Epidemiologic synergy – the contribution of heterosexual HIV transmission to the spread of HIV among men who have sex with men (MSM) in South Africa

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For Michael Hangula, the first boy I kissed, rest in peace.

Abstract

Background: Could heterosexual HIV transmission be a driver of HIV infections that occur in men who have sex with men (MSM)? Noting the disproportionately high HIV prevalence among MSM across a variety of settings, this subpopulation is often considered as sources of new infections, overlooking the possibility of HIV transmission from the heterosexual – general – population to MSM.

Objective: To assess the relative contribution of heterosexual transmission of HIV for onwards transmission of HIV from one man to another.

Method: An agent based model of heterosexual transmission of HIV in South Africa was extended to simulate the HIV epidemic among MSM from 1990 to 2012. The model included gay men (who only have sex with men), bisexual men (who have partners of both sexes) in addition to men who have sex with women. HIV prevalence and sexual behaviour data collected among MSM in South Africa served as calibration data.

Results: The model estimated that 28.7% (IQR: 27.4-28.9%) of MSM were HIV positive in 2010. By simulating a counterfactual HIV epidemic in South Africa, where HIV only spreads via male-male sex, we observe a decline in HIV incidence occurring in MSM by 56% over the period of 1990-2010, relative to the historical reality of HIV spreading via heterosexual and male-male sex. Analogously, HIV prevalence among MSM in 2010 under the counterfactual scenario reached only 10.0% (IQR 2.8-17.4%), substantially less than HIV prevalence estimates from samples of MSM in South Africa.

Conclusion: Roughly half of the HIV infections among MSM in South Africa can be attributed to the high levels of HIV prevalence in the general population. Scale up of interventions to target high risk behaviours with male partners should dispel possible misconceptions of bisexually active or heterosexual MSM as lower risk partners, relative to those MSM in gay communities.

DECLARATION

I, **Pancho Mulongeni**, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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Contents

Part A: Study protocol

1. Background

South Africa is a country with a widespread, generalized, Human Immunodeficiency Virus-1 (HIV) epidemic, with an HIV prevalence that grew from 0.7% among pregnant women in 1990, to reach roughly one quarter of pregnant women in 2000 (1). Although South Africa has made considerable gains in addressing the HIV epidemic, achieving a reduction in AIDS mortality via the largest antiretroviral treatment (ART) programme in the world (2), it must now address the unacceptably high HIV infections among marginalized subpopulations (3).

Until recently, there have been few studies from South Africa that assessed the burden of disease in men who have sex with men (MSM), in comparison to men who do not report sex with other men. Two recent studies – one measuring self-reported HIV status in a convenience sample (4) and the other a population based seroprevalence study (5)– found that MSM have a higher prevalence of HIV, compared to their similarly aged counterparts (who only report sex with w6omen). These data underscore a greater vulnerability to HIV infection among MSM compared to men who do not have sex with other men.

An important feature of the HIV epidemic in South Africa, is the interconnectivity of the MSM epidemic to that of the general population. Numerous samples of MSM, using both convenience and probabilistic sampling methodologies, concur that MSM in South Africa typically have female partners (4,6-9). Furthermore, evidence from a molecular epidemiological study has demonstrated that HIV subtype C – the predominant subtype in the general population of South Africa – has nearly supplanted subtype B among white MSM, among whom the HIV epidemic began as result of transmission from MSM in countries where subtype B predominates (10). These data suggest that HIV transmission chains in the general population connect to those driving new infections in MSM.

Investigators have advanced a framework for specifying the relationship between the epidemic of HIV among MSM and that of the larger – general – population(11,12). Under this framework, MSM in

South Africa run concurrent risks of HIV acquisition from both male and female partners. However, these risks were not quantified, since the framework merely compared HIV prevalence in the general population to that of samples of MSM within a particular country. Moreover, existing studies on HIV risk in MSM from South Africa rely on prevalence surveys which cannot estimate the risk of infection, owing to a lack of temporality in the study design. The molecular epidemiologic studies that enable investigators to ascertain common sources of HIV infection – and thus infer a sexual contact network – by genetic sequencing of HIV surveillance data at a national scale (in high income countries) (13) are likely to prove too costly to implement beyond specific geographic areas within middle-income countries, such as South Africa. Alternatively, one can turn to mathematical modelling of the HIV epidemic. Modellers use existing information, on the sexual risk behaviours of individuals in a population, to create simulated epidemics that shed light on the possible contribution of these behaviours to the incidence of disease.

Mathematical models of the HIV epidemic typically simulate one of two epidemic settings. In the first, the epidemic is presumed to be exclusively driven by heterosexual transmission (14-16) . Such models overlook the contribution of MSM to HIV infection (17). In the second, the models assume HIV transmission occurs only between MSM, as an approximation to the concentrated epidemic situation in numerous countries, where MSM account for a high fraction of new HIV cases (18-21). For example, one recent model of the HIV epidemic among South African MSM (22) is based on an exclusively male population. Hence, this model overlooks the epidemiologic context of South Africa, where the sexual networks of MSM and the heterosexual population are interconnected. This model is also parameterized based on a single, convenience sample of urban MSM (23), and the conclusions might therefore not be generalizable to other South African MSM.

We will construct a model where men are allowed to have sexual contact with partners of either sex, and we will simulate the formation of sexual networks between 1990 and 2012, allowing for male to male transmission of HIV. In addition, the model will consider the counterfactual scenario of zero HIV transmission via the heterosexual route. Essentially we will perform a *gedankenexperiment* (thought experiment) to ask what would have happened to the HIV epidemic among MSM in South Africa, in the event HIV transmission was confined to sex between men. Hence, we will quantify the extent to which HIV transmission in the general population potentiates the risk of HIV via male-male sexual contact.

