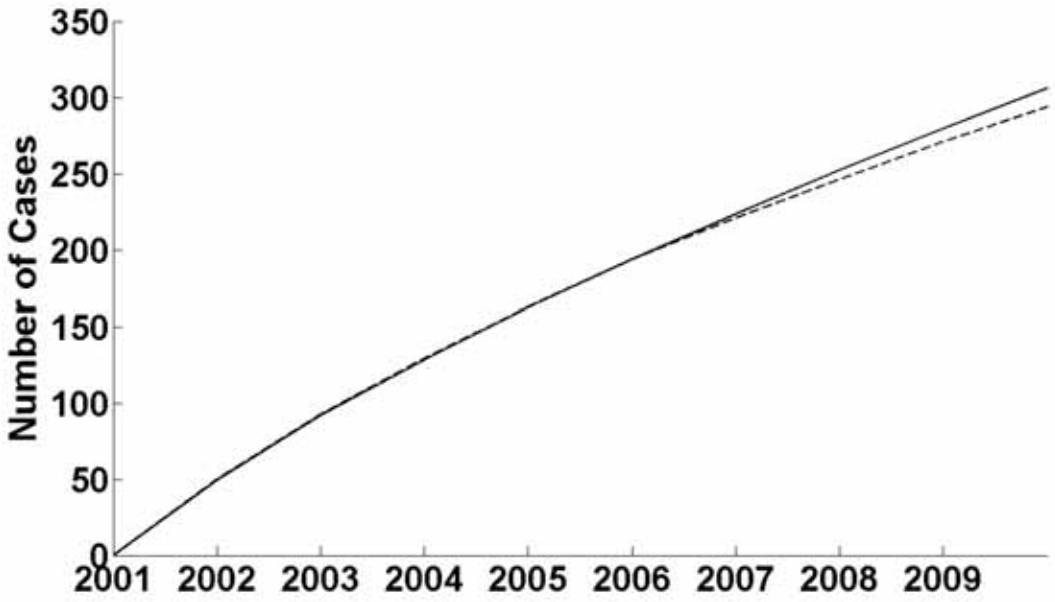


Figure 26: Cumulative number of HIV incident infections among men who have sex with men in South Australia (solid curve) compared with expected cumulative number of incident HIV infections if rates of condom use had not changed (dashed curve)

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. Disclosure of HIV serostatus has been increasing in many settings but has not changed markedly in South Australia (Figure 20). If the change in rates of disclosure of HIV serostatus to casual partners over this period had not occurred then, according to the model, there would have been 0.48 (median, 0.51-0.27 IQR) less HIV infections among men who have sex with men in South Australia (Figure 27).

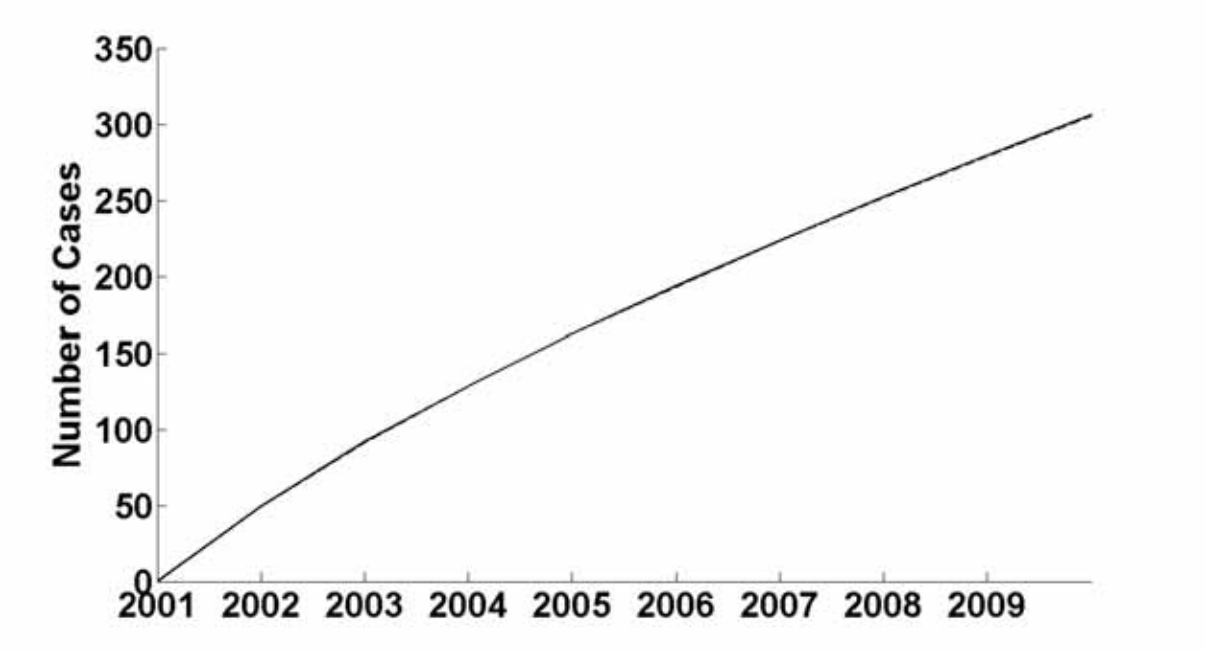


Figure 27: Cumulative number of HIV incident infections among men who have sex with men in South Australia (solid curve) compared with expected cumulative number of incident HIV infections if rates of disclosure of HIV serostatus had not changed (dashed curve)

The influence of the effectiveness of ART

Clinical surveillance data has indicated an increase in the proportion of patients treated with combination antiretroviral therapy (ART) that have undetectable viral load (Table A.1). If the increase in effectiveness of ART over this period had not occurred then, according to the model, an additional 2.20 (median, 2.12-2.40 IQR) HIV infections would have occurred among men who have sex with men in South Australia (Figure 28).

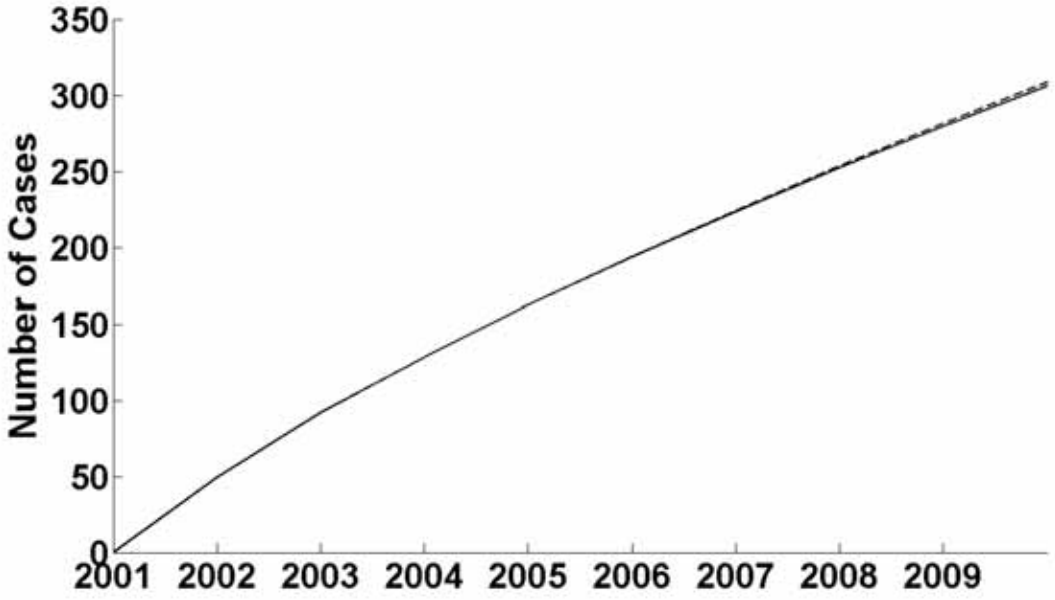


Figure 28: Cumulative number of HIV incident infections among men who have sex with men in South Australia (solid curve) compared with expected cumulative number of incident HIV infections if change in the effectiveness of ART had not changed (dashed curve)

Clean needle program

The evaluation of needle and syringe programs in South Australia is based on the 2009 Return on Investment 2 study [10].

The 'Clean Needle Program' (CNP) in South Australia, operated by the Drug and Alcohol Services, commenced in 1989. Pharmacy programs in South Australia for distributing needles and syringes commenced in the early 1990s. South Australia has 81 CNPs, consisting of one primary outlet, 69 secondary outlets and 11 enhanced secondary outlets. There are over 170 pharmacies that sell needles and syringes on a commercial basis. Primary and secondary outlets are based in metropolitan Adelaide and in rural areas. Some outreach services are also provided. Disposal facilities are provided at all community CNP sites, most pharmacies and some local councils also provide disposal facilities.

Number of CNP sites in South Australia:	81 (plus pharmacies)
Number of syringes distributed 1999-2008 (Figure 29):	31,569,283
Average number of syringes distributed per year:	3,156,928
Total spending 2007/8:	$1,536,115

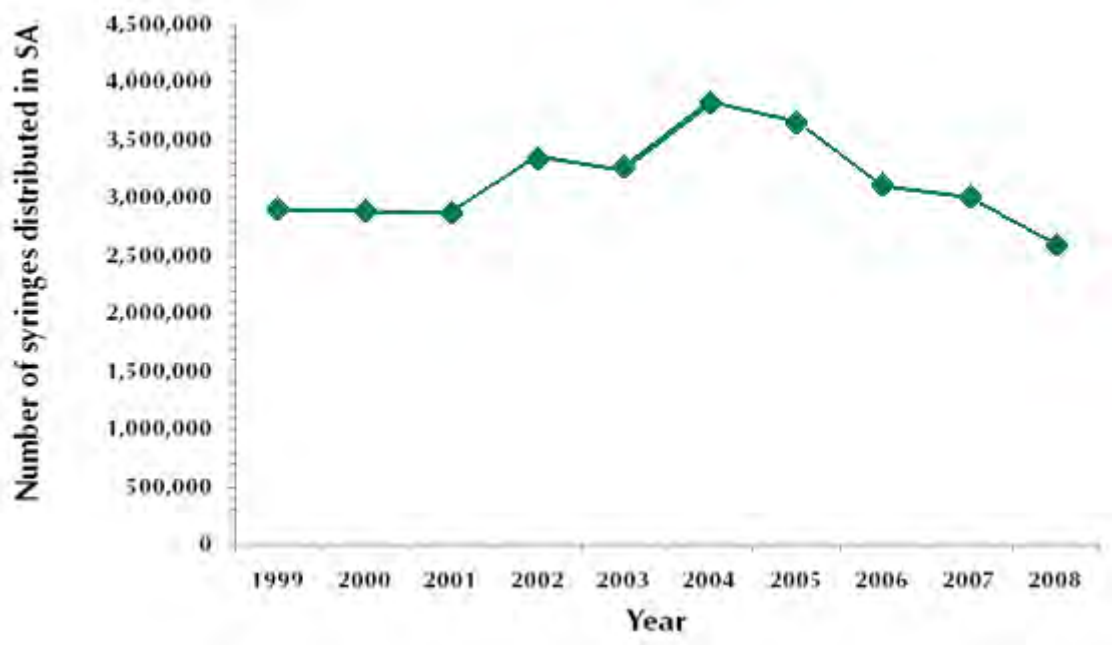


Figure 29: Number of needles and syringes distributed in South Australia (1999-2008)

The proportion of Australian injecting drug users (IDUs) that are in South Australia has remained relatively steady. The number of needles and syringes distributed through CNPs in South Australia increased during 2002-2004 but has started to decline in recent years. The average frequency of injecting by IDUs in South Australia has remained steady but sharing rates have tended to increase slightly.

Despite this, the incidence of HIV has remained relatively low among South Australian IDUs.

In 2007/8, 2,763,030 sterile injection equipment units were provided in South Australia: 20% were distributed through secondary sites with 63% of these through enhanced secondary sites. 241,900 needles and syringes were distributed through pharmacies. Pharmacists charge an average of $5-$10 per five-pack out-of-pocket costs. The number of CNP sites in South Australia is listed in Table 3. Table 4 reports the spending by financial year in 2008 dollars, unadjusted and adjusted for the consumer price index (CPI).

Table 3: Number of CNP sites in South Australia

	Primary	Secondary	Enhanced secondary
2007/8	1	69	11
2006/7	1	67	9
2005/6	1	65	6
2004/5	1	64	6
2003/4	1	66	6
2002/3	1	66	5
2001/2	1	65	5
2000/1	1	63	5

Table 4: Summary of expenditure on CNPs in South Australia (2000/1-2007/8)

	2000/1	2001/2	2002/3	2003/4	2004/5	2005/6	2006/7	2007/8
Consumables ($'000)								
Sterile injecting equipment	494	456	501	504	430	489	405	401
Disposal equipment	253	233	256	109	260	260	274	227
sub-total	747	690	757	613	690	749	679	629
CNP SUPPORT ($'000)								
Primary CNPs Operations	182	216	215	215	215	215	215	215
Support for Secondary CNPs	147	309	370	322	388	661	386	637
sub-total	329	526	585	537	603	877	601	853
TOTAL ($'000) (unadjusted for CPI)	1,077	1,216	1,342	1,150	1,294	1,625	1,280	1,482
TOTAL in 2008 ($'000) (CPI adjusted)	1,361	1,490	1,597	1,337	1,466	1,792	1,367	1,536

Evaluating CNPs over the period 1999-2009

The ROI mathematical epidemiological transmission model was applied to IDUs and CNPs specifically in South Australia. The model was used to evaluate current CNPs versus no program and to project likely epidemiological impacts of potential changes to the program. The model estimated the expected number of HIV cases in South Australia with and without CNP distribution of sterile injecting equipment (Figure 30). The estimated number of infections averted is presented in Figure 31. An estimated 122 (89-175, IQR) HIV infections were averted due to CNPs in South Australia over the decade, 1999-2009.

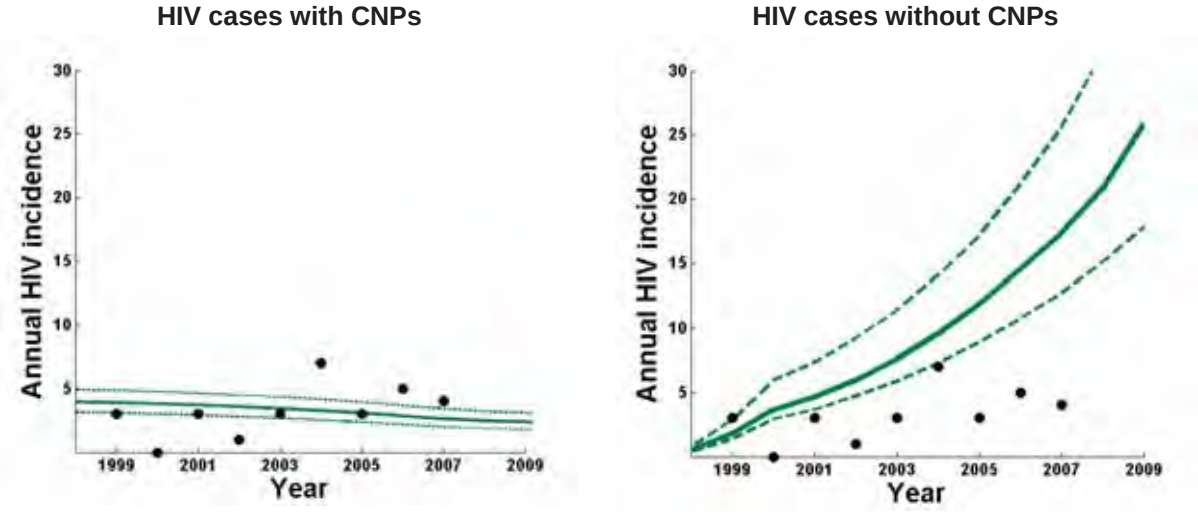


Figure 30: Estimated HIV incidence in South Australia with and without CNPs

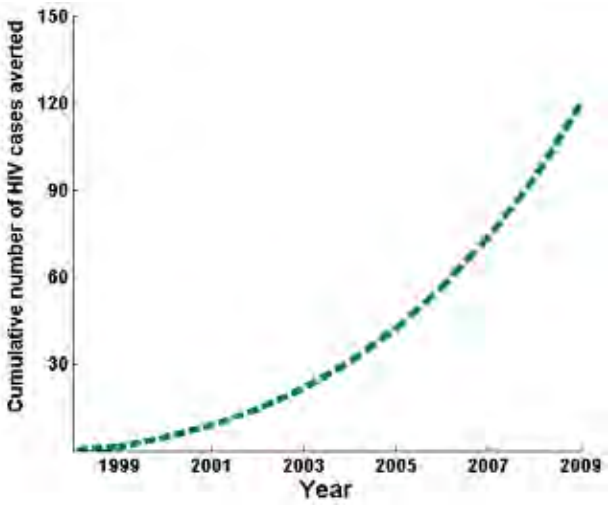


Figure 31: Estimated cumulative number of HIV cases averted in South Australia due to CNPs

Epidemic projections in South Australia

The South Australian model was used to project the expected number of HIV cases in the future among IDUs, according to scenarios whereby current syringe distribution levels are maintained or if there are increases or decreases in the provision of syringes through South Australian CNPs. It was forecasted that few HIV transmissions were likely to occur through exposure to contaminated injecting equipment; however, if there are significant decreases in CNP provision of sterile injecting equipment then an HIV epidemic is likely to emerge (Figure 32)

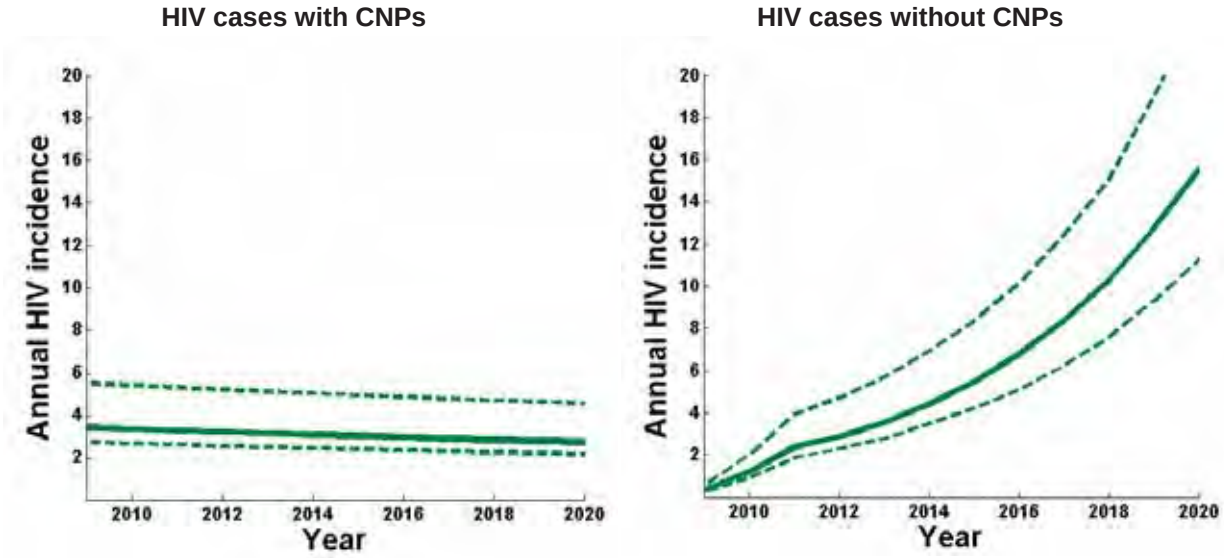


Figure 32: Projections of the expected number of HIV cases in South Australia according to current syringe distribution or no CNPs

Economic evaluation of CNPs in South Australia

The spending of $15m in the funding of CNPs in South Australia from year 2000-2009 has resulted in a saving of $93m in healthcare costs, with more than 15,000 Disability Adjusted Life Years saved with a net financial saving of $80m. However, these savings are attributable not only to HIV infection but also hepatitis C virus

infections averted. A summary of the return on investment of CNP funding in South Australia is shown in Table 5. The mathematical and economic modelling estimated that if CNPs are continued at the same level of funding in SA for the next ten years, $295m of net financial savings will accrue ($258m discounted at 3%) and for twenty years $605m ($458m discounted at 3%). The lifetime net present value of investment in CNPs that took account of all healthcare costs and savings (but not costs associated with productivity losses) would be $3.85bn ($1.26bn discounted at 3%).

Table 5: Return on Investment of CNP funding in South Australia (2000-2009)

	2000	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**
Healthcare costs saved $m (IQR)	11 (10-13)	11 (10-14)	10 (9-13)	9 (8-12)	9 (8-11)	9 (7-11)	8 (7-10)	8 (7-10)	9 (7-10)	9 (8-11)
CNP funding $m (median)	1	1	2	1	1	2	1	2	2	2
Net cost savings $m (median)	10	9	9	8	8	7	7	7	7	8
DALY gain (median)	1,369	1,573	1,643	1,641	1,611	1,560	1,493	1,427	1,387	1,382

Projecting future HIV trends in South Australia

Status quo

The long-term vision of the South Australian HIV Action Plan [2] is to minimise the transmission of HIV in South Australia. Mathematical modelling projections of the expected epidemic trends according to different conditions can inform appropriate public health responses to achieve this aim. The model was used to project the future epidemic course according to the status quo, that is, if current behavioural and testing and clinical practices remain unchanged (Figure 33). The model projects suggest that South Australia is likely past the peak of infection and incidence should decline moderately from about 30 cases per year to about 24 cases per year by 2015 if conditions do not change. It is estimated that the cumulative number of HIV infections, 2010-2015, would be 124.76 (median, 116.78-131.68 IQR).

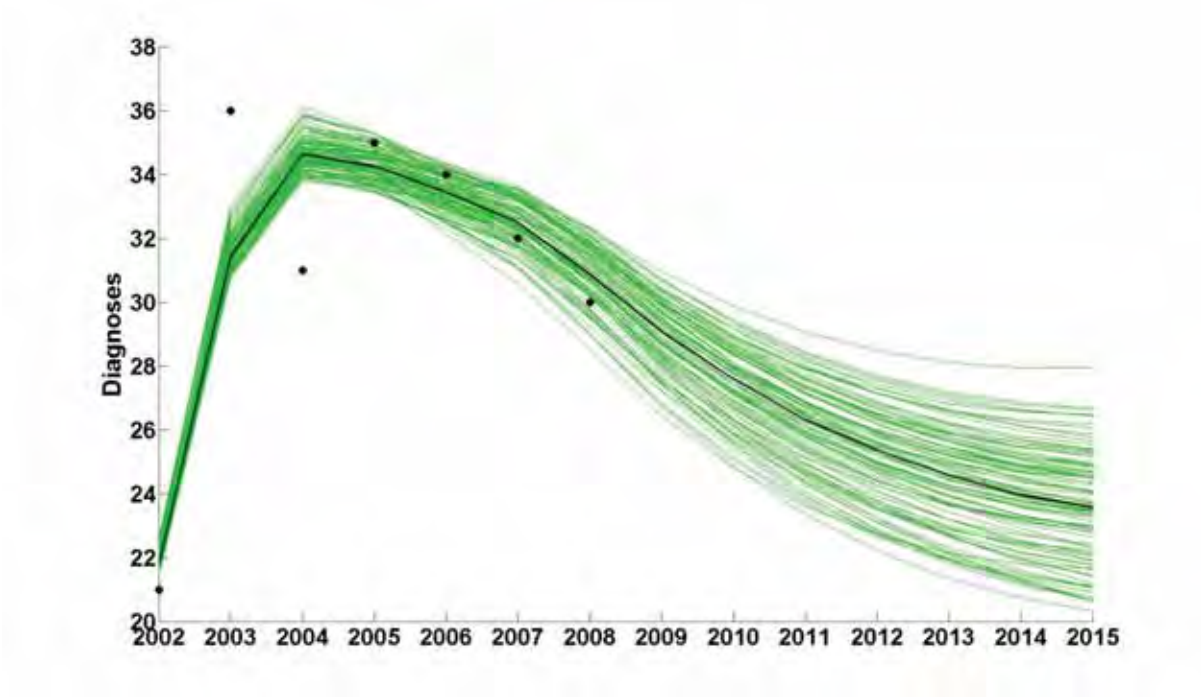


Figure 33: Projections of the expected number of HIV diagnoses among MSM in South Australia to 2015 according to current conditions

The South Australian HIV mathematical model was also used to forecast the expected number of HIV cases according to changes in behavioural conditions or effective implementation of interventions.

Behaviour change

Partner acquisition

Rates of partner acquisition have remained relatively stable and it is probably unlikely that they will change substantially. But even small changes in partner numbers could have a noticeable impact on epidemic trends [30]. Engagement with focus groups of gay men in other Australian jurisdictions and with stakeholders in the HIV sector have suggested that it is highly unlikely that gay men will change their number of sexual partners, however, they may consider a change for a short period of time if it would benefit the rest of the community [29]. The impact of an intervention that results in halving the number of sexual partners for a period of one year before resorting back to prior behaviour was simulated (Figure 34). It is estimated that the cumulative number of HIV infections, 2010-2015, would be 122.13 (median, 113.78-127.99 IQR); that is, a median reduction of 2.63 infections compared to the status quo.

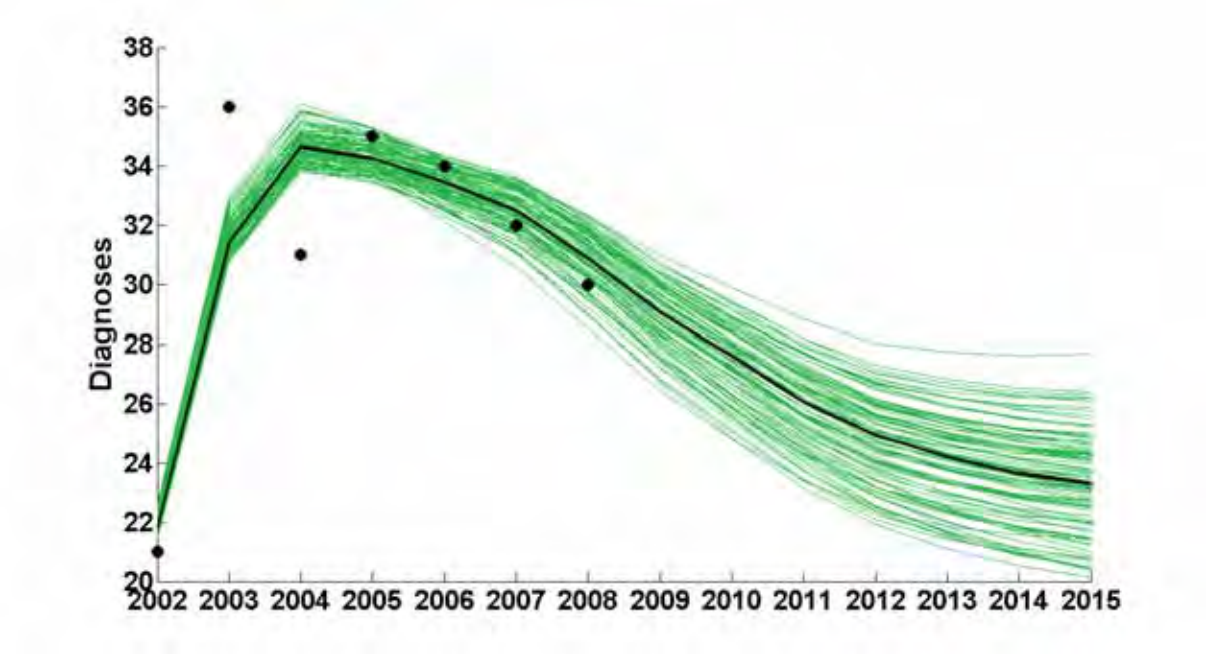


Figure 34: Projections of the expected number of HIV diagnoses among MSM in South Australia to 2015 according to a short-term (1 year, 2010) intervention involving halving the number of sexual partners

Condom use

Rates of condom use have been declining in South Australia and have likely contributed to higher rates of HIV infection (Figure 26). If the current trends continue then HIV diagnoses will undoubtedly be higher. Similar to partner numbers, MSM are unlikely to increase condom use in the modern era of HIV unless it was for a relatively short time and if it would benefit the rest of the community [29]. The impact of an intervention that results in increasing condom use to 100% with all casual partners for a period of one year before resorting back to prior behaviour was simulated (Figure 35). It is estimated that the cumulative number of HIV infections, 2010-2015, would be 120.92 (median, 112.17-126.92 IQR); that is, a median reduction of 3.84 infections compared to the status quo.

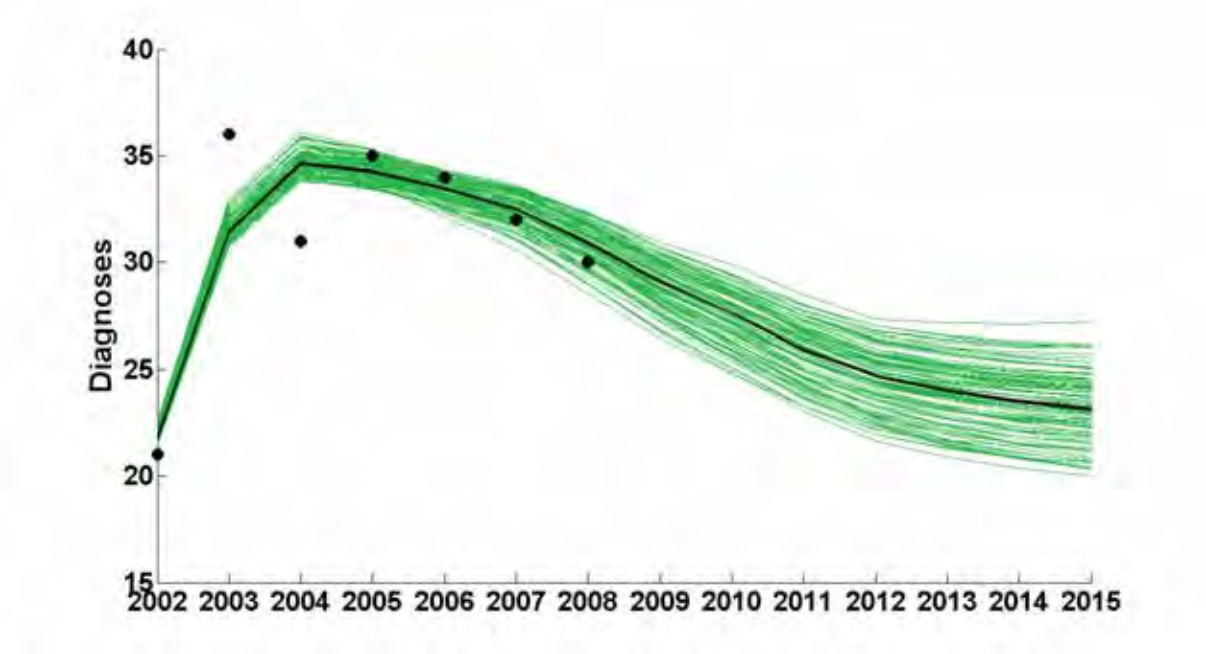


Figure 35: Projections of the expected number of HIV diagnoses among MSM in South Australia to 2015 according to a short-term (1 year, 2010) intervention involving universal condom use with casual sexual partners

Test and treat

Increasing HIV testing rates

One of the cornerstones of effective prevention programs is the promotion of HIV testing. Newly-infected people have higher viral loads (for about 3-6 months [78-80]) than at any other time during the course of infection and consequently have the greatest infectiousness per sexual encounter [72, 81]. Newly-infected people are generally unaware of their new serostatus and their potential to cause secondary HIV transmissions. Detecting newly-infected people generally only occurs if there are high rates of testing for HIV (in terms of coverage, i.e., the proportion of people who are tested, and the frequency of testing, i.e., number of times people are tested per year). High testing rates can also have additional epidemiological benefits. One benefit is that individuals who are diagnosed as HIV-positive typically change their behaviour in order to reduce onward transmission to others. Although some individuals may increase sexual activity and/or the acquisition of new sexual partners, most individuals diagnosed with HIV significantly decrease sexual partner acquisition by as much as 50% on average [57-65]. Frequent testing also benefits effectiveness of risk reduction strategies such as serosorting, strategic positioning and negotiated safety as well as facilitates the initiation of antiretroviral treatment for HIV-infected people detected with their infection.

Priority Action Area 2 of the South Australian HIV Action Plan is on HIV testing [2]. HIV testing is critical for the prevention of HIV and to ensure that care and early treatment is provided to people with HIV. The objective of this action area is to increase the uptake of HIV testing.

Approximately 60-65% of MSM that are socially engaged with the gay community report receiving an HIV tested within the last 12 months. The impact of an intervention that results in increasing HIV testing rates among socially engaged gay men to 80% testing each year was simulated (Figure 36). It is estimated that the cumulative number of HIV infections, 2010-2015, would be 123.59 (median, 116.04-130.05 IQR); that is, a median reduction of 1.17 infections compared to the status quo. If 70% or 80% of all men who have sex with men receive an annual test for HIV then the cumulative number of HIV infections, 2010-2015, would be 124.04 (median, 118.62-128.58 IQR) or 122.90 (median, 118.38-127.53 IQR) respective; that is, median reductions of 0.72 and 1.86 infections compared to the status quo (Figures 37 and 38).