2. Rational for the study

Present understanding of the HIV epidemic among MSM in sub-Saharan Africa posits that interventions targeted at this sub-population will yield the greatest reduction in male-to-male transmission of HIV (12). The present study will assess how sexual networks link HIV transmission in the general population to the MSM subpopulation. With findings from our study, policy makers will better understand to what extent interventions in the general population will be of benefit in reducing transmission in MSM.

3. Objectives

3.1 Primary

To quantify the relative contribution of heterosexual HIV transmission towards HIV infections among MSM in South Africa.

3.2 Secondary

i) To provide a national estimate of HIV prevalence among MSM in South Africa.

ii) To estimate the fraction of bisexual men – the fraction of men who have propensity for sex with women and men – among all men who have a propensity for sex with other men in South Africa.

iii) To estimate how the preference for male partners among bisexual men changes over the life course, in South Africa.

iv) To compare the HIV prevalence in MSM to that of all other men in South Africa.

v) To identify the demographic traits and sex of infecting partner (male or female) among all men who have at least one sexual contact with other men and who acquire HIV during the course of the model simulations.

4. Method

4.1 Study Design

Dynamic modelling of infectious disease. As such, there will be no human subject data collection.

4.2 Overview of the model

The present study will extend an agent-based version of the Sexually Transmitted Infection-Human Immunodeficiency Virus (STI-HIV) interaction model, a previously-developed model of heterosexual HIV and STI transmission in South Africa (24). For the present mini-dissertation, we will only simulate the HIV epidemic and will not consider the effect of STIs on the HIV epidemic, even though the name of the model refers to this interaction. Like other models of infectious disease (25), the STI-HIV interaction model classifies individuals into different states, such as the HIV negative (susceptible) state and the HIV positive (infected) state, and projects the change in HIV incidence over time as a function of current HIV prevalence. The agent-based version of the STI-HIV interaction model has been described in detail elsewhere (24).

We shall introduce structural changes to the STI-HIV interaction model so as to accommodate the sexual transmission of HIV between men. A fraction of male agents in the model will have the option of sexual contacts with only female or male agents, while a subset of male agents shall remain heterosexual –forming sexual contacts with female agents. The final subset of male agents will thus be exclusively homosexual – forming sexual contacts with just men. As anal sex between men entails two possible roles during sexual contact – either receptive or insertive role – the model will allow for differences in role preference between MSM and differences in HIV transmission risk depending on whether a receptive or insertive role is adopted.

The extended model shall be referred to as “the MSM inclusive model” in this protocol. We shall use the literature to estimate the parameter values for the modelling of sex between men, including both biological and behavioural factors that facilitate HIV transmission. Specifically, this study shall seek to model sexual relationships between men, including probabilities of transmission with and without protective measures (condoms and ART), their role preferences during sex, the rates at which they engage in protected sex and the context within which they have sex – casual sex or steady partnerships.

4.2.1 Specifications of the MSM inclusive model

The MSM inclusive model will also be identical to the agent-based version of the STI-HIV interaction model with respect to the simulation of the sexual behaviour of women and men who are exclusively heterosexual, as described previously (24). The MSM inclusive model shall modify the sexual activity state variables for men who have propensity for sex with other men.

Sexual orientation in men shall be modelled as a variable that remains constant or changes over the course of life. The following sexual orientations shall be modelled, by assigning men different specifications of the male preference parameter:

1. Heterosexual men – have a male preference set to zero. These men can only choose female partners.
2. Gay men – have a male preference parameter of 1. These men can only choose male partners.
3. Bisexual men – men who can have sex with both men and women. A sexual preference parameter, between 0 and 1, will be used to randomly assign the propensity for choosing male partners as opposed to female ones. For example, if the preference parameter is set to 0.6 for a given individual, that individual will choose male partners 60% of the time. The male preference parameter will depend on the age of the bisexual man. For example, at age 20 the male preference parameter may be 0.6, but at age 30 the male preference parameter may have decreased to 0.4. Thus, the model can capture common changes in sexual behaviour of MSM that depend on socio-cultural factors.

The values of male preference parameter most consistent with available data will be identified during model calibration (Section 3.2.3).

Male sexual activity will take place in the context of the following relationship types within the model (Figure 1):

a) Short term (non-cohabiting) partners.

b) Long term (cohabiting) partners.

c) Casual sex – This refers to a context where sexual contacts occur outside of a formal partnership, without explicit exchange of money, but encompasses transactional sex (26,27). This is a new type of sexual contact that will be added to the model for gay and bisexual men only.

d) Sex work – the STI-HIV interaction model allows for women to engage in sex work with male clients. Limited data is available on the social-sexual contexts of male sex work in South Africa. As such, there is insufficient data to include male sex work in the model. Available evidence, however, suggests male sex workers likely represent only a small fraction of the total sex worker population in South Africa (28).