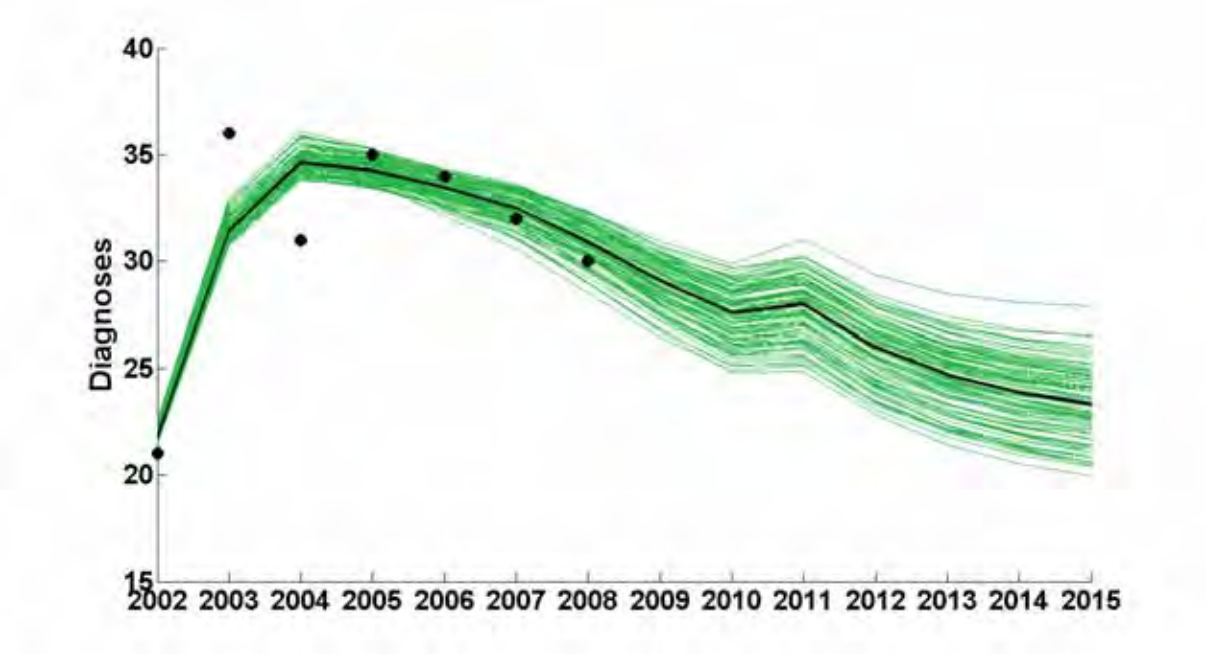


Figure 36: Projections of the expected number of HIV diagnoses among MSM in South Australia to 2015 according to increases in HIV testing rates such that 80% of socially engaged MSM receive a test each year

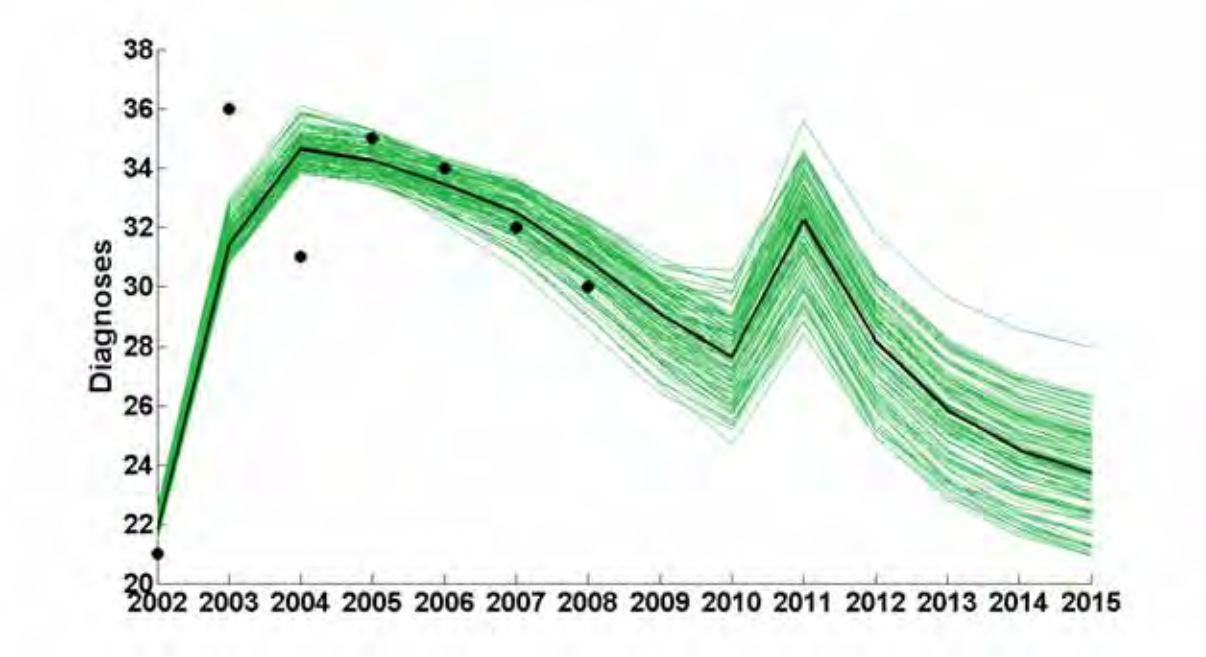


Figure 37: Projections of the expected number of HIV diagnoses among MSM in South Australia to 2015 according to increases in HIV testing rates such that 70% of all MSM receive a test each year

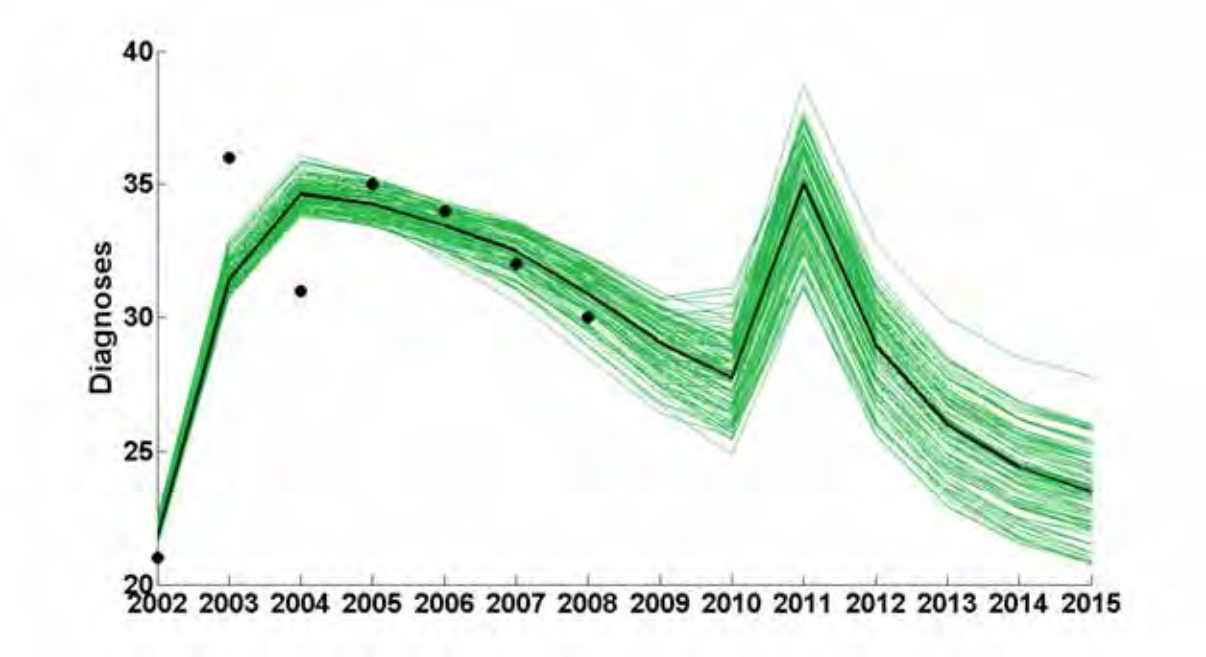


Figure 38: Projections of the expected number of HIV diagnoses among MSM in South Australia to 2015 according to increases in HIV testing rates such that 80% of all MSM receive a test each year

If an intervention targeted frequency rather than coverage of testing then the epidemiological impact would be modest but there would be an incremental benefit. The impact of interventions that result in 70% of MSM who are socially engaged with the gay community or 70% of all MSM testing twice per year was simulated (Figure 39, 40). It is estimated that the cumulative number of HIV infections, 2010-2015, would be 120.23 (median, 112.90-124.87 IQR) and 119.99 (median, 116.59-124.31 IQR) respectively; that is, median reductions of 4.53 and 4.77 infections compared to the status quo.

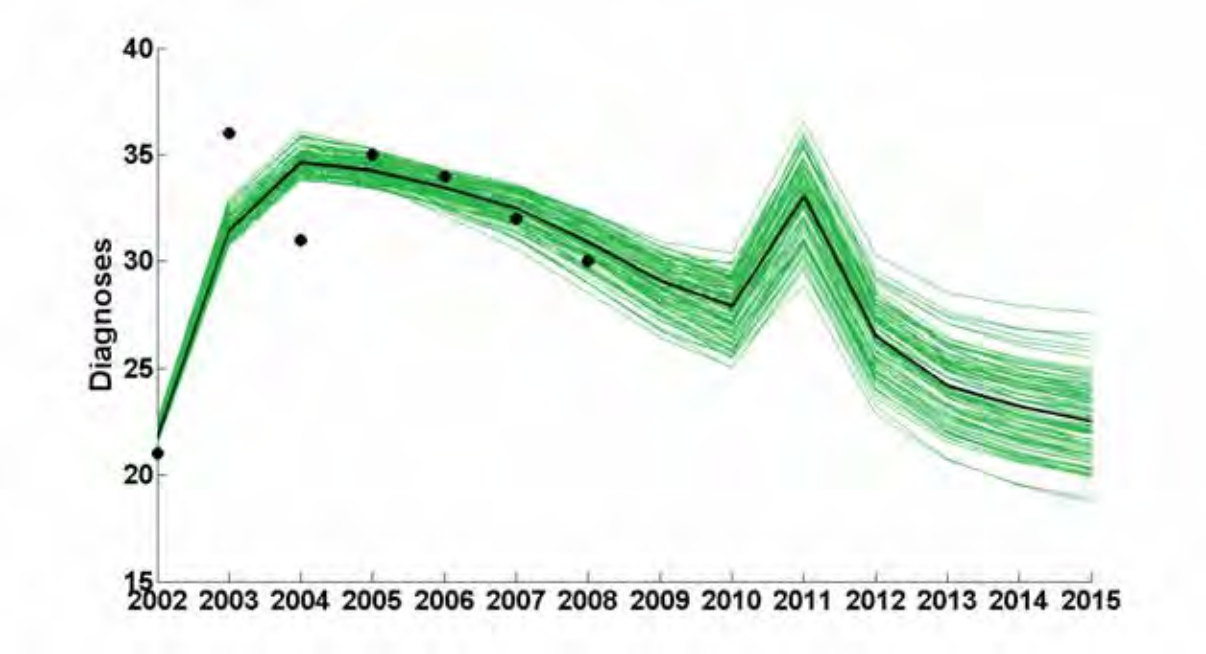


Figure 39: Projections of the expected number of HIV diagnoses among MSM in South Australia to 2015 according to increases in HIV testing rates such that 70% of socially engaged MSM receive two tests each year

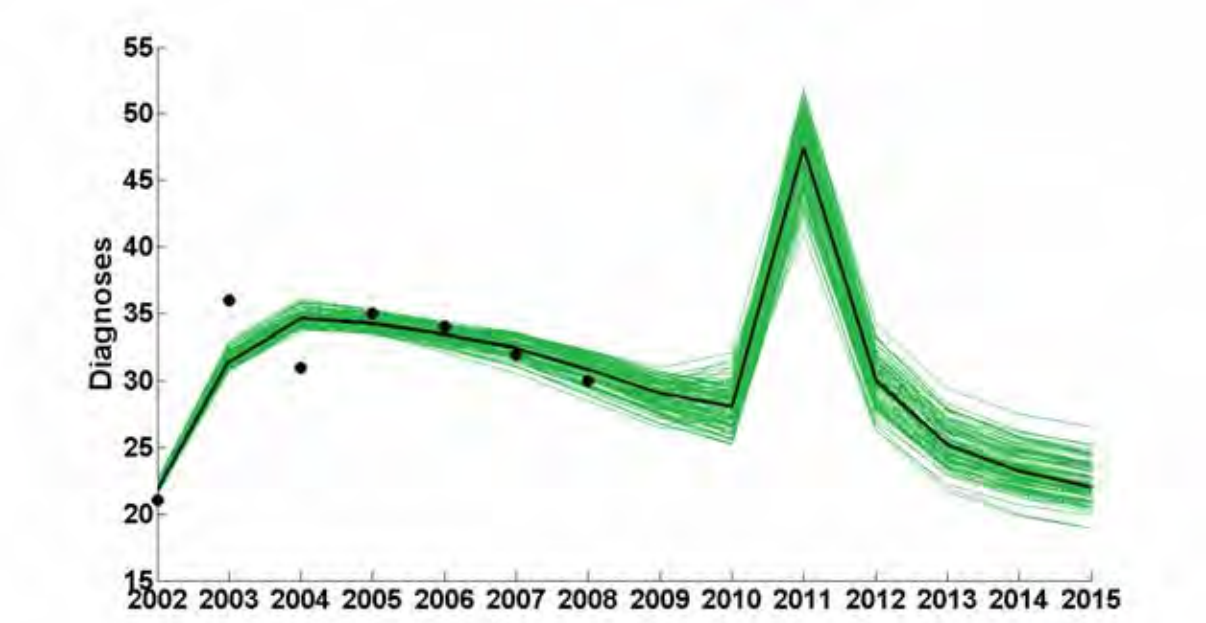


Figure 40: Projections of the expected number of HIV diagnoses among MSM in South Australia to 2015 according to increases in HIV testing rates such that 70% of all MSM receive two tests each year

Testing rates in South Australia are already relatively high. Although the health care system and infrastructure is well-equipped to conduct screening for HIV, increasing rates may not be very acceptable to most gay men. But greater efforts may be required to reach individuals who are not regularly tested for HIV or who are at higher risk, and this may include extending hours of operation of sexual health clinics

or providing alternative testing facilities. Persons who have higher HIV risk exposure tend to test more frequently [82] but there may be a saturation level to the frequency of testing that is attainable. It is also important to increase the uptake of testing among other priority populations including Aboriginal people and priority CALD populations.

Rapid tests

One way for facilitating an increase in HIV testing could be utilising rapid testing technologies. A concern around use of rapid tests in Australia is that they are associated with a longer window period compared with standard EIA tests and so they may not detect a number of infections that would otherwise be detected. A benefit of rapid testing is that the individual will receive their test result on the same day which will allay fears of uncertainty associated with waiting times (of days or weeks) between testing and receiving results for EIA tests. Another benefit is that extra days of known HIV positivity, especially if in acute infection where there is greater infectiousness, may lead to slightly greater duration of preventing secondary transmissions. Detailed distribution data from the Melbourne Sexual Health Centre on testing frequency and time between testing and receiving test results, along with data on the window period was used in a mathematical model to evaluate rapid tests compared to standard EIA tests. By accounting for testing frequencies and window periods, it was calculated that for approximately 95% (94.81%) of HIV-positive cases diagnosis would occur at the next test for all diagnostic tests and in 5.19% of cases the window period would result in a delay in diagnosis until the second HIV test for rapid tests (Figure 41). However, when adjusting for all cases on average rapid tests would reduce the number of days until diagnosis by 11.40 days (median, 7.06-16.89 IQR) compared to the fourth generation EIA test.

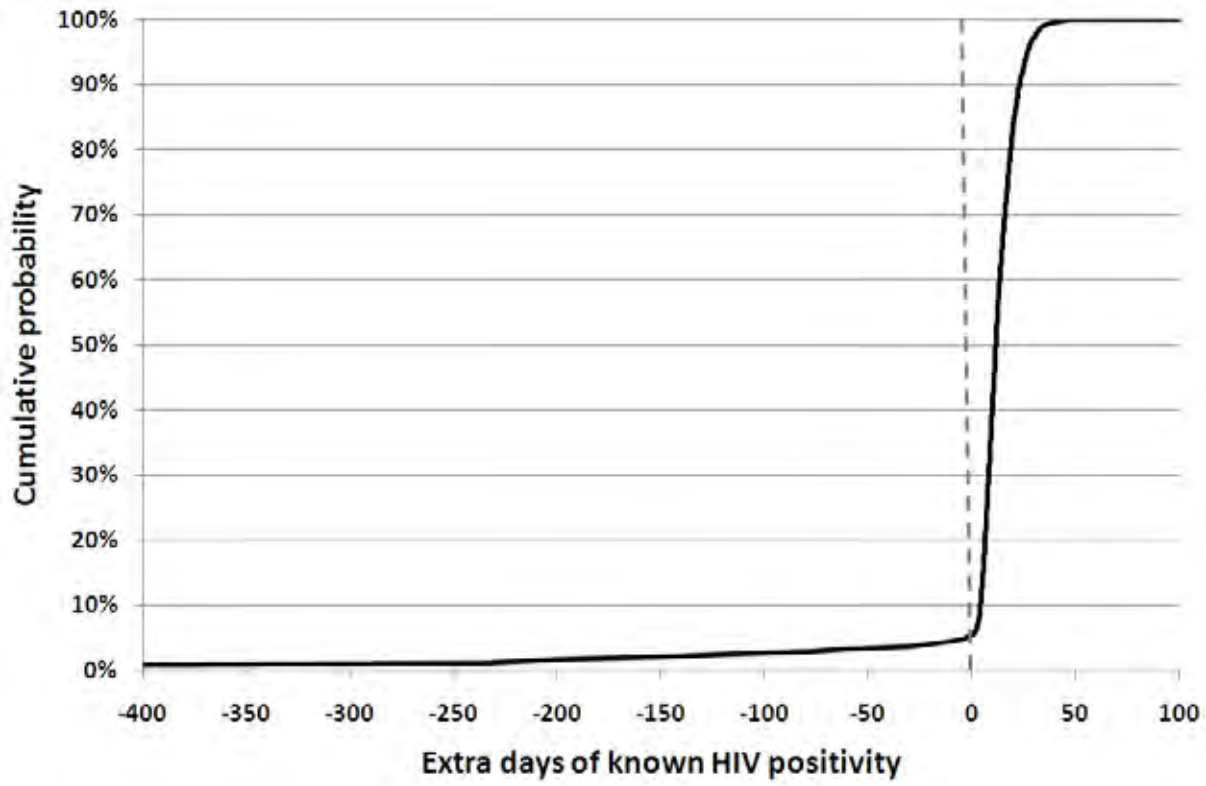


Figure 41: Model generated results from simulation of 100,000 gay men of the expected distribution of the number of days of known HIV positivity due to use of a standard rapid test compared to use of the 4th generation EIA test

Increasing treatment rates

The introduction of combination antiretroviral therapies (ART) has had a positive impact for many people living with HIV/AIDS, including increasing life expectancy and quality of life. Priority Action Area 3 of the South Australian HIV Action Plan is on treatment, care and support of people living with HIV [2]. It emphasises the importance to increase the appropriate uptake of ART. One barrier to be overcome is removing financial constraints. A cost-effectiveness analysis of removing copayments associated with ART for treatment-eligible HIV-infected South Australians is presented in Appendix B.

Recently there has been considerable discussion in the international HIV/AIDS community around using ART for prevention. Interest around the potential role of ART as a measure to reduce sexual transmission of HIV at the population level was stimulated by a World Health Organisation research group which reported results of a model showing that universal annual HIV testing with immediate ART of all those diagnosed (known as “test and treat”) could substantially reduce, or even eradicate, severe generalised heterosexual HIV epidemics [83]. Although eradication has been challenged (e.g. [84]), the strategy should lead to reduced HIV incidence because effective ART reduces average viral load levels in populations and thus also reducing infectiousness. Very recently, large financial investment has been

committed to implementing “test and treat” or “seek and treat” in British Columbia, Vancouver and this strategy is also being considered in other regions. Therefore, the expected epidemiological impact of implementing versions of this strategy in South Australia was investigated.

It is likely to be more feasible to seek after and recruit men who are attached to the gay community than those who are not socially engaged to the gay community. Thus, interventions targeting socially engaged MSM compared with targeting all MSM were explored. The expected impact of an intervention that results in 70% testing rates among socially engaged MSM and all HIV-diagnosed MSM receiving antiretroviral therapies is shown in Figure 42. It is estimated that the cumulative number of HIV infections, 2010-2015, would be 51.01 (median, 46.82-54.42 IQR); that is, a median reduction of 73.74 infections compared to the status quo.

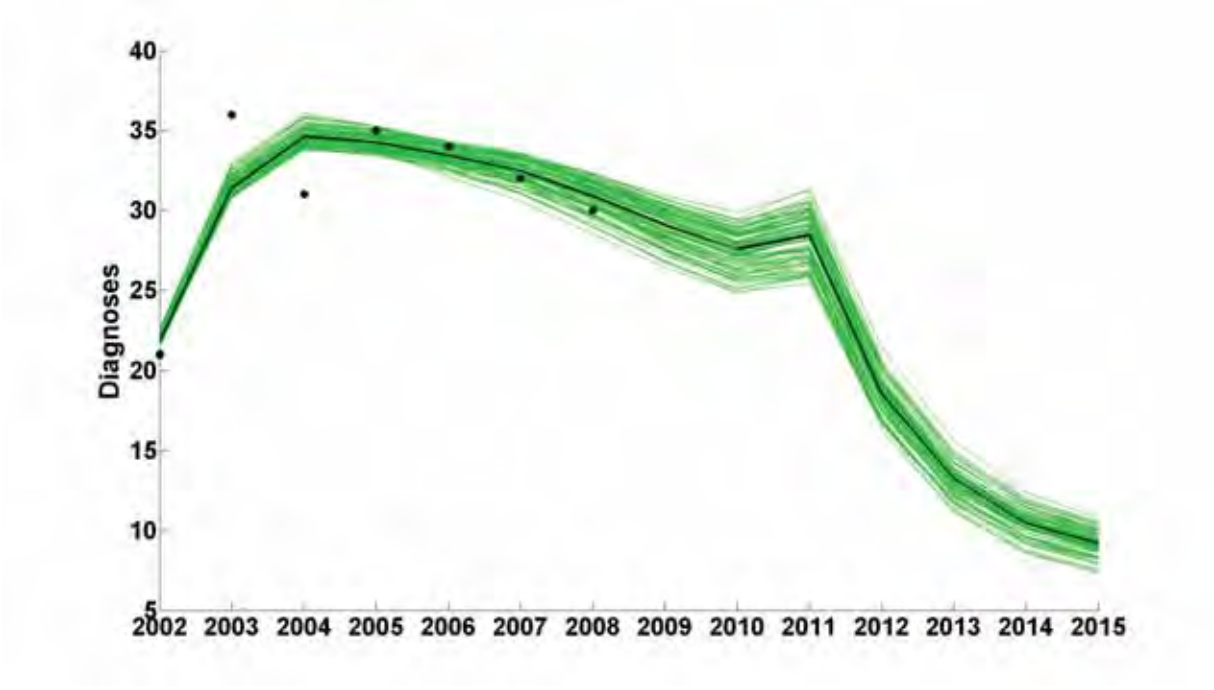


Figure 42: Projections of the expected number of HIV diagnoses among MSM in South Australia to 2015 according to 70% testing rates among socially engaged MSM and all HIV-diagnosed MSM receiving ART

If not just socially engaged MSM but all MSM are targeted with ‘test and treat’ such that 70% are tested at least once per year and all diagnosed people receive ART regardless of their CD4 count then the estimated cumulative number of HIV infections, 2010-2015, would be 48.52 (median, 44.30-48.66 IQR); that is, a median reduction of 76.24 infections compared to the status quo (Figure 43).

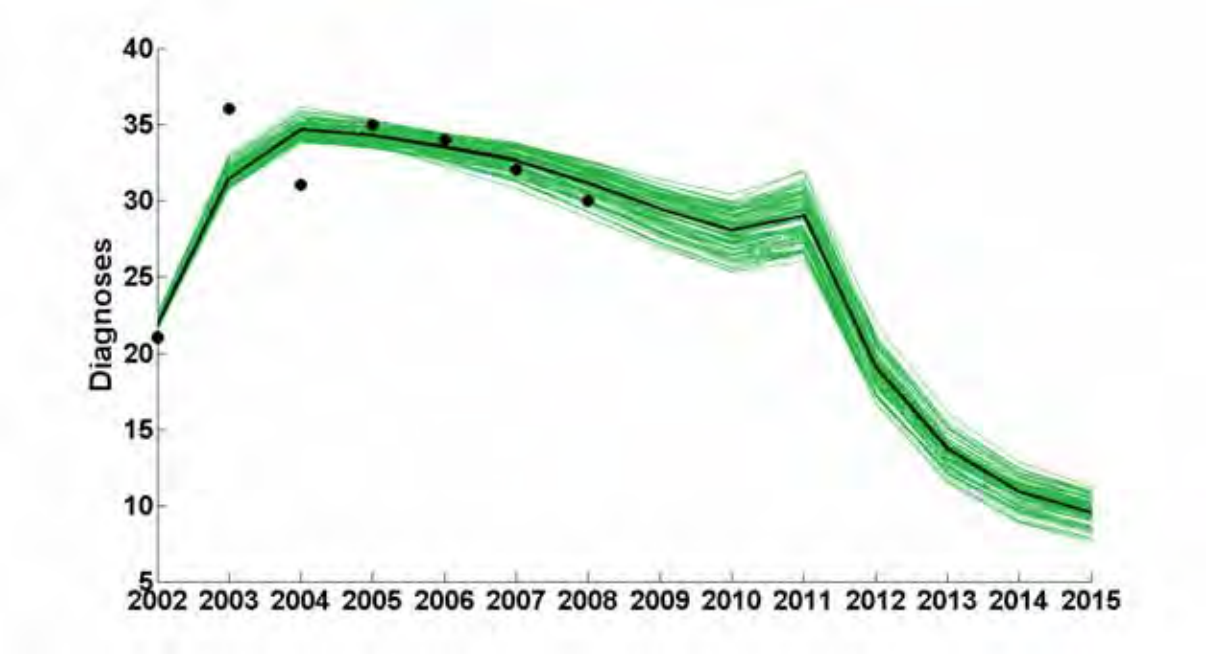


Figure 43: Projections of the expected number of HIV diagnoses among MSM in South Australia to 2015 according to 70% testing rates among all MSM and all HIV-diagnosed MSM receiving ART

The impact of 'test and treat' interventions that test 70% of all MSM twice per year and provide ART for all diagnosed individuals was simulated (Figure 44). It is estimated that the cumulative number of HIV infections, 2010-2015, would be 39.41 (median, 37.30-39.83 IQR); that is, a median reduction of 85.35 infections compared to the status quo.

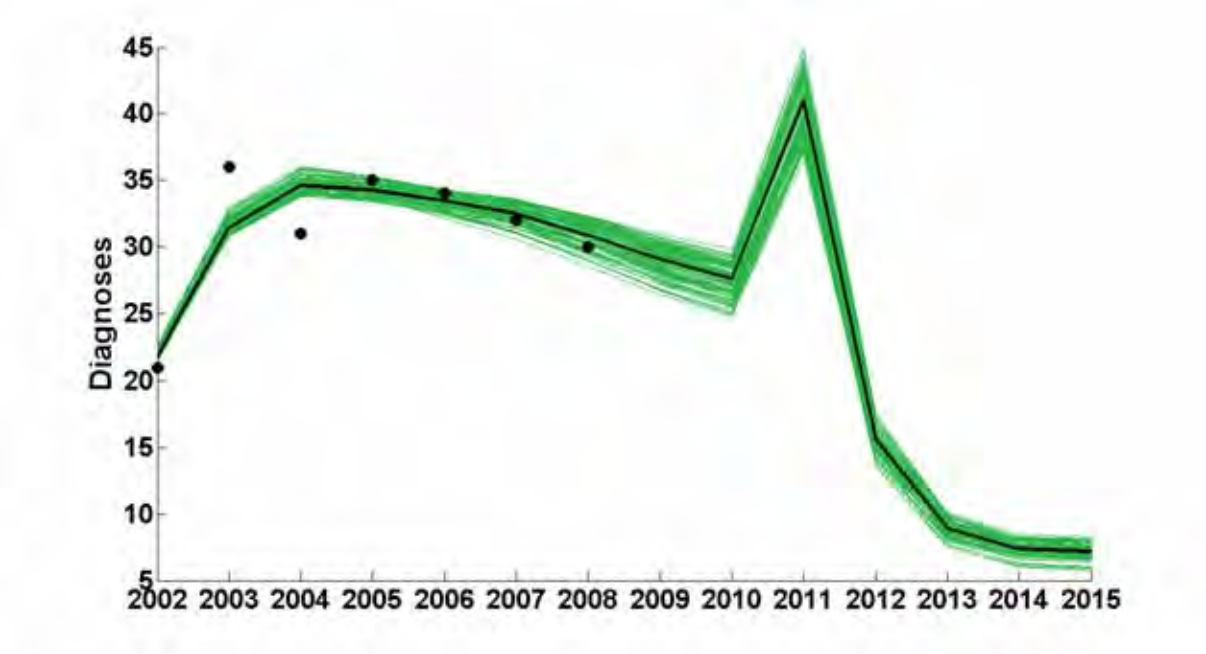


Figure 44: Projections of the expected number of HIV diagnoses among MSM in South Australia to 2015 according to 70% of all MSM testing twice per year and all HIV-diagnosed MSM receiving ART

Currently, HIV-infected individuals in Australia are eligible for antiretroviral therapies under the s100 scheme if their CD4 count is less than 500 cells per µl. Therefore, 'test and treat' interventions were investigated in which all HIV-infected men with CD4 counts less than 500 cells per µl initiated antiretroviral treatments but not if their CD4 counts were greater than 500 cells per µl. If 70% of socially engaged MSM test for HIV each year and all diagnosed men with CD4 counts less than 500 cells per µl initiate ART then the estimated median cumulative number of HIV infections, 2010-2015, would be 91.26; that is, a median reduction of 33.50 infections compared to the status quo (Figure 45). If 70% of all MSM test for HIV once or twice per year and diagnosed men initiate ART then the estimated median cumulative number of HIV infections, 2010-2015, would be 90.92 and 86.32 respective; that is, reductions of 33.84 and 38.44 infections compared to the status quo (Figure 46, 47)

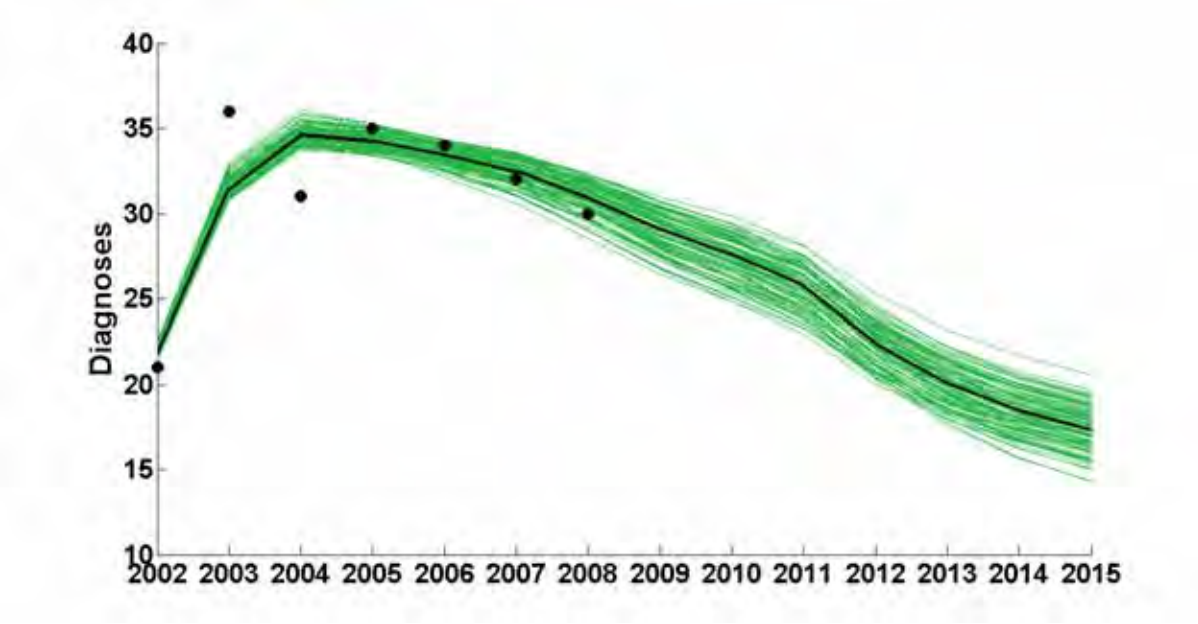


Figure 45: Projections of the expected number of HIV diagnoses among MSM in South Australia to 2015 according to 70% of socially engaged MSM testing for HIV each year and all HIV-diagnosed MSM with CD4 count less than 500 cells per µl receiving ART