4.2.2 Extension of the STI-HIV interaction model

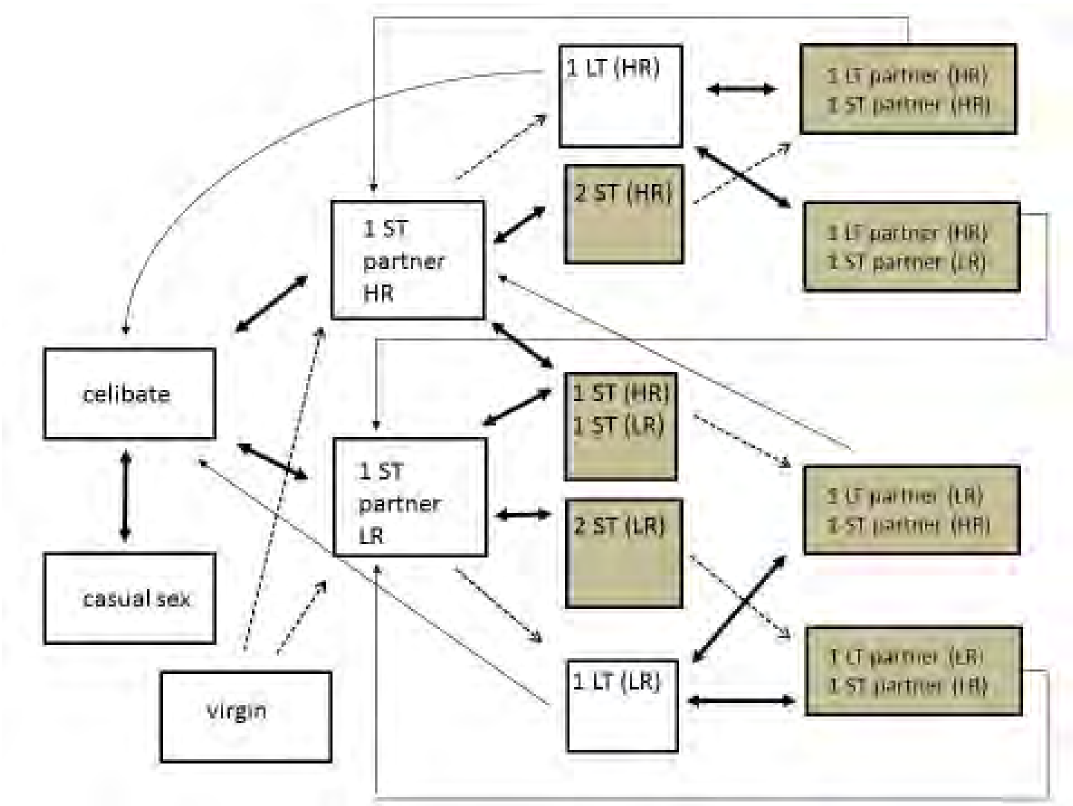

Figure 1 Sexual activity states for gay and bisexual men. Note that bisexual men can choose partners of either sex, while gay men choose only male partners. Arrows with dotted lines denote change in partnership type with the same partner. Partners are either long term (LT) or short-term (ST), partners can be either "high-risk" (HR) or "low-risk" (LR). White boxes refer to sexual activity states occupied by LR or HR men, while shaded boxes are states exclusive to HR men. Note that casual sex is a state that HR men can enter while being in a partnership. Figure adapted from the STI-HIV interaction model (29).

Individuals will be further subdivided into two sexual activity states, "high risk" and "low risk", with respect to the type of sexual behaviour. "High risk" men have the propensity for concurrent partnerships. "Low risk" men are monogamous, never having more than one sex partner at any time. Bisexual men who are "high risk" also have the option of soliciting the services of female sex workers, in addition to casual sex with men and the formation of short or long-term relationships with men or women.

Casual sex and long- and short-term partnerships differ further in terms of the following model parameters:

- Rates at which partnerships are formed
- frequency of sex
- probability of HIV transmission per sex act
- rates of condom use during sex

The simulation consists of agents who move between the states specified in the model. The HIV epidemic is simulated in a population with an initial size of 20 000 men and women, whose age-sex distribution is specified by a predefined population pyramid, as described in the STI-HIV interaction model (29). Individuals in the model move between sexual activity states over the course of the simulation, which begins in 1985 and ends in 2012, proceeding in weekly time steps. The unshaded blocks in Figure 1, for example, shows the sexual activity states for gay and bisexual men in the model (adapted from the STI-HIV interaction model (29)). The model assumes that these men are either in the celibate state or in various sexually active states. Further assumptions include:

- Short-term partnerships can become long-term, but long term partnerships cannot revert to short term partnerships.
- Sex between men will be modelled as anal intercourse or non-penetrative intercourse, because a cursory review of the literature has found MSM reporting frequent non-penetrative sex (5,30). In line with available evidence, HIV transmission will be set to zero for non-penetrative intercourse (31). Probability of transmission via anal intercourse will be set after review of the available evidence (see Section 3.2.3**).** The assumptions for anal sex – how and when it takes place in relation to non-penetrative sex – will be modelled after review of the relevant studies among South African MSM. The model will allow for different roles in anal

sex, because modelling has shown segregation of roles in sex can have substantial impacts on HIV incidence among MSM in other settings (32).

4.2.3 Calibration: Estimation of parameters

Data sources for the calibration of model parameters will include observational studies on the sexual behaviour, demographics and risk of HIV among MSM in South Africa and observational studies from other countries, where the HIV transmission probabilities for sexual intercourse between men are estimated.

Studies selected for calibration will comprise of observational studies, where investigators have reported near representative samples or samples with the lowest chance of selection bias of MSM in South Africa. Studies reporting non-representative – convenience – samples of MSM in addition to qualitative studies will be considered in the event there is a scarcity of data available from studies with near representative samples.

For those parameters that are difficult to determine precisely, parameterization will follow the Monte Carlo (33) and Bayesian (34) approaches described by previous modelling studies:

1) The parameters will be assigned prior distributions (probability density functions) to represent the uncertainty regarding the parameter values, based on findings from the literature review.
2) A random sample is drawn from the distribution of each parameter and all random values are combined into a set. Using *n* draws for each parameter, *n* such parameter combinations will be generated.
3) For each parameter combination, the model will be run and levels of HIV prevalence estimated by the model will be calculated.
4) For each model run, a likelihood function will be calculated to represent how well the modelled HIV prevalence levels match the observed HIV prevalence levels in South African MSM.

5) As more than one set of parameters will fit the observed HIV prevalence, we will generate uncertainty ranges by randomly sampling the parameter combinations that yield the highest likelihood values.

The extent to which the model output varies as a function of the variation in the set of best-fitting parameters used will constitute uncertainty analysis. The procedure for calculating the likelihood with respect to sexual behavioural outcomes will be the same as that described above for HIV prevalence.