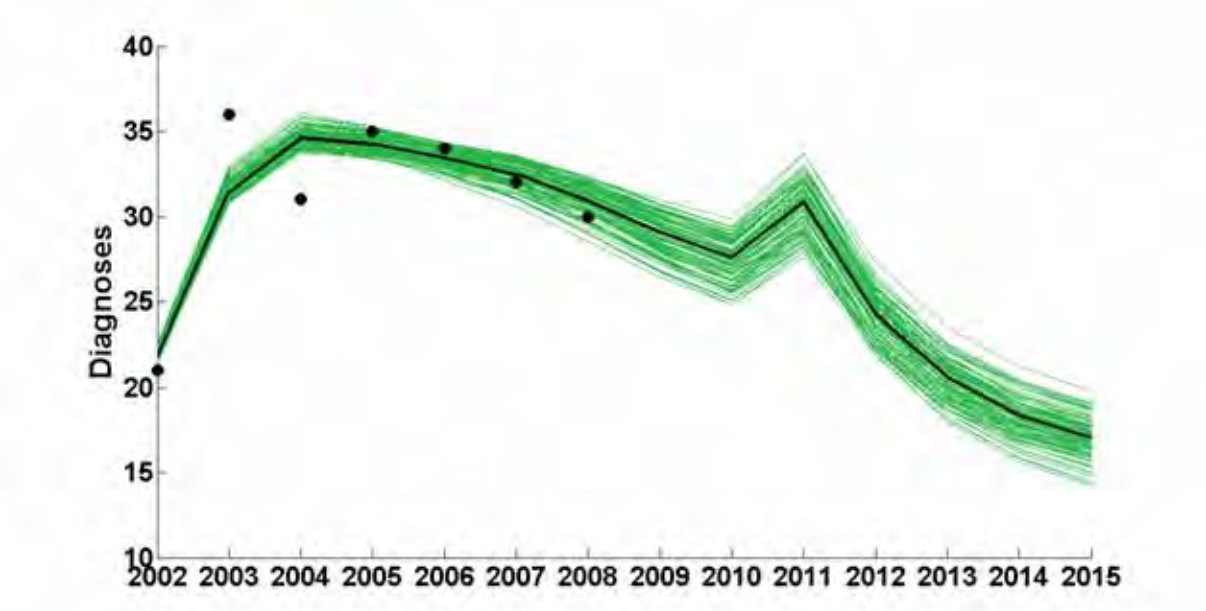


Figure 46: Projections of the expected number of HIV diagnoses among MSM in South Australia to 2015 according to 70% of MSM testing for HIV each year and all HIV-diagnosed MSM with CD4 count less than 500 cells per µl receiving ART

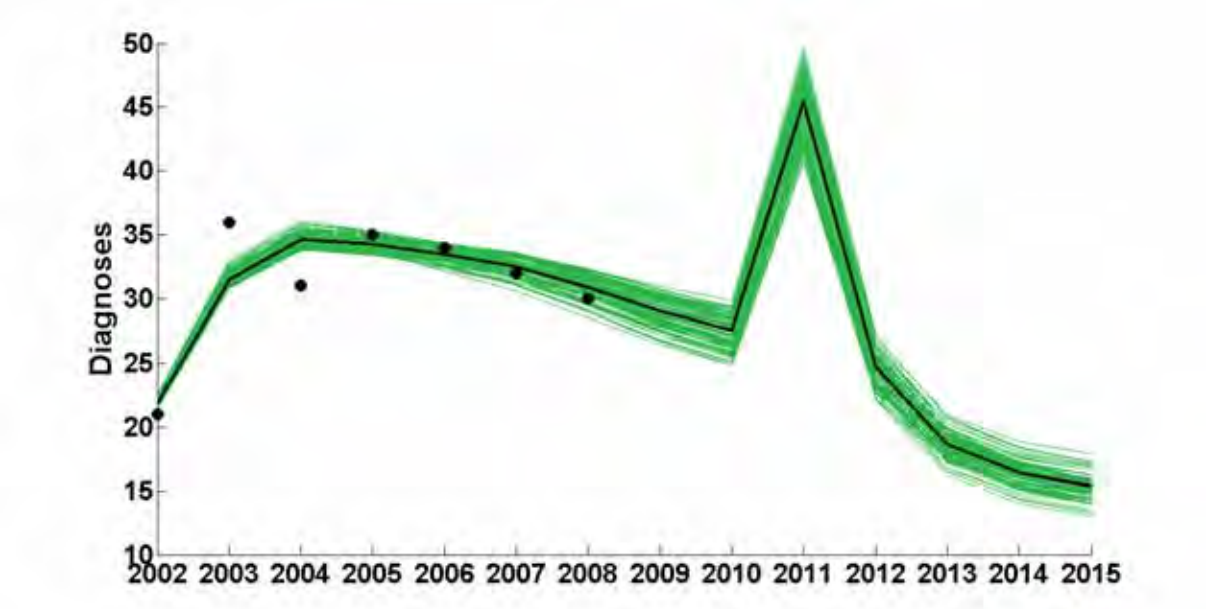


Figure 47: Projections of the expected number of HIV diagnoses among MSM in South Australia to 2015 according to 70% of MSM testing for HIV twice per year and all HIV-diagnosed MSM with CD4 count less than 500 cells per µl receiving ART

Comparison of interventions

A comparison of expected numbers of infections averted is shown in Figure 48.

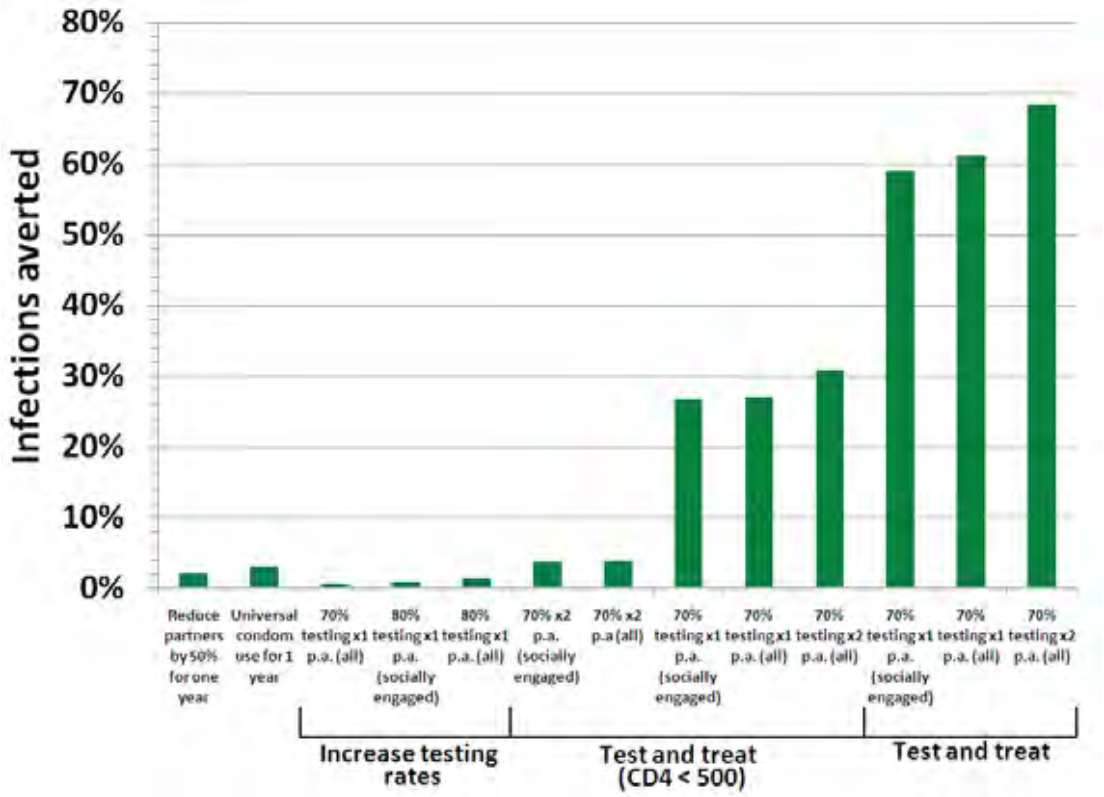


Figure 48: Expected number of HIV infections averted among MSM in South Australia, 2010-2015, according to a number of interventions

Other biomedical interventions

PrEP

Pre-exposure prophylaxis (PrEP) with antiretroviral drugs is a proposed strategy for reducing the risk of HIV transmission between discordant sexual partners. Animal studies have demonstrated encouraging results (e.g. [85-89]) but so far only one phase II human trial of PrEP has released (inconclusive) findings [90] after stopping early due to concerns about study design [91]. Other clinical trials of PrEP are currently being conducted or in planning stages for populations of heterosexuals or gay men, with results expected to be released progressively over the next few years [92]. If found to be efficacious in humans PrEP would be an additional option to barrier protection for those who are at risk of HIV acquisition. In preparation for public health decision-making if and when a PrEP candidate passes clinical testing, it is important to determine thresholds of PrEP usage, efficacy, and reduction in condom use that will render PrEP beneficial or detrimental for individuals and populations of gay men.

There are concerns that the introduction and use of PrEP may lead people to feel protected against HIV and therefore less likely to use condoms; this could result in Replacing condoms with PrEP [93] could lead to less protection against HIV transmission if the efficacy of PrEP is substantially less than the high efficacy of condoms and in settings where condom use is currently high [94]. A mathematical model was used to determine thresholds for the relative effectiveness of PrEP for

gay men in Australia. In Figure 49 it is demonstrated that any risk disinhibition (swapping condoms for 70% effective PrEP) will have a more noticeable impact for men who currently use condoms in a higher proportion of sexual acts. If there is little risk disinhibition and high usage then PrEP can result in significant decreases in risk (Figure 49).

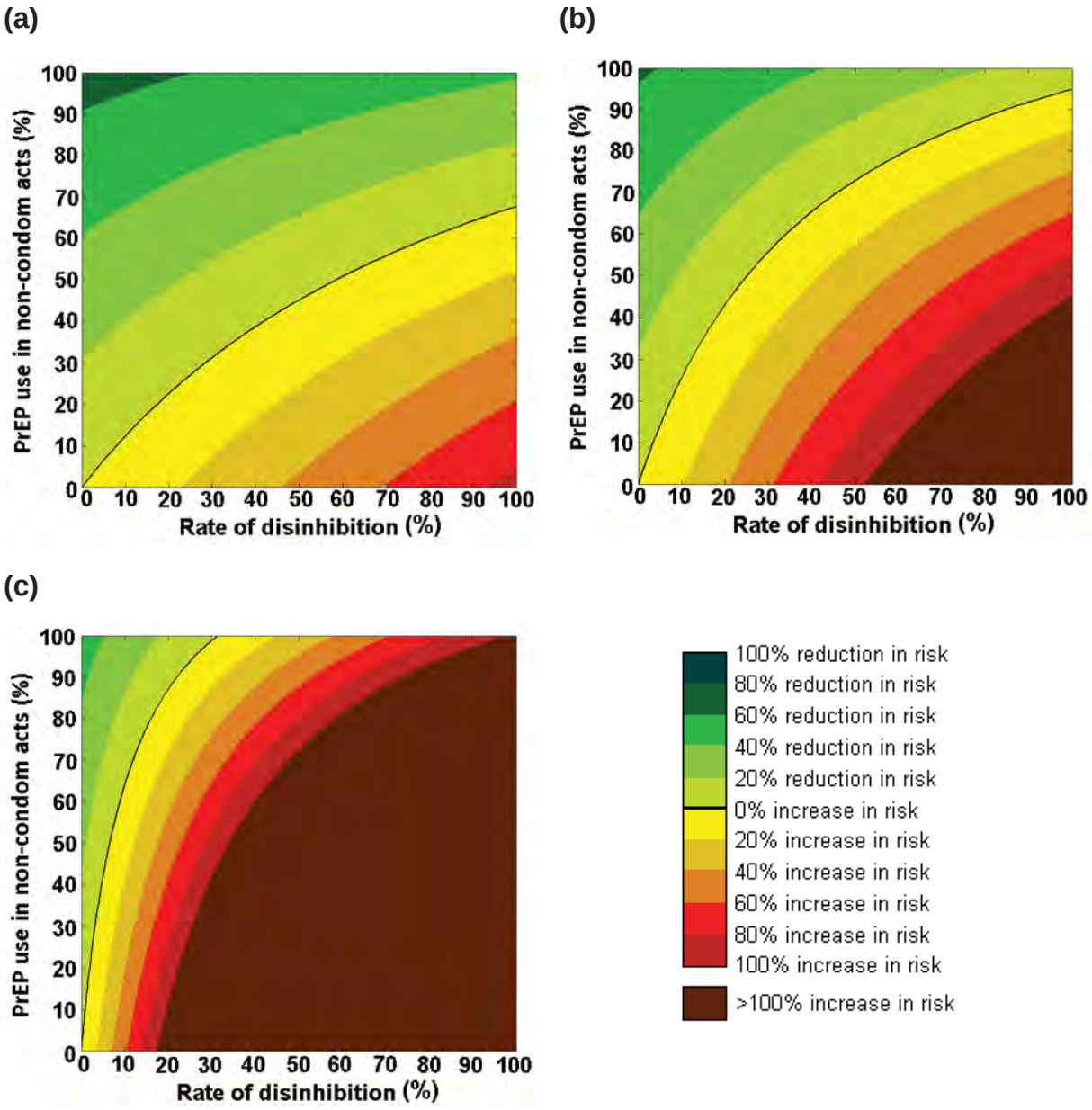


Figure 49: Contour plots of the relative effectiveness of PrEP on the risk of HIV transmission versus PrEP usage and level of condom replacement (disinhibition) for gay men who use condoms in (a) 50%, (b) 70%, and (c) 90% of sexual acts.

Accounting for the large heterogeneity in populations of gay men in Australia, the average change in population-level incidence according to average levels of PrEP usage and risk disinhibition is shown in Figure 50 for PrEP efficacies of 50%, 70% or 90%. If the efficacy of PrEP is 50% then there will be little advantage to its introduction unless there is almost no reduction in condom use and PrEP supplements current condom use (Fig. 50a). In the likely best-case scenario, if high-

efficacy (90%) PrEP is used to complement current condom usage then HIV incidence in the population can decrease by up to ~70% (Fig. 50c).

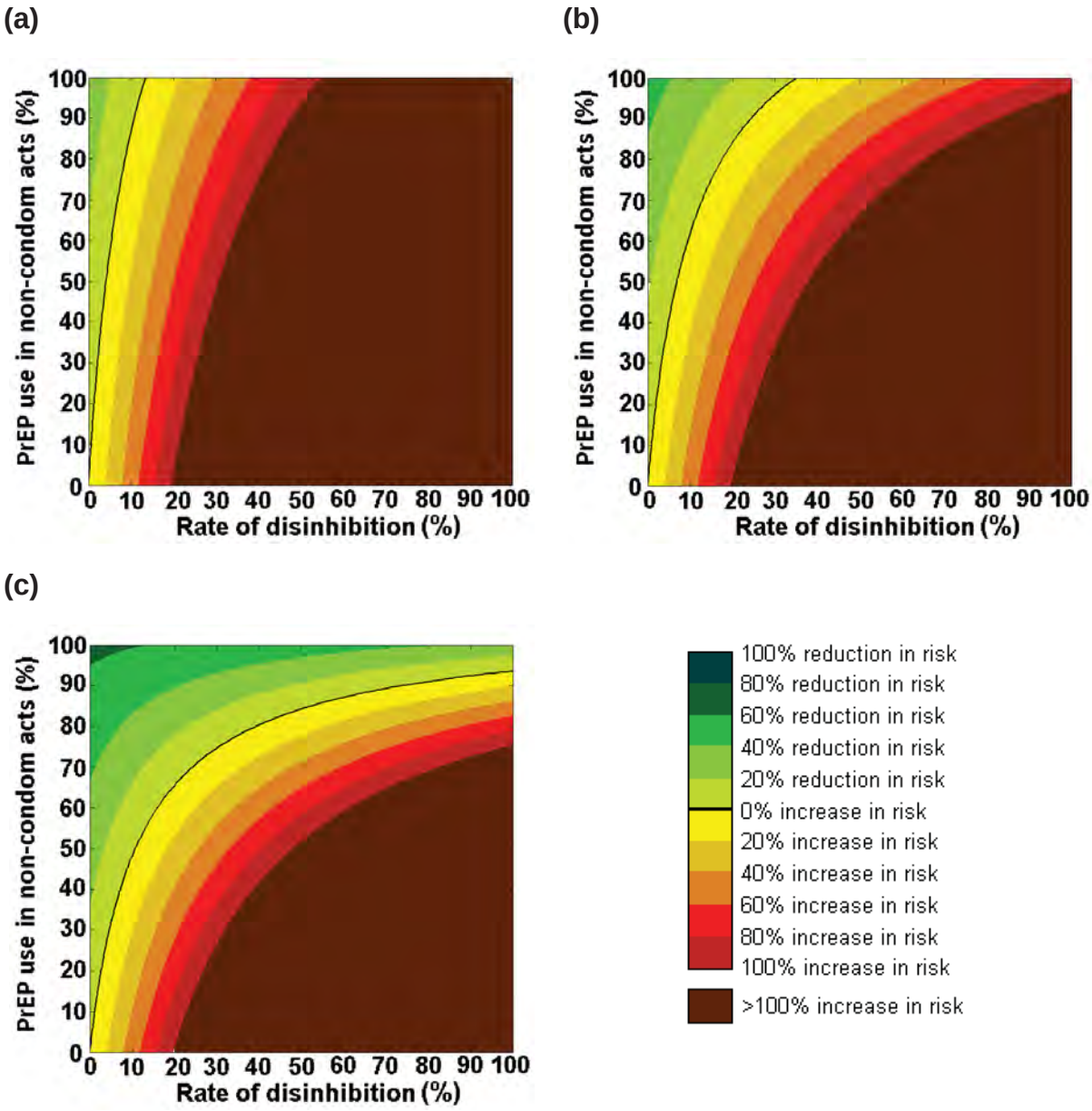


Figure 50: Contour plots of the relative effectiveness of PrEP on population-level HIV incidence versus PrEP usage and level of condom replacement (disinhibition) for PrEP efficacies of (a) 50%, (b) 70% and (c) 90%.

The modelling suggests that although the use of moderately effective PrEP may result in a reduction in the average risk of HIV infection among gay men, even small degrees of condom replacement can outweigh this benefit and lead to increased risk. The relative impact of PrEP will differ between men based on levels of risk disinhibition and their current levels of condom usage with greater benefit for men who currently use condoms less frequency and are at higher risk of HIV acquisition. Targeting a PrEP-based intervention at men at highest risk would have the greatest

preventative benefit and would lead to decreased chance of detrimental population-level outcomes from risk disinhibition.

Circumcision

Adult male circumcision has been shown to be effective for the prevention of acquisition of HIV in three randomised trials in heterosexual men in Southern and Eastern Africa [95-97]. In 2008, a large Australian community-based cohort reported a significant reduced risk of HIV seroconversion among circumcised MSM who predominantly took the insertive role in anal intercourse with a hazard ratio of 0.11, (95% CI 0.03-0.80, p=0.041) after controlling for age and unprotected anal intercourse [98]. Recently the authors of this report co-authored a published study on the expected effectiveness and cost-effectiveness of introducing circumcision as an interventions among Australian men who have sex with men [99]. It was determined that under the (unrealistic) situation of large-scale implementation of circumcision among gay men would result in 2-5% of HIV infections being averted per year with initial costs ranging from $3.6m to $95.1m depending on coverage. The number of circumcisions needed to prevent one HIV infection was estimated to be between 118 and 330. Circumcision would be cost-effective but would no longer be effective if there was minor behavioural disinhibition and the large financial investment may be more effectively spent on other interventions.

Conclusions

Historically South Australia has responded successfully to contain and minimise the spread of HIV such that the prevalence of infection among all South Australians has remained at or below 0.1%. The success of South Australia's past response to HIV is in part due to the coordination of HIV prevention programs and partnership approach between government, NGOs, researchers, clinicians and community representatives. However, the rate of HIV diagnoses in South Australia has increased significantly over the past decade particularly among men who have sex with men, which is the population group greatest affected by HIV in South Australia. This is similar to what has occurred in most other jurisdictions in Australia and in comparable settings internationally. The research of this study suggests that the main contributor to changes in HIV infections in South Australia was a decline in condom use. Over the past few years HIV diagnoses have stabilised or even started to decline in South Australia.

Using the South Australian HIV mathematical model it was shown that the TT123 campaign carried out in Adelaide likely had a small impact. It does not appear to have decreased the proportion of MSM who have never received an HIV test. However, the TT123 campaign likely had an effect of encouraging MSM who have received an HIV test to receive another one and thus the campaign modestly increased testing rates. The increase in testing rate due to the TT123 campaign prevented an estimated 0.2 of an infection. That is, an HIV infection would be averted for every five years of implementation of the campaign.

The South Australian model was used to forecast the trajectory of HIV in South Australia until the end of 2015. The model estimated that if behaviour and testing practices do not change then the number of HIV infections would decline by about 20% over five years but the number of HIV diagnoses would still be higher than a decade ago. Changes in conditions can substantially alter the epidemic trajectory. Changes in sexual behaviour among men who have sex with men could have a substantial impact on HIV incidence in the population. However, decreases in partner acquisition rates and increases in condom usage are unlikely to be widely acceptable among populations of MSM. Short-term behavioural changes may be more feasible and will have a moderate impact.

Whilst the rates of HIV testing in South Australia remain very high, a significant proportion of people infected with HIV in South Australia are unaware of their HIV status, with a significant impact on new transmission rates. To have a noticeable impact on HIV trends men who have not received an HIV test should be targeted and other men should be targeted to have an HIV test at least twice per year.

Of all interventions considered, only one was observed to have the potential to have a large epidemiological impact, namely, 'test and treat'. If a 'test and treat' intervention targeted 70% of MSM who are socially engaged with the gay community (i.e. a likely proportion of the main population group that can be more easily targeted) then 'test and treat' is likely to have a very small impact. However, if a significant

proportion (70%) of men who are not connected to gay networks can be reached with ‘test and treat’ then the intervention would be expected to have a very substantial epidemiological impact. Other interventions, such as preventative prophylaxis or male circumcision are less likely to be viable options for effective public health strategies.

One particularly important aspect highlighted by the modelling is that any intervention has to be continued over the long term for its impact on the epidemic to be sustained; otherwise an HIV epidemic is likely to re-emerge. Thus the long term acceptability of an intervention to populations of men who have sex with men is a highly important consideration.

In order to design effective and specific interventions the model was structured in a way to investigate the behaviour and epidemiology of men who are attached to the gay community compared with those who are not actively engaged in gay networks. The expected impact of targeting interventions at particular populations was explored. This is the first time any modelling analysis has incorporated this separation in populations for any setting. The model yielded mixed results with testing interventions likely to be effective by targeting men who are engaged in the social networks of the gay community whereas ‘test and treat’ needs to target all men. This result could be due to men in the gay community being at greater risk of infection and so they are like a core group such that targeting them would have the greatest preventative benefit. However, for ‘test and treat’ to be effective it would have to be adopted by most of the HIV-infected population in order to reduce population-level viral load.

Other priority populations cannot be ignored. Prevention activities should also be targeted to people who arrive in South Australia from countries in which there is a high HIV prevalence and people who travel to these countries. There is a continuing risk of an accelerated epidemic among other at-risk populations that must be tracked over the rest of the term of the current South Australian HIV Action Plan, including amongst Aboriginal people, people who inject drugs, prisoners and sex workers. Prevention efforts must remain vigilant to the needs of these particular groups, as well as the priority population of men who have sex with men, with flexibility to respond decisively and quickly when changes to the pattern of the epidemic emerge.

Appendix A: Mathematical model equations

The equations of the mathematical model used in this research are described below. The model tracks distinct populations of men who have sex with men who are socially engaged to the gay community and those who are not. The ordinary differential equations for uninfected and HIV-infected but undiagnosed socially engaged men are:

$$\frac{dS_{SE}}{dt} = \pi - S_{SE}(\mu_s + \lambda)$$

$$\frac{dU^{SE}_{>500}}{dt} = \lambda S_{SE} - U^{SE}_{>500}(\mu_s + \gamma^{SE}_{>500} + \omega_{>500} + \delta_{>500})$$

$$\frac{dU^{SE}_{500-350}}{dt} = \omega_{>500}U^{SE}_{>500} - U^{SE}_{500-350}(\mu_s + \gamma^{SE}_{500-350} + \omega_{500-350} + \delta_{500-350})$$

$$\frac{dU^{SE}_{350-200}}{dt} = \omega_{500-350}U^{SE}_{500-350} - U^{SE}_{350-200}(\mu_s + \gamma^{SE}_{350-200} + \omega_{350-200} + \delta_{350-200})$$

$$\frac{dU^{SE}_{<200}}{dt} = \omega_{350-200}U^{SE}_{350-200} - U^{SE}_{<200}(\mu_s + \gamma^{SE}_{<200} + \omega_{<200} + \delta_{<200})$$

The ordinary differential equations for uninfected and HIV-infected but undiagnosed men who are not socially engaged to the gay community are:

$$\frac{dS_{OM}}{dt} = \pi - S_{OM}(\mu_s + \lambda)$$

$$\frac{dU^{OM}_{>500}}{dt} = \lambda S_{OM} - U^{OM}_{>500}(\mu_s + \gamma^{OM}_{>500} + \omega_{>500} + \delta_{>500})$$

$$\frac{dU^{OM}_{500-350}}{dt} = \omega_{>500}U^{OM}_{>500} - U^{OM}_{500-350}(\mu_s + \gamma^{OM}_{500-350} + \omega_{500-350} + \delta_{500-350})$$

$$\frac{dU^{OM}_{350-200}}{dt} = \omega_{500-350}U^{OM}_{500-350} - U^{OM}_{350-200}(\mu_s + \gamma^{OM}_{350-200} + \omega_{350-200} + \delta_{350-200})$$

$$\frac{dU^{OM}_{<200}}{dt} = \omega_{350-200}U^{OM}_{350-200} - U^{OM}_{<200}(\mu_s + \gamma^{OM}_{<200} + \omega_{<200} + \delta_{<200})$$

The ordinary differential equations for all men who have sex with men who are HIV-infected and diagnosed with their infection but untreated are:

$$\frac{dD_{>500}}{dt} = \gamma^{SE}_{>500} U^{SE}_{>500} + \gamma^{OM}_{>500} U^{OM}_{>500} - D_{>500}(\mu_s + \omega_{>500} + \eta_{>500} + \delta_{>500})$$

$$\frac{dD_{500-350}}{dt} = \gamma^{SE}_{500-350} U^{SE}_{500-350} + \gamma^{OM}_{500-350} U^{OM}_{500-350} + \omega_{>500} D_{>500} - D_{500-350}(\mu_s + \omega_{500-350} + \eta_{500-350} + \delta_{500-350})$$

$$\frac{dD_{350-200}}{dt} = \gamma^{SE}_{350-200} U^{SE}_{350-200} + \gamma^{OM}_{350-200} U^{OM}_{500-350} + \omega_{500-350} D_{500-350} - D_{350-200}(\mu_s + \omega_{350-200} + \eta_{350-200} + \delta_{350-200})$$

$$\frac{dD_{<200}}{dt} = \gamma^{SE}_{<200} U^{SE}_{<200} + \gamma^{OM}_{<200} U^{OM}_{<350} + \omega_{350-200} D_{350-200} - D_{<200}(\mu_s + \omega_{<200} + \eta_{<200} + \delta_{<200})$$

The following ordinary differential equation represents the change in the number of men who have sex with men who are on antiretroviral treatment:

$$\frac{dT}{dt} = \eta_{>500} D_{>500} + \eta_{500-350} D_{500-350} + \eta_{350-200} D_{350-200} + \eta_{<200} D_{<200} - T(\mu_s + \nu + \delta_T)$$

The following ordinary differential equation represents the change in the number of men who have sex with men who are experiencing treatment failure:

$$\frac{dF}{dt} = \nu T - F(\mu_s + \delta_{TF})$$

The most important term in this system of equations is the force of infection, represented by λ, which denotes the per-capita rate of becoming infected. Its mathematical expression is:

$\lambda = \lambda_1 + \lambda_2 + \lambda_3 + \lambda_4 + \lambda_5 + \lambda_6 + \lambda_7 + \lambda_8 + \lambda_9 + \lambda_{10}$, where:

$$\lambda_1 = \frac{c^{SE}_{reg}(\beta^{>500_{SE}}_{reg} U^{SE}_{>500} + \beta^{500-350_{SE}}_{reg} U^{SE}_{500-350} + \beta^{350-200_{SE}}_{reg} U^{SE}_{350-200} + \beta^{<200_{SE}}_{reg} \theta_{AIDS} U^{SE}_{<200})}{N'_{SE}}$$

$$\lambda_2 = \frac{c^{SE}_{reg} f(\beta^{>500_{SE}}_{reg} D_{>500} + \beta^{500-350_{SE}}_{reg} D_{500-350} + \beta^{350-200_{SE}}_{reg} D_{350-200} + \beta^{<200_{SE}}_{reg} \theta_{AIDS} D_{<200} + \beta^{T_{SE}}_{reg} T + \beta^{F_{SE}}_{reg} F)}{K_{SE}}$$

$$\lambda_3 = \frac{(1 - SE_{mix}) SE_{pop}}{UnDXandS} \cdot \frac{c^{SE}_{cas}(\beta^{>500_{SE}}_{cas} U^{SE}_{>500} + \beta^{500-350_{SE}}_{cas} U^{SE}_{500-350} + \beta^{350-200_{SE}}_{cas} U^{SE}_{350-200} + \beta^{<200_{SE}}_{cas} \theta_{AIDS} U^{SE}_{<200})}{N'_{SE}}$$

$$\lambda_4 = \frac{(1-SE_{mix})SE_{pop}}{UnDXandS} \times$$

$$\frac{c_{cas}^{SE} f(\beta_{cas}^{>500_{SE}} D_{>500} + \beta_{cas}^{500-350_{SE}} D_{500-350} + \beta_{cas}^{350-200_{SE}} D_{350-200} + \beta_{reg}^{<200_{SE}} \theta_{AIDS} D_{<200} + \beta_{cas}^{T_{SE}} T + \beta_{cas}^{F_{SE}} F)}{K_{SE}}$$

$$\lambda_5 = \frac{c_{reg}^{OM}(\beta_{reg}^{>500_{OM}} U_{>500}^{OM} + \beta_{reg}^{500-350_{OM}} U_{500-350}^{OM} + \beta_{reg}^{350-200_{OM}} U_{350-200}^{OM} + \beta_{reg}^{<200_{OM}} \theta_{AIDS} U_{<200}^{OM})}{N_{OM}^{'}}$$

$$\lambda_6 = \frac{c_{reg}^{OM} f(\beta_{reg}^{>500_{OM}} D_{>500} + \beta_{reg}^{500-350_{OM}} D_{500-350} + \beta_{reg}^{350-200_{OM}} D_{350-200} + \beta_{reg}^{<200_{OM}} \theta_{AIDS} D_{<200} + \beta_{reg}^{T_{OM}} T + \beta_{reg}^{F_{OM}} F)}{K_{OM}}$$

$$\lambda_7 = \frac{(1-OM_{mix})OM_{pop}}{UnDXandS} \cdot \frac{c_{cas}^{OM}(\beta_{cas}^{>500_{OM}} U_{>500}^{OM} + \beta_{cas}^{500-350_{OM}} U_{500-350}^{OM} + \beta_{cas}^{350-200_{OM}} U_{350-200}^{OM} + \beta_{cas}^{<200_{OM}} \theta_{AIDS} U_{<200}^{OM})}{N_{OM}^{'}}$$

$$\lambda_8 = \frac{(1-OM_{mix})OM_{pop}}{UnDXandS} \times$$

$$\frac{c_{cas}^{OM} f(\beta_{cas}^{>500_{OM}} D_{>500} + \beta_{cas}^{500-350_{OM}} D_{500-350} + \beta_{cas}^{350-200_{OM}} D_{350-200} + \beta_{cas}^{<200_{OM}} \theta_{AIDS} D_{<200} + \beta_{cas}^{T_{OM}} T + \beta_{cas}^{F_{OM}} F)}{K_{OM}}$$

$$\lambda_9 = \frac{SE_{pop}SE_{mix} + OM_{pop}OM_{mix}}{UnDxandS} \times$$

$$c_{cas}^{all}(\beta_{cas}^{>500_{all}}(U_{>500}^{SE} + U_{>500}^{OM}) + \beta_{cas}^{500-350_{all}}(U_{500-350}^{SE} + U_{500-350}^{OM}) + \beta_{cas}^{350-200_{all}}(U_{350-200}^{SE} + U_{350-200}^{OM})$$

$$\frac{+\beta_{cas}^{<200_{all}}(U_{<200}^{SE} + U_{<200}^{OM})\theta_{AIDS})}{N_{all}^{'}}$$

$$\lambda_{10} = \frac{SE_{pop}SE_{mix} + OM_{pop}OM_{mix}}{UnDxandS} \times$$

$$\frac{c_{cas}^{all} f(\beta_{cas}^{>500_{all}} D_{>500} + \beta_{cas}^{500-350_{all}} D_{500-350} + \beta_{cas}^{350-200_{all}} D_{350-200} + \beta_{cas}^{<200_{all}} \theta_{AIDS} D_{<200} + \beta_{cas}^{T_{all}} T + \beta_{cas}^{F_{all}} F)}{K_{all}}$$

$$SE_{pop} = S_{SE} + U_{>500}^{SE} + U_{500-350}^{SE} + U_{350-200}^{SE} + U_{<200}^{SE}$$

$$OM_{pop} = S_{OM} + U_{>500}^{OM} + U_{500-350}^{OM} + U_{350-200}^{OM} + U_{<200}^{OM}$$

$$UnDxandS = SE_{pop} + OM_{pop}$$

$$N_{SE}^{'} = S_{SE} + U_{>500}^{SE} + U_{500-350}^{SE} + U_{350-200}^{SE} + U_{<200}^{SE}\theta_{AIDS}$$

$$N_{OM}^{'} = S_{OM} + U_{>500}^{OM} + U_{500-350}^{OM} + U_{350-200}^{OM} + U_{<200}^{OM}\theta_{AIDS}$$

$$N_{all} = N_{SE}^{'} + N_{OM}^{'}$$

$$K_{SE} = N_{SE}^{'} + f(D_{>500} + D_{500-350} + D_{350-200} + \theta_{AIDS}(D_{<200} + T + F))$$

$$K_{OM} = N_{OM}^{'} + f(D_{>500} + D_{500-350} + D_{350-200} + \theta_{AIDS}(D_{<200} + T + F))$$

$$K_{all} = N'_{SE} + N'_{OM} + f(D_{>500} + D_{500-350} + D_{350-200} + \theta_{AIDS}(D_{<200} + T + F))$$

Appendix B: The case for providing free antiretroviral therapy in South Australia

This is a paper prepared by Kelly-Jean Heymer (NCHECR), Matthias Wentzlaff-Eggebert (SA Health), Elissa Mortimer (SA Health), and David Wilson (NCHECR).