4.2.4 Assessment of objectives

We shall consider the following model scenarios:

Scenario 1: HIV transmission occurs via vaginal (between men and women) and anal intercourse (between men).

Scenario 2 (counterfactual): HIV transmission occurs only via anal intercourse (between men), and the probability of transmission for vaginal intercourse is set to zero.

- By comparing whether there is a meaningful difference in the HIV incidence and prevalence among MSM in the two scenarios, we will address the primary objective.
- By obtaining the median HIV prevalence among MSM in Scenario 1, from model simulations most consistent with calibration targets, we will address secondary objective i)
- By obtaining the mean fraction of bisexual men, among all bisexual and gay men, from model simulations most consistent with calibration targets, we will address secondary objective ii)
- By obtaining the mean rate of change of male preference, among bisexual men, from model simulations most consistent with calibration targets, we will address secondary objective iii)
- By comparing the median HIV prevalence among MSM, obtained in secondary objective i), to the median HIV prevalence among all other men, accounting for age, we will address secondary objective iv)

By identifying the traits of all HIV positive men who had sexual contact with at least one male partner over the course the simulation, in addition to recording the sex of their infecting partners, we will address objective v).

5. Ethical Considerations

No human subject data will be collected. The study hence presents no risk to any human beings. The primary benefit of the study is the improvement of HIV prevention strategies for MSM in South Africa. A larger benefit will be to raise the level awareness of MSM in sub-Saharan Africa.

6. What happens at the end of the study?

Once a preliminary set of model outputs are produced, stakeholders in healthcare services targeted towards MSM – as well as MSM in grass-roots non-governmental organizations - shall be consulted. With stakeholder input, a final set of model parameters may be identified for modelling of the scenarios described in this proposal. In this way, ownership of the study by the MSM and health provider community will make it a just use of resources.

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Part B: Literature review

Part B

1. Aims and Methods

1.1 Objectives of the Review

i) Review of models of HIV transmission among MSM in Africa

ii) Review the extent to which HIV transmission networks in MSM and heterosexuals are connected.

iii) Review data on HIV prevalence and sexual behaviour among MSM in South Africa, for the purpose of incorporating MSM within an existing model of heterosexual HIV transmission in South Africa.

1.2 Search Strategy

In July 2015, we undertook a search for articles on HIV among MSM in South Africa, using Google Scholar, Africa-Wide and PubMed. PubMed was selected to because it has a near comprehensive inclusion of the public health literature. However, as it is known that numerous journals, particularly from the Global South are not indexed in PubMed. We thus included Google Scholar and Africa Wide to identify articles appearing in African based journals and grey literature that may be absent from PubMed, given our focus on South Africa. (Table 1).

We also undertook citation tracking - examining reference lists of identified review articles - in addition to examining citations of all chosen articles, in addition to Google Scholar alerts of newly published articles. Each objective of the review has its own inclusion criteria (described at the start of each section). Titles of articles returned by the search strategy served as a first check of eligibility. The abstracts of identified articles then served to determine eligibility for inclusion, under the respective objective of the review. Finally, the introductory sections for each objective of the review included seminal articles selected for pedagogic value.

Table 1 Search strategy

Database	Search terms	Results and Limits
Pubmed	(HIV OR AIDS) AND (MSM OR Gay) AND (South Africa)	220 (No Limits)
Africa Wide	(HIV OR AIDS) AND (MSM OR Gay OR Homosexual) AND (South Africa)	346 (Limit: Articles in English)
Google Scholar	(HIV OR AIDS) AND (men who have sex with men) OR Gay OR Homosexual AND (South Africa)	64 (Limit: All in title)

2. Mathematical Modelling

2.1 Background

2.1.1 Models of infectious disease

Mathematical modelling allows investigators to understand the propagation and persistence of infectious disease – by considering the essential features of the phenomena. There exist static and dynamic models of infectious disease. Static models are amenable to understanding the population-level burden of disease at particular point in time, while dynamic models allow one to understand the temporal change in infectious disease (1).

2.1.2 Dynamic models

The likelihood that a person - in a population where an infectious disease is spreading - acquires the disease is proportional to the prevalence of that disease. Factors that alter the prevalence of disease, such as treatment of infectious persons or their demise from disease will thus alter the likelihood any person becomes infected. The fact that epidemics have characteristic growth curves means the dynamics are amenable to description with systems of differential equations (compartmental models), or a simulation of disease spreading in contact networks (microsimulation models) (2). Dynamic models of infectious disease are thus appealing, because they mimic an epidemic by accounting for how the incidence of disease depends on prevalence.

In addition, dynamic models allow investigators to chart the course of an epidemic either by recreating likely historical trajectories of prevalence or forecasting how the epidemic may change in response to interventions. Models benefit epidemiology, because they integrate various data sources, from disease surveillance to human behaviour, to provide evidence-based answers to research questions that are beyond the scale of studies on human populations (3). Yet this is also a weakness of modelling, because even in instances where the model outcomes correspond to real-world data, predictions from models often fail to account for unanticipated changes in population-level behaviour and interventions that impact on an epidemic (4).

While assessing the changes in epidemics under various interventions is a common use of modelling, fundamentally models allow researchers to gain insight into the underlying mechanisms that drive disease propagation. By allowing for counterfactual scenarios that are often unobservable, such as setting a known route of HIV transmission to zero, models permit investigators to assess the contribution of different routes of transmission to propagation of infection (1). Examples include assessing the effects of eliminating inter-generational partnerships (5) on the HIV epidemic among heterosexuals in Zimbabwe, and assuming HIV is only transmitted between female sex workers and their clients, to test if this is sufficient to establish the HIV burdens observed in Central and West Africa (6).