Introduction

In South Australia around 750 people are currently living with HIV and diagnosed with their infection [6]. Approximately 76% of the diagnosed cases are receiving antiretroviral therapy (ART) to delay or reverse disease progression and improve survival [1]. Although it is not necessarily optimal for all patients diagnosed with HIV to be on ART, there exist a proportion of HIV-infected people who are aware of their positive serostatus, are eligible for treatment, but are not yet receiving antiretrovirals. It is an important health issue to remove barriers to treatment uptake to ensure that all in need of life-sustaining ART have access. One of the primary barriers could be financial constraints.

In Australia, the Pharmaceutical Benefits Scheme (PBS) provides subsidised prescription drugs to Australian residents. Patients are required to contribute a co-payment for their prescription medication when purchasing under the PBS. Those who receive government pensions, are low-income earners or hold a Health Care Card (HCC) are entitled to pay a reduced "concession" co-payment amount. A recent increase in co-payment costs has led to concern about patients' abilities to afford essential medications [100]. According to the HIV Futures survey, over 40% of patients reported the co-payments for antiretroviral medications to be either 'a little difficult' or 'very difficult' to afford [33]. Therefore, it is likely that the inability to afford HIV antiretroviral medication has led patients to delay, cease or interrupt treatment. Not only does this impact on the health of HIV-infected people but on the spread of the virus through the population.

Antiretroviral medications are available from public hospital pharmacies in all Australian States and Territories. Unlike other Australian states, South Australia has an additional community pharmacy agreement for dispensing HIV medications whereby the pharmacy acts as an agent for the Royal Adelaide Hospital for dispensation of Highly Specialised Drugs for HIV treatment. Previously, Centre Pharmacy charged one co-payment for a 3 month-supply of HIV medication in contrast to the one co-payment per month supply charged by SA public hospital pharmacies. More recently, Centre Pharmacy has been required to charge one patient co-payment per one month supply. The increase in costs is due to the implementation of increased PBS requirements to comply with the administrative agreement between the Commonwealth and the State for the Highly Specialised Drugs Program.

Currently, the patient co-payment stipulations in the Commonwealth Highly Specialised Drugs Program Administrative arrangement state that each client is to be charged 1 co-payment for 1 month's drug supply. The co-payment for clients with a Health Care Card is $5.30 per drug and $26.30 for those without, up to an annual family threshold (inclusive of same sex couples) of $1,200. Once the threshold has been reached, clients can then access a HCC and have their co-payment reduced to match the HCC level. In the last quarter of 2005, the HIV Futures Five study [33] reported that 28.3% of people with HIV in Australia were living below the poverty line. When questioned about affordability, 31.5% of patients reported that co-payments for their antiretroviral medications were 'a little difficult' and an additional 8.9% 'very difficult' to afford. Additionally, anecdotal reports from tertiary treatment centres affirm that due to financial reasons some patients are postponing, interrupting or even ceasing treatment.

The outcomes of antiretroviral treatment are of benefit at both the population and individual level. Clinical outcomes such as a slow-down or reversal of disease progression [101] benefits the patient. Furthermore, effective treatment results in successful viral suppression (reducing plasma viral load to undetectable levels, less than 50 copies per ml) in approximately 90% of cases [1]. Local and international research has demonstrated that such reductions in viral load results in an average of 90-95% reduction in the infectiousness of HIV-infected people on ART compared with those not on ART [47, 71-72]. Consequently, there has been a recent call among the HIV/AIDS global health community to substantially increase rates of treatment uptake for the purposes of preventing new infections [102].

In this study we evaluate the cost-effectiveness of removing the co-payment requirement from HIV medications in South Australia. The analysis is conducted from a health sector (government as third party payer) perspective. Specifically, a mathematical model based on risk equations is used to calculate the expected average number of new HIV infections caused by persons who are not currently on ART compared with the average number expected from those who are on ART. The model reflects the HIV epidemiology in South Australia and is informed by available behavioural and biological data. We compare the extra financial investment required to cover the co-payments with the total treatment costs saved due to preventing HIV infections with increased treatment uptake.

Methods

In South Australia from 2004 to 2008, 93.1% of HIV diagnoses were attributed to three predominant routes of exposure: intercourse between men who have sex with men (MSM, 60%), heterosexual sex (25.3%) and transmission via injecting drug use (IDU, 7.8 %). We developed a mathematical model consisting of equations that measure HIV transmission risk for each of these transmission routes. Specifically,

the risk equations conservatively calculate the average number of new HIV infections that could be attributed to one infected person each year.

The mathematical model incorporated the risk of HIV transmission per act for each type of sexual or injecting act and the prevalence of HIV in the relevant partnership groups. Additional biological factors that were included were the rate of circumcision among the male population and the reduction in infectiousness due to antiretroviral medication. To account for sexual behaviour, the model includes the average annual number of casual and regular sexual partners each person has and the frequency of sex with these partners. Similarly, for IDUs the model included the average yearly number of injection acts. HIV protection measures depicted in the model include the rate of condom use in each partnership type (with the efficacy of condoms) and the proportion of acts/partnerships in which a person discloses their HIV serostatus (and the resultant sexual position they generally perform as a consequence). In the context of transmission via injection, the rates of sharing injections and cleaning of injecting equipment (with the efficacy of cleaning) are included. Mathematically, the average number of new HIV transmissions per HIV-infected MSM per year can be expressed according to these factors as

$$
\begin{aligned}
MSM = {} & C_{cas}^{msm}(1-P_{msm})\{(1-r_{cas}^{msm})\delta(re^{+}\beta_{re}+in^{+}(\beta_{in}^{nc}(1-c)+\beta_{in}^{c}c)+wi^{+}\beta_{wi}) \\
& +(1-\delta)(re^{?}\beta_{re}+in^{?}(\beta_{in}^{nc}(1-c)+\beta_{in}^{c}c)+wi^{?}\beta_{wi})+r_{cas}^{msm}(0.5(1-\epsilon_{c})(\beta_{re}+\beta_{in}))\} \\
& +C_{reg}^{msm}(1-P_{msm})\{0.5(1-(1-(\beta_{in}^{nc}(1-c)+\beta_{in}^{c}c))^{n_{reg}^{msm}(1-r_{reg}^{msm})}(1-(1-\epsilon_{c})(\beta_{in}^{nc}(1-c)+\beta_{in}^{c}c))^{n_{reg}^{msm}r_{reg}^{msm}}) \\
& +0.5(1-(1-\beta_{re})^{n_{reg}^{msm}(1-r_{reg}^{msm})}(1-(1-\epsilon_{c})\beta_{re})^{n_{reg}^{msm}r_{reg}^{msm}}))\}
\end{aligned}
$$

where C is the average number of partners for each relationship type, P is the prevalence of the relevant partnership group, r is the rate of condom use, β is the transmission risk for each act type, δ is the rate of disclosure of serostatus, n is the number of acts per relationship type per year and ε is the efficacy of condoms/ cleaning of injecting equipment. The risk of male-to-female transmission (MtoF), female-to-male transmission (FtoM) and transmission via injecting drug use (IDU) have the following similar expressions:

$$
MtoF = C_{reg}^{het}\left(1-P_{fem}\right)\left\{1-\left(1-\beta_{mf}\right)^{n_{reg}^{het}\left(1-r^{het}\right)}\left(1-\left(1-\grave{o}_{c}\right)\beta_{mf}\right)^{n_{reg}^{het}r^{het}}\right\},
$$

$$
FtoM = C_{reg}^{het}\left(1-P_{mal}\right)\left\{1-\left(1-\beta_{fm}\right)^{n_{reg}^{het}\left(1-r^{het}\right)}\left(1-\left(1-\grave{o}_{c}\right)\beta_{fm}\right)^{n_{reg}^{het}r^{het}}\right\};
$$

$$
IDU = n^{inj}\sigma(1-P_{idu})(q(1-\epsilon_{q})\beta_{idu}+(1-q)\beta_{idu}).
$$

These model equations are first used to calculate the risk of each exposure type prior to treatment and then recalculated with an allowance for the reduction in infectiousness (β) due to treatment. The difference between the resultant risk calculations is the expected number of new infections averted per person per year due to initiation of treatment. By estimating the number of extra people who would

initiate treatment due to removal of the co-payment requirement we calculated the expected number of infections averted. The costs of covering all co-payments were then evaluated in comparison with treatment costs. We also calculated the number of people needed to be on treatment to avert 1 HIV-infection and thus the financial cost per infection averted. All parameter values used in the analyses are provided in Table B.1.

Table B.1

Parameter definition		Value
Reduction in transmission risk per risk event due to treatment compared to no treatment		92% [47]
Transmission risk per act of unprotected receptive anal act (with ejaculation)		1% [103]
Transmission risk per act of unprotected receptive anal act (without ejaculation)		0.7% [103]
Transmission risk per act of unprotected insertive anal act (with circumcision)		0.1% [103]
Transmission risk per act of unprotected insertive anal act (without circumcision)		0.5% [103]
Transmission risk per act of unprotected receptive vaginal act		0.1% [104-110]
Transmission risk per act of unprotected insertive vaginal act (w/out circumcision)		0.05%[104-110]
Proportion of men that are circumcised		65% [111]
Proportion of sexual acts in which condoms are used	HIV discordant	80-69% [112]
	HIV concordant	10% [112]
	HIV status not disclosed	40% [112]
Efficacy of condoms		95% [51-55]
Rate of disclosure of HIV status by HIV-positive MSM		45.9% [113]
Distribution of the number of casual partners of gay men per 6 months (proportion of men in each category)	1-1.5	26% [114]
	2-5	21% [114]
	6-10	16% [114]
	11-50	30% [114]
	51-60	7% [114]
Estimated population size of gay men in South Australia		12,500 [115-116]
Condom use among heterosexual couples in which discordant HIV status is known		80% [33]
Prevalence of HIV among heterosexual population		0.1% [12]
Average number of regular sexual partners per year for heterosexuals		1
Transmission probability of HIV per injection with a contaminated syringe		0.7%[117-118]
Weighted average annual injecting frequency for IDUs in South Australia		300 [119]
Proportion of IDUs who share syringes in South Australia		15% [11]
Proportion of injections that are shared for IDUs who share syringes in South Australia		14% [11]
Prevalence of HIV among IDUs in South Australia		0.86% [119]
Average number of acts per year in regular MSM partnership		100 [120]

Average number of casual partners of HIV-positive MSM		14 [114]
Average number of regular partners MSM		0.65 [50]
Average number of acts per casual MSM partnership		1[120]
Condom use in casual partnerships MSM		0.75 [50]
Condom use in regular partnerships MSM		0.31[50]
Rate of disclosure of serostatus by positive MSM		0.459[50]
Prevalence of HIV in partners of positive MSM		0.398 [50]
Prevalence of HIV in general MSM		0.1 [1, 12]
Average number of acts per year in regular MSM partnership		100 [120]
Average number of casual partners of HIV-positive MSM		14 [114]
Average number of regular partners MSM		0.65 [50]
Average number of acts per casual MSM partnership		1[120]
Condom use in casual partnerships MSM		0.75 [50]
Condom use in regular partnerships MSM		0.31[50]
Rate of disclosure of serostatus by positive MSM		0.459[50]
Prevalence of HIV in partners of positive MSM		0.398 [50]
Prevalence of HIV in general MSM		0.1 [1, 12]
Proportion of MSM that are circumcised		0.65 [111]
Number of acts per regular heterosexual partnership per year		100
Transmission risk per injection act		0.007 [121-122]
Number of injecting acts per year		320 [119]
Rate of needle cleaning		0.75 [119]
Proportion of injections that are shared for those that share needles		0.14 [119]
Efficacy of cleaning syringes		0.675 [119]
Prevalence of HIV in injecting drug users		0.0086 [119]
Proportion of acts in which the negative partner will take role when partner is known to be positive	Receptive with ejaculation	0.11[114]
	Receptive with withdrawal prior to ejaculation	0.33 [114]
	Insertive	0.56 [114]
Proportion of acts in which the negative partner will take role when partner's serostatus is unknown	Receptive with ejaculation	0.21 [114]
	Receptive with withdrawal prior to ejaculation	0.33 [114]
	Insertive	0.46 [114]

Results

According to the model, the expected number of new transmissions resulting from each infected person per year is much less than one for all transmission routes even without antiretroviral treatment. Injecting drug users have the highest average transmission rate, with an average of 0.1535 new infections per year without treatment, which is equivalent to 1 transmission every 6.5 years. In comparison, without treatment one transmission would occur after an average of 6.8 years per MSM, 42.2 years for heterosexual males, and 137 years for heterosexual females (or equivalently, an average of one infection would occur per year for every 137 HIV-infected females). With treatment, the transmission rates are substantially reduced across the population.

The model was used to estimate the annual per-capita rate of HIV transmission for each transmission route due to initiation of treatment, adjusting for the cumulative number of exposure events and average behaviours of each population group. It was conservatively estimated that an HIV infection is prevented each year for every: 7.6 MSM, 45.9 heterosexual males, 91.3 heterosexual females, or 14.3 IDUs who receive ART that would have otherwise been untreated. Over the last 5 years in South Australia (2004-2008), a reported 60% of HIV diagnoses were among MSM, 16.7% among heterosexual males, 8.6% among heterosexual females, and 7.8% among IDUs (and 6.9% were among other categorisations). Adjusting for the proportion of diagnoses associated with each risk group as a weighted average, one HIV infection is prevented per year for every 26.7 people who receive treatment in South Australia.

With current annual treatment costs of approximately $14,000 [123-126], the amount of treatment required to prevent one new infection (26.7 person-years of treatment) would cost $373,800. This is below the estimated $400,000 of lifetime treatment costs per HIV-infected person [126]. Therefore, if a treatment program targets people who would not have otherwise received therapy, then from a purely economic perspective, not only is provision of full treatment cost-effective but it is cost-saving. By considering the incremental change in costs and outcomes of a change in program from the current status quo such that co-payments are covered for people who would otherwise not receive treatment, then the cost-savings are very substantial: it would cost $15,187 per infection averted if ART is provided only according to a three drug combination or $11,812 per infection averted according to current treatment patterns whereby two-thirds of patients receive their three-drug regimen as a two-pill dose. This is an extremely cost-saving strategy.

If co-payment costs are covered for all patients, including those who are currently able to pay these amounts, then the financial savings from the governmental perspective are reduced. According to the HIV Futures Five Study [33], approximately 8.9% report that co-payments for antiretroviral medications are ‘very difficult’ to afford. Conservatively we assume that one-half of these people (4.5% of

all HIV-infected people) are postponing or ceasing treatment for financial reasons and the others receive charitable financial assistance from elsewhere. Therefore, if the 95.5% of HIV-infected people who are currently making their own co-payments have them covered by the health system in addition to the 4.5% who additionally receive antiretroviral medications, then the financial return on investment changes. The extra expenses of financing the co-payments, adjusting for Medicare status of people in the population, would cost an estimated $337,488 (unadjusted, or $262,491 adjusted for drug combination) per infection averted compared to the status quo; this is still below the costs associated with treating a new infection. Since the program of covering co-payments for all HIV-infected patients would be cost-saving, from a health economic perspective an analysis with health utilities is not required to determine the cost-effectiveness of the program.

Discussion

Policy in South Australia requires that the State pay for the co-payments of each 1 month supply of antiretrovirals dispensed, regardless of whether it is recouped from the patient. This is similar to the policy in New South Wales, Queensland, Australian Capital Territory and Tasmania, although some of these States have no community pharmacy dispensation. In Victoria, antiretrovirals are dispensed for free from the Melbourne Sexual Health Centre; otherwise a co-payment is required from all other Victorian public hospital pharmacy outlets. In Western Australian and the Northern Territory, antiretrovirals for HIV treatment are supplied free of charge.