2.1.3 Modelling HIV epidemics at country level

Models have varying scope; they describe only a given set of factors leading to the spread of disease in the simulation. The omission of key factors, however, compromises the utility of the model to explain the aetiology of epidemics (3).

The United Nations Joint Programme on HIV/AIDS (UNAIDS) categorization of HIV epidemics as either generalized or concentrated may be, at least in part, responsible for the omission of male-male transmission in most models of HIV epidemics in Southern Africa. As generalized epidemics imply widespread transmission of HIV in reproductive aged adults, sex between men was considered to contribute little to expansion of the epidemics in Southern Africa (7). This oversight meant little attention was paid to specific HIV prevention needs of MSM in generalized epidemics, (8) due to the often unsubstantiated belief that resources targeted to HIV prevention in the general population will suffice for all high-risk groups (9) (6).

Current modelling of generalized HIV epidemics makes untenable assumptions about the relationship between HIV circulating in this subpopulation and the epidemic in the overall population. With the adoption of the "Know Your Epidemic/Know Your Response" framework in the 2000s, UNAIDS allowed countries to assess the degree to which HIV infections in MSM contributed to incidence in the whole population, by using the Modes of Transmission (MoT) model (10). Yet, this model neglects the possibility that MSM can acquire HIV from female partners. Instead it assumes that MSM connect to the heterosexual population only by onward transmission of HIV to their female partners (11). This means that UNAIDS models are limited in their ability to characterize the HIV epidemic among MSM within generalized HIV epidemics.

The focus of HIV models in South Africa has also been heterosexual transmission of HIV, at least from the 1990s (12) until the 2000s (13,14). We thus review models of HIV transmission in MSM in African countries, where most of the generalized HIV epidemics occur, with the aim of understanding how the models simulate the transmission of HIV in MSM, in relation to the overall epidemics of these countries.

2.2 Structured review of HIV modelling studies

2.2.1 Inclusion criteria

HIV modelling studies which mention MSM in African populations.

2.2.2 Identified articles

We identified 6 articles meeting our inclusion criteria. Five mathematical models were described in the 6 articles (Table 2).

In terms of populations simulated, two of the models - MoT and Optima - are designed for use across a wide range of different populations. Both of these models aimed to address resource allocation in HIV epidemics, by understanding the distribution of infection across population sub-groups. Both models assumed that MSM only acquired HIV from other MSM. The MoT model does allow for MSM to transmit infection to females, while Optima assumes infections due to MSM remain within this sub-population.

Two microsimulation models were identified and they differed in their approach to modelling HIV among MSM. One microsimulation model assumed a static, closed sexual network of MSM, with no heterosexual contact (15,16). The parameters – explicit assumptions regarding the simulation of HIV transmission and risk behaviour – for this model were calibrated to data from a single survey among a cohort of MSM in Cape Town (17). Similarly, the other microsimulation model assumed a closed sexual network of MSM in Kenya and was calibrated to data from a single cohort of MSM in Kenya, but the model allowed for dynamic partnerships formation and dissolution (18).

In contrast, the other model of the HIV epidemic in Kenya explicitly modelled sexual contact and HIV transmission between MSM and the general population. In this model, investigators based parameters concerning HIV transmission among MSM from the peer-reviewed literature and a nationwide study on 'most at risk' groups for HIV infection in Kenya. The model assumed MSM had either only male partners or were bisexual. For bisexual men, investigators modelled the preference for male partners by considering the ratio of male to female partners reported in an observational study. The model assumed bisexuals had a fixed propensity for sex with other men over the life course. Furthermore, the model assumed MSM sexual behaviour was either high or low risk for HIV acquisition (19).

Table 2 Mathematical modelling studies included in the review

First author of modelling study (reference No.)	Population simulated	Type of Model	MSM assumptions
MoT: Gouws (20)	User inputs population data	frequency dependent (binomial function)	All infections in MSM acquired from other MSM.
Optima: Kerr (21)	User inputs population	frequency dependent (Compartmental model)	All infections in MSM acquired from other MSM.
Sullivan (18)	MSM in Kenya (22)	microsimulation (network model, partnership formation and dissolution)	MSM transmission in the context of generalized epidemic
Anderson (19)	MSM in Kenya (22)	frequency dependent (Compartmental model)	1. MSM transmission in the context of generalized epidemic 2. MSM divided into three risk groups (high risk exclusive homosexuals, high risk bisexual, low risk bisexuals) 3. Bisexual men are indistinguishable from heterosexual men in simulating partnerships with women.
Brookmeyer, McNaghten (16,23)	MSM in Cape Town	microsimulation (network model, partnership formation and dissolution)	MSM only have sexual contact with other men. Allows for main,

		regular and casual partnerships. Parameters determining partnership formation, frequency of sexual contact based on a data from a South African MSM cohort (24)

2.2.3 Discussion of articles

There are few studies modelling the spread of HIV among MSM in African populations. Only one of the studies identified allowed for MSM to acquire HIV from contact with the heterosexual population (19).

None of the studies estimated the fraction of HIV infections in MSM that result from sexual contact with heterosexual women. The absence of modelling studies that address heterosexual acquisition of HIV in this population represents a gap in the literature.

The population-level data that informed model parameters was often limited, with only one study integrating data from a comprehensive review of literature of HIV among MSM (19). However, even in this study, key model assumptions, such as the fraction of partners who are male among bisexual MSM, were based on limited data. The paucity of data available for the construction of models of HIV among MSM is a challenge to furthering our understanding of their HIV risks.

There were no studies that assumed MSM had a changing preference for other men over the duration of their lives. By contrast, data emanating from prospective studies of human sexual behaviour indicate MSM can have fluid same-sex preferences (25-28). Though these studies come from high-income countries – and may not be transferable to developing country settings – it is nevertheless possible that changing sexual preferences of MSM may be important for the epidemiology of HIV in generalised epidemics.

2.2.4 Conclusion

There is at present no network model of HIV in generalized epidemics in Africa that firstly incorporates MSM within the heterosexual network and secondly allows MSM to have changing preferences for other men, relative to women. Importantly, no modelling studies reported on the HIV acquisition from the general population among MSM.

3. Evidence of connectedness – HIV in MSM and the general population

3.1 Background

3.1.1 Types of epidemic: generalised or concentrated

An understanding of the global distribution of HIV initially cast most of sub-Saharan Africa as having generalized HIV epidemics, where HIV infection would persist in the wider population, in the absence of ongoing infections in subpopulations at elevated risk of infection, such as MSM (7). Boily et al. have emphasized, however, that this view of HIV epidemics in the region is misleading, because it fails to account for the amount of transmission between key populations and the general population (6). Recent data emerging from across the sub-Saharan African region has shown that even in generalized epidemics, MSM bear a disproportionate HIV burden in comparison to their heterosexual counterparts (29). This revised understanding ushered in the notion that MSM are situated in a concentrated epidemic within generalized settings (30). One can thus conclude the higher HIV prevalence observed in MSM from the region is due to transmission within clustered sexual networks comprising of men, as the definition of concentrated epidemic necessitates that HIV expansion is sustained by transmission within a particular subpopulation (7). Notwithstanding, investigators have noted that MSM in Africa are at substantial risk of HIV acquisition from women, who in turn are infected by men in the heterosexual population (29). The present review aims to assess to the extent to which HIV epidemics in MSM are connected to those of the wider population, in Africa.

To this end, we reviewed observational studies of the sexual behaviour of MSM and the molecular phylogeny of HIV pertinent to links between HIV circulating among MSM and the epidemic among heterosexuals in Africa. While the sexual behaviour data provides evidence for potential transmission, the phylogenetic studies provide evidence of occurrence of transmission between population groups. The method employed in phylogenetic studies is predicated upon viral strains of HIV-1 M group, which has several subtypes, and the distribution of which varies according to population group. Alignment of HIV sequences isolated from patients allows one to infer the transmission chains that exist in the population. As the rate of change of sequences is known for HIV-1, individuals who occupy proximal positions in a sexual network will have sequences that have significantly fewer differences, compared to other individuals at more distal positions in a chain of transmission (31).

3.2 Structured review

3.2.1 Inclusion criteria

Articles explicitly referring to HIV transmission between MSM and female partners in addition to any evidence - or lack thereof - of potential connectedness of HIV transmission chains in MSM and heterosexuals in Africa.

3.2.2 Identified articles

We identified three articles from our search and after tracking the citations of the initial three, we identified a further 8 articles (Table 3). In total, we found 11 eligible articles.

Table 3 Studies with evidence for links between HIV epidemics in heterosexuals and MSM

First author (Reference No.)	Location	Study design and sampling	N	Type of Evidence
Smith (32)	Kenya	Prospective diary of sex acts; Venue-based and chain referral	85 MSM SW	Quantification of sex acts with male and female partners.
Tovanabutra (33)	Kenya	Retrospective cohort study and cross-sectional; Venue-based and chain referral	13 MSM, 9 FSW, 1 heterosexual man (n=23)	Molecular phylogeny
Mannava (34)	Kenya	Cross sectional; Times Space Sample	867 MSM SW	Behavioural survey
Sheehy (35)	Nigeria	Cross-sectional; RDS	557 MSM	Seroprevalence survey with behavioural data
Sathane (36)	Mozambique	Cross-sectional; RDS	1325 MSM	Seroprevalence survey with behavioural data
Sandfort (37)	South Africa	Cross-sectional; RDS	480 MSM	Seroprevalence survey with behavioural data
Bezemer (38)	Kenya	Retrospective cohort study; cross-sectional; Select from individuals enrolled in cohorts – no detail on sampling method	84 MSM, 226 other men, 364 women	Molecular phylogeny

Ndiaye (39)	Senegal	Cross-sectional Snowball sample	70 MSM	Molecular phylogeny
Ndiaye (40)	Senegal	Cross-sectional Snowball sample	97 MSM	Molecular phylogeny
Leye (41)	Senegal	Cross-sectional Snowball sample	69 MSM	Molecular phylogeny
Middelkoop (42)	South Africa	cross-sectional study; Venue-based and snowball sample	194 MSM	Molecular phylogeny

3.2.3 Discussion of articles

There is countervailing evidence for bisexual activity as a conduit of HIV transmission from heterosexual to MSM networks in sub-Saharan Africa. Sandfort et al., hypothesized that bisexual identified men in South Africa permit the bidirectional transmission of HIV, between MSM and the general population (37). Yet there is limited evidence for this hypothesis from the data investigators collected in their bio-behavioural survey of MSM sampled in Pretoria, South Africa. That study reported the odds of HIV infection increased by roughly two fold with each reported male lifetime partner and decreased by nearly 2.5 fold for men who ever reported sex with a woman, after adjustment for potential confounders. Therefore, the data from South Africa suggest that HIV acquisition in MSM results from having sexual contact with other men and not women. In Nigeria and Kenya, on the other hand, there is evidence that MSM engage in unprotected sex with men at comparable frequencies as they engage in unprotected sex with women. In particular, in a sample of MSM in urban Nigeria, roughly half of the respondents were bisexually active; they had had recent sex with women. The majority of these bisexually active MSM reported unprotected anal sex with a man (62.7%), which was comparable to the proportion who reported unprotected vaginal sex with a woman (66.0%), while unprotected anal sex with women was the most common behavior (74.0%) (35). Similarly, prospective and cross-sectional studies from Kenya have found that MSM engage in frequent unprotected vaginal (32) and anal sex with women (32,34). The prospective study further found comparable rates of unprotected penetrative intercourse with men and women (32). These Kenyan and Nigerian studies thus indicate there is ample opportunity for MSM to acquire HIV from female partners and transmit to MSM sexual networks. Yet it is unclear whether these behaviours actually mediate transmission between the heterosexual population and MSM.