There exist precedents for provision of free treatment and/or immunisation for diseases that present a public health risk. In South Australia, treatment and/or immunisation for TB, hepatitis B, seasonal influenza and sexually transmitted infections other than HIV are available without cost to the patient.

The inability to access consistent treatment for HIV not only impacts upon the individual, but also the health system and the general population. By delaying treatment uptake or ceasing it altogether due to inability to finance co-payment costs, HIV-infected individuals can experience persistently increased viral load. This can have a damaging effect on the general health of individuals and the population. At a macro level, increased average viral loads in the population will lead to increased incidence of HIV. Ultimately this will lead to increased costs associated with ART, as well as more hospital admissions and outpatient appointments.

Facilitating increases in treatment rates by removing the co-payment requirement for HIV medication is likely to result in numerous beneficial outcomes including reductions in HIV transmissions and less resistance to antiretrovirals, improved health outcomes for HIV-infected individuals, and a reduced burden on public health resources. Recent discussions and recommendations about novel prevention strategies are also promoting increased treatment rates among all HIV-infected people [102]. There is strong clinical and epidemiological support for increasing

treatment rates in addition to the financial benefits. We carried out a health economics analysis from a governmental perspective of covering co-payments for HIV antiretroviral drugs and found that this initiative is not only cost-effective but cost-saving, and we therefore recommend its implementation.

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Appendix for Chapter 5

Expected value analysis for costs and utilities for gonorrhoea and chlamydia

Introduction

There are no published data of the costs or utilities of chlamydia and gonorrhoea infection in men. We use an expected value analysis to estimate the costs and utilities of infection and associated complications in men who acquire infection over a 12 month period, from a health perspective. The costs are undiscounted in Australian dollars and based on costs for 2006-7.

Method

An expected value tree was constructed using TreeAge with input variables drawn from Australian government medical and pharmaceutical rebates and the published literature; when variables were not available we use the assumptions of an experienced sexual health physician (BD) and primary care doctor (JA); for epididymitis we adapt the utility loss associated with erectile dysfunction to mimic the loss of quality of life associated with sexual dysfunction. No utility loss is assumed for simple uncomplicated cases of infection. The variables include costs, probabilities and the decrements in utility over a 12 month period associated with specific complications.

The expected value analysis tree for both conditions is represented in Figure 1. Input variables for chlamydia are in Table 1 and for gonorrhoea in Table 2. The components for reactive arthritis related to chlamydia and septic arthritis for gonorrhoea are calculated from the clinical pathways described in Tables 3 and 4 respectively.

We assume that 3% of men will experience arthritis and/or epididymitis associated with each condition. In the chlamydia tree, arthritis is reactive arthritis, in the gonorrhoea tree it is septic arthritis. We also assume that 10% of men with epididymitis will become infertile.

To estimate the costs of admission with septic arthritis due to gonorrhoea, a multi- step approach is taken: the International Classification of Diseases version 10 classifies septic

arthritis due to gonorrhoea as A54.4+ [1]; using this code we search the clinical profiles of National Admitted Patient Care Collection (NAPCC) [2] to identify the diagnostic related group (DRG) codes associated with admission for septic arthritis, I67A/B; with these DRG codes, we search the 2006-7 National Admitted Patient Care Collection[3] to discover the number of separations for each DRG; the values of both DRGs is contained in Round 11 (2006-07) Cost Report[3]; a weighted-average cost per separation is calculated using the proportions of each type of DRG to produce a cost per inpatient separation with septic arthritis.

Conclusion

Our expected value analysis estimates the cost per case of chlamydia infection of $57 and the cost of gonorrhoea of $82. The utility lost in a year for each case of disease is 0.0085 quality adjusted life years or just over 3 quality adjusted life days.

The estimate is only slightly sensitive to the cost of treatment of arthritis and epididymitis; for example, the cost of gonorrhoea falls by $3 when the cost of inpatient care is 50% of the base-case value.

Tables

Table 1: chlamydia	**Value**	**Comment**
Cost arthritis	$1310	See Table 3
Cost of epididymitis	$56	Azithromycin[4]+ medical [5]
Cost treating simple chlamydia	$56	Azithromycin[4]+ medical [5]
Utility decrement arthritis	0.25	Utility arthritis aged 18-35 [6]
Utility decrement epididymitis	0.016667	Assume 0.1 decrement for 8 weeks similar to erectile dysfunction [7]
Utility decrement infertility	0.18	[8]
probability arthritis after infection	0.03	expert opinion
probability epididymitis	0.03	[9] + expert opinion

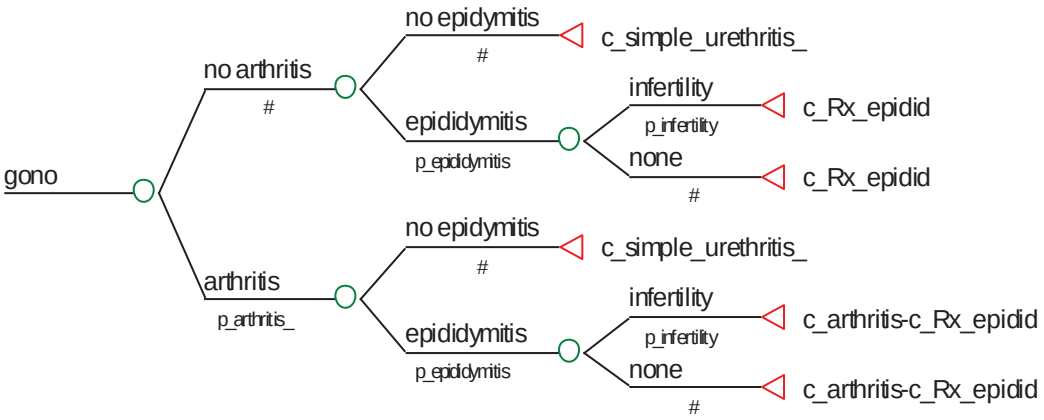
probability infertile after epididymitis	0.1	[10]

Table 2: Gonorrhoea	**Value**	**Comment**
Cost septic arthritis	$6413	See Table 4
Cost of epididymitis	$302	Medications [4] + medical consultations [5]
Cost treating simple gonorrhoea	$70	Medication [4] + medical [5]
Utility decrement arthritis	0.25	Utility arthritis aged 18-35[6]
Utility decrement epididymitis	0.016667	Assume 0.1 decrement for 8 weeks similar to erectile dysfunction[7]
Utility decrement infertility	0.18	[8]
probability arthritis after infection	0.03	expert opinion
probability epididymitis	0.03	[9, 11] + expert opinion
probability infertile after epididymitis	0.1	[10]

Table 3 Cost reactive arthritis (chlamydia)	**Unit cost**	**Number of units year**	**Total**	**Sources [4, 5]**
Full blood examination	$14.65	4	$59	MBS item 65070
C-reactive protein test (3 monthly)	$7.35	4	$29	MBS item 66500
X-ray of feet, knees	$32.55	1	$33	MBS item 57521
Physiotherapy	$44.85	2	$90	MBS item 10960
GP consultations quarterly	$32.40	4	$130	MBS item 23
Specialist consultation(Initial)	$128.05	1	$128	MBS item 110
Specialist consultations (review)	$48.10	3	$144	MBS item 116
Diclofenac 50mg tds	$11.03	12	$132	PBS item 1300K
Methotrexate or similar	$47.10	12	$565	PBS items 2272N and
Total			$1,310	

Table 4 cost of septic arthritis	**Unit cost**	**number of units**	**total**	
GP	$32.40	4	$130	initial consult and 3 follow-up to give injections
Admission hospital	$5,921	1	$5,921	weighted average DRG code I67A and I67B
Specialist consultations initial outpatient	$115.60	1	$116	MBS item 110
Specialist consultations review outpatient	$58.00	1	$58	MBS item 116 f
ceftriaxone 1 g IM/IV q24 h after discharge for 5 days	$37.79	5	$189	PBS
TOTAL			$6,413	

Figure 1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Appendix for Chapter 6

A mathematical model was developed to estimate the relationship between the proportion of the HIV-infected population that is undiagnosed and the relative risk per contact of unprotected anal intercourse (UAI); acts where condoms are used were not considered because the majority of transmissions occur due to UAI. The model was formulated as follows.

If serosorting does not occur then each casual partnership formed with an HIV-uninfected MSM has average probability of being serodiscordant represented by the following mathematical expression:

$$Q_{serosort} = (N_{ND}+N_D+N_T)/(N_S+N_{ND}+N_D+N_T). \quad (1)$$

Here N_S, N_{ND}, N_D, and N_T represent the number of HIV-uninfected MSM who are potentially susceptible to infection, HIV-infected MSM who are not diagnosed and thus unaware of their serostatus, HIV-infected MSM who have been diagnosed with their infection, and MSM who are on antiretroviral therapy (ART) for their known HIV infection, respectively. If serosorting does occur and false disclosure does not occur then each new partnership has average probability of being discordant given by:

$$Q_{no\ serosort} = N_{ND}/(N_S+N_{ND}). \quad (2)$$

Average transmission probabilities per serodiscordant act of UAI with a casual partner who is undiagnosed (β_{ND}), diagnosed but untreated (β_D), and on ART (β_T), can be estimated as weighted averages based on the proportion of acts that are insertive, receptive with withdrawal, or receptive with ejaculation, according to the perceived HIV status of the partner. We use detailed behavioral data from the Health in Men (HIM) cohort [1,2], a highly studied cohort of gay men, to inform these estimates (see Fig. 1a). For example, based on the HIM study [2], if a partner's HIV status is unknown then an average of q_i^U =46% of UAI acts are likely to be insertive, q_{rw}^U =33% are likely to be receptive but with withdrawal prior to ejaculation, and q_r^U =21% are likely to be receptive with ejaculation (Fig. A1). Then, the average risk of HIV transmission per serodiscordant act of UAI with a partner whose serostatus is unknown is given by

$$\beta_U = q_i^U \beta_i + q_{rw}^U \beta_{rw} + q_r^U \beta_r, \quad (3)$$

yielding a value of ~0.0032, where the respective transmission probabilities are taken to be β_i =0.001, β_{rw} =0.002, and β_r =0.010 [3,4].

Similarly, the risks per contact with a partner of known HIV infection, based on the change in sexual positioning (Fig. 1a), are given by

$$\beta_D = q_i^D \beta_i + q_{rw}^D \beta_{rw} + q_r^D \beta_r , \quad (4)$$

yielding a value of ~0.0023 and

$$\beta_T = (1-\phi)\beta_D , \quad (5)$$

yielding a value of ~0.0001, where $\phi = 0.95$ is the estimated reduction in infectiousness due to effective treatment [4].

The average HIV transmission probability per act of UAI with a partner who is HIV-positive but is not aware of his infection is given by

$$\beta_{ND} = q_i^N \beta_i + q_{rw}^N \beta_{rw} + q_r^N \beta_r , \quad (6)$$

yielding a value of ~0.0069, which is considerably greater than the risk of UAI with partners of any other perceived HIV status.

We do not consider different infectiousness periods during the natural history of infection but use estimates from the chronic asymptomatic stage of infection (ignoring the greater infectiousness of newly acquired infections) [3,5].

We estimate the relative risks of HIV acquisition associated with serosorting compared with not serosorting and refer to this as the relative risk of serosorting. For serosorting, if HIV status is disclosed then partnerships where UAI takes place will only form if the partner is thought to be seroconcordant and the sexual positioning (insertive or receptive UAI with or without ejaculation) within the partnership is then based on perceived knowledge of the partner's serological concordance (Fig. A1). In comparison, if serosorting does not occur a sexual partnership may form regardless of the partner's serostatus and sexual positioning within the partnership is more conservative (Fig. A1). Accordingly, if the prevalence of HIV in the population is P, p_{ND} is the proportion of HIV-infected MSM that are not diagnosed, and p_T is the proportion of HIV-infected MSM who are diagnosed that are on treatment, then

$$N_S = N(1-P),\ N_{ND} = NPp_{ND},\ N_D = NP(1-p_{ND})(1-p_T),\ N_T = NP(1-p_{ND})p_T, \quad (7)$$

and the relative risk of serosorting compared with not serosorting can be represented mathematically by the ratio of the chance of transmission when serosorting to the chance of transmission when not serosorting, namely,

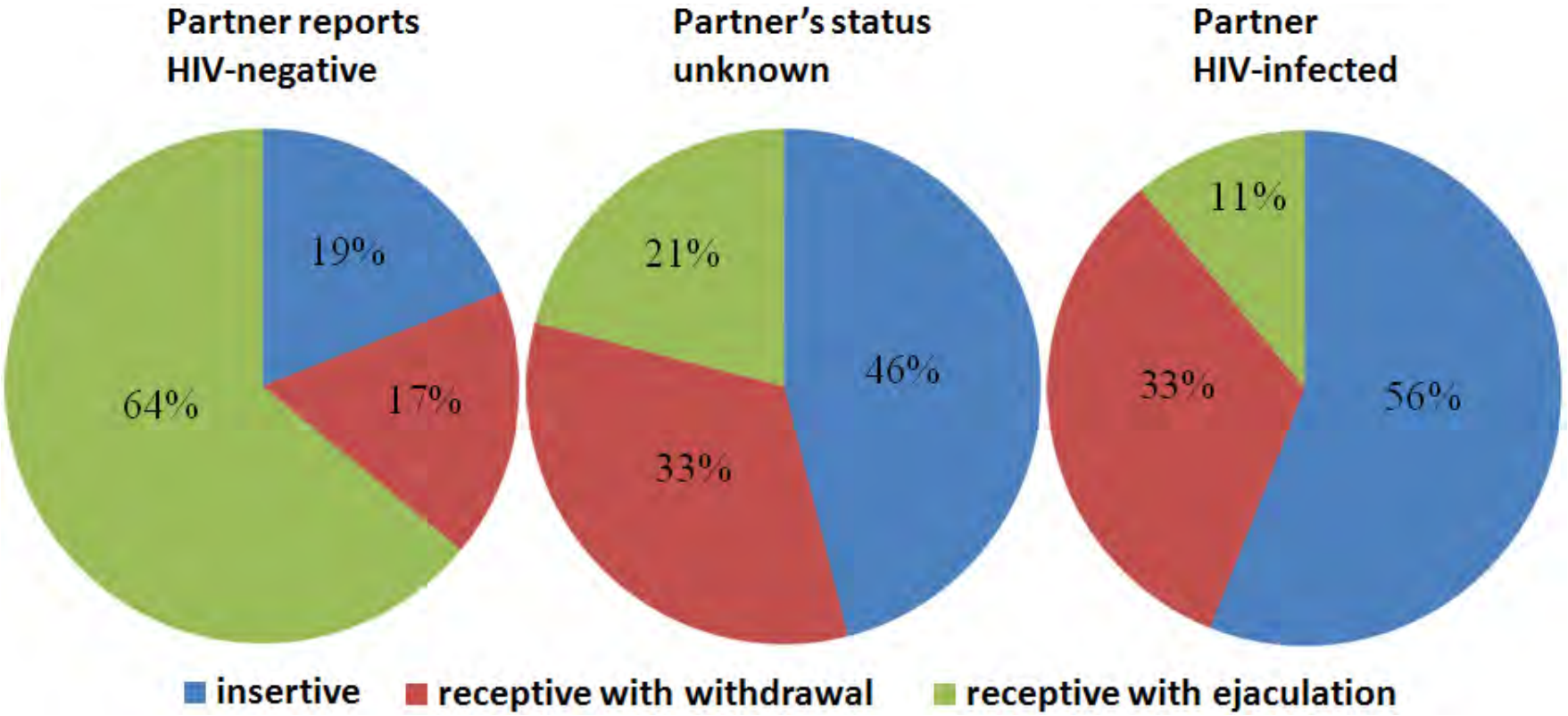
$$\rho = \beta_{ND} p_{ND} \Big/ \left[(1-P+Pp_{ND})\left(\beta_U p_{ND} + \beta_U (1-p_{ND})(1-p_T) + \beta_U p_T (1-\phi)(1-p_{ND})\right)\right]. \quad (8)$$

This relative risk has maximum value (when there is no HIV testing) of

$$\rho_{\max} = \frac{q_i^N \beta_i + q_{rw}^N \beta_{rw} + q_r^N \beta_r}{q_i^U \beta_i + q_{rw}^U \beta_{rw} + q_r^U \beta_r}, \quad (9)$$

yielding a value of ~2.15, and a minimum value (when everyone knows their true HIV status) of $\rho_{\min} = 0$.

Figure A1: Breakdown of self-reported sexual positioning practice: percentage of acts of unprotected anal intercourse (UAI) that are insertive, receptive with withdrawal, or receptive with ejaculation, based on the reported HIV serostatus of the partner (from the HIM study[1,2]).



References for Appendix

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