Recent findings from Mozambique, however, have begun to resolve the contrasting findings on the role of bisexual activity in the transmission of HIV in MSM. In this study, investigators defined bisexual men in terms of recent sexual contact with women, in addition to enrolling a sufficient number of bisexual men to ascertain their specific HIV acquisition risks (36). They found that bisexual men had a higher HIV prevalence than exclusively homosexual men in one of the three cities where the study took place. Noting furthermore that transactional sex with women was the single most important risk factor for HIV infection among MSM in that sample, notwithstanding the cross-sectional design of the study, these finding suggests that bisexual men in Mozambique acquired HIV from women. Importantly, these findings contrast those from the two other cities in Mozambique – akin to studies in South Africa (37) and Nigeria (35) – where HIV prevalence in MSM who report only male partners was markedly higher to those who report recent female partners. The reasons for these disparate findings may be due to differences in sampling from existing HIV transmission chains, or differences in MSM behaviours between populations.

Phylogenetic studies have produced conflicting findings regarding the extent of HIV transmission between heterosexual adults (the general population) and MSM. Studies in both South Africa (42) and Senegal (39,40) have relied on known distinctions in the distributions of HIV-1 subtypes in MSM and the general population, to investigate possible overlap of sexual HIV transmission between the two populations. In these instances, investigators advanced that changes in the type and distribution of HIV-

1 subtypes were indicative of one two trends: either the introduction of new HIV subtypes (initially limited to heterosexuals) into the MSM population (42) or the enlargement of MSM sexual networks to include potential female partners (41). In some instances, investigators have identified putative transmission links between HIV isolates from a MSM and a woman in the general population (41). However, studies have also used phylogenetic clustering of MSM sequences to demonstrate that sexual networks among MSM are predominantly separate from those in the general population (30); such women with HIV sharing only 26% of clustered HIV sequences isolated among MSM with HIV, from two cohorts in Kenya (38). These findings appear incongruous with those of a study where the phylogenetic evidence suggested intermingling of the sexual networks through which HIV was spread in MSM and heterosexuals in Kenya (33).

An explanation for these divergent findings forwarded by Smith et al., is that there is heterogeneity in behaviour of men who have sex with men, with some men being more sexually exposed to women with HIV than other men. That phylogenetic studies in Kenya overlooked the distribution of bisexually active men in their samples meant they could not account for the sexual behaviours that could explain their findings (32). In the event a sample was predominantly comprised of MSM with frequent heterosexual contact – bisexually active men – the phylogenetic evidence stemming from such a sample would likely indicate acquisition from the heterosexual population, while the converse would also be true. Differences in the fractions of bisexual men across phylogenetic studies may have accounted for disparate findings.

3.2.4 Conclusion

It has been hypothesized that bisexual men can convey HIV from the general population to MSM communities. However, there is insufficient evidence to support this conclusion from bio-behavioural studies of HIV, because they could not account for time of infection, the sexual role of the infecting partner and whether or not the infecting partner was bisexually active (32,34,35,37) . In conclusion, there is too little bio-behavioural data to support or undermine the notion that bisexually active men mediate HIV infection from heterosexuals to MSM.

Phylogenetic studies have also provided countervailing evidence of epidemiologic links between heterosexuals and MSM (33,38-42). More precisely, the phylogenetic studies reviewed here did not measure recent sex with women among MSM. Hence, the studies are limited in the extent to which they can provide insight into their HIV acquisition risks from female partners. In high income settings, investigators have the benefit of population based HIV surveillance data to ascertain relationships between transmission chains in MSM and those in the general population (43). Until such study designs become available in low and middle income settings, phylogenetic studies are unlikely to resolve the question of how much HIV transmission in MSM results from contact with heterosexual networks. Moreover, improved sampling of MSM living with HIV is required to counter the possible selection biases inherent in most phylogenetic studies, which rely on non-random,convenience samples (44). In this way, investigators can investigate sections of the HIV transmission chain that may have been hitherto overlooked to uncover possible transmission from heterosexuals to MSM.

Overall, we conclude there is insufficient evidence that MSM in sub-Saharan African, generalized epidemics are within their own – MSM exclusive – concentrated epidemics settings (30) or are merely components of the larger generalized epidemics(45). Further research is required to resolve this question, which bears upon the effectiveness of envisaged HIV prevention interventions for this population.

4. Review studies on HIV risk and bisexuality in MSM in South Africa

4.1 Background

4.1.2 Calibration of mathematical models

Because HIV spreads as a consequence of sexual contact between individuals, the pattern of disease propagation follows that of a network of social relations. Network models are thus statistical models or computer simulations that capture the web-like pattern through which HIV spreads (44). Agent-based (microsimulation) models are computer simulations of interacting autonomous individuals (46). Though agent-based models hold the promise of elucidating how sexual network structure impacts on incident infections, they require calibration to observational data in order to validate their findings (7). Hence, modellers require data collected from behavioural and HIV prevalence surveys to calibrate their models.

Hence we aim to assess what data exists upon which one could calibrate an agent-based model of the HIV epidemic among South African MSM, within the wider heterosexual population. Towards this end, we sought and appraised studies estimating the two fundamental quantities necessary for such a model: the prevalence of HIV and propensity for sex with women (bisexuality) among MSM in South Africa.

4.2 Structured review

4.2.1 Inclusion criteria

Observational studies estimating i) the prevalence of HIV ii) or bisexuality among South African MSM

4.2.2 Identified articles

We identified 39 studies. Of these, we identified one triangulation report of observational studies on HIV prevalence among South African MSM, over the period between 2008 and 2013 (47). Investigators employed various sampling approaches in arriving at the prevalence of HIV and the fraction of bisexual men, among MSM. In half of the retrieved studies, investigators sampled these men using non-probability methods (Tables 4a, 4b). These ranged from institutional samples - of MSM at health facilities (48) - to venue based approaches and chain-referral (snowball) samples (49) . Nonetheless, a sizeable fraction of the studies deployed probability sampling methods such as respondent driven sampling (RDS) (50) and multi-stage clustered sampling (conventional sampling) (51) (Tables 4c, 4d).

4.2.3 Discussion of articles

Challenges to sampling of MSM

There is a clear progression of sampling approaches for HIV prevalence estimation, from health facility-recruited samples in the early years of the epidemic in South Africa, to venue-based and finally probability samples, in studies conducted in the 2000s (Table 4a,4c). The health facility recruited samples of MSM were likely biased towards men who were suspected AIDS cases, as Sher and Dos Santos suggest (52), and rates of participation in HIV testing were unreported (53) . These studies nevertheless provide an indication, albeit non-representative, of the prevalence of HIV among MSM in the early years of the epidemic in South Africa. Venue based samples appeared in the 2000s, with the renewed interest in HIV among key populations (54). These studies (Table 4 a) are valuable proxies of HIV prevalence among a subset of MSM - those who frequent venues where gay or bisexual men congregate, though they are unlikely to be representative of the larger MSM population.

In comparison, the RDS studies attempt to access ‘hidden’ MSM, whose covert same-sex practices may occur outside of the visible and accessible MSM communities. Yet the extent to which these RDS studies reached hidden MSM is unclear. In fact, investigators of the South African RDS studies have acknowledged that socio-economic status, seeking of clinically competent HIV services and general willingness to participate in the study as potential sources of selection bias in recruiting MSM (37,55,56), while one study reported failure to implement the RDS methodology, owing to limited onward recruitment by the initial seed participants (57). The remaining RDS studies (37,55,56,58,59) do not confirm that their samples reached equilibrium (recruitment of participants proceeds until the distribution of traits in the sample remains constant), a necessary condition for a generalizable RDS sample (50). Hence, the assumption that RDS studies of MSM in South Africa yielded generalizable samples of this population is tenuous. Yet in the absence of a more rigorous sampling design to recruit members of this hidden population, the estimates from RDS studies are probably less prone to the selection bias towards socially visible MSM; a bias inherent in venue based sampling (60).

Challenges to measuring bisexuality among MSM

In spite of the large number of estimates of the proportion of MSM who are bisexual, the reliability of these estimates is unclear. The estimates of bisexuality differ markedly across and within studies, depending on how this behaviour is defined. Some studies measured bisexuality using self-reported identity as “bisexual”, “straight” or “heterosexual”, while other studies also reported on recent or lifetime sexual contact with women. These self-reported identities serve as proxies for sex with women among MSM, as one would assume these identities correspond to men who had recent or lifetime sexual contact with other men. Yet, there is a marked incongruence between the fraction MSM reporting such identities and the fraction who report sex with women. For instance, Batist et al., found that the proportion of MSM who reported recent sex with women (75% in their convenience sample) was over threefold greater than the proportion of men who identified as bisexual (17.7%) (Table 4b).

Similar incongruities in the proportion of bisexual men are found among the probability samples (Table 4d). In one RDS study, a larger fraction of MSM had sexual intercourse with women than those who are sexually attracted to women or self-identify as men who have sex with women ("bisexual" or "straight") (37). The corollary of this that at least some MSM who are not sexually attracted to women nevertheless may have sex with women, given the context of social sanctions against homosexuality. This may explain part of the incongruity in the measures of bisexuality. (37).

In addition, incongruities extend to differences between behavioural measures of bisexuality within a single study. In particular, the Mpumalanga Men's (59) study reported the proportion of MSM who had any female partners in past 6 months (8.1% in Gert Sibande, 2.3% Ehlanzeni) was less than the proportion of MSM who had a current female partner (40.6% in Gert Sibande, 25.7% in Ehlanzeni) (Table 4b). These are contradictory, as all men who have a current female partner are expected to have had at least one female partner in the past 6 months. It is possible MSM respondents had different understandings of the question, which implies low reliability of these questions as measures of bisexuality. Hence, measurement error in the ascertainment of bisexuality among MSM may account for the heterogeneity in estimates.

The only conventional sample of MSM, where investigators sampled households, contrasts the other studies. The investigators found that nearly all MSM in this study reported attraction to women (86%). In agreement with this finding, nearly all MSM reported bisexual behaviour (98.9%) – (having ever had sex with women) with a disproportionate fraction of the sample (85%) reporting having a current female partner. The MSM in this conventional sample may differ substantially from those sampled via convenience or RDS. Since this household sample did not target MSM, the total sample size was much smaller than those of the aforementioned sampling designs, which limits the precision of estimates of bisexuality among these men.

By contrast, unlike the RDS studies that recruit men reporting recent sexual contact with other men, the household survey only required lifetime sexual contact with another man for enrolment. Studies from other developing countries suggest the fraction of men reporting lifetime sexual contact with other men is substantially larger than those with ongoing sexual relations with men (61). Thus, the MSM population from which the sole household survey arose may be the overall MSM population, which includes MSM with ongoing sexual contact with other men, in addition to men who have had only transient male-male sexual contact. It is therefore difficult to compare the fraction of bisexual men in the household survey with those in the venue-based and RDS samples, as the former may represent an upper bound of that reported in the latter.

4.2.4 Conclusion

To date numerous studies have been conducted on South African MSM. Investigators seeking representative estimates of HIV prevalence and bisexuality among MSM will have to grapple with the absence of a nationally representative study for these estimates. While non-probability samples constitute the majority of studies, the extent of selection bias towards open, non-hidden MSM in these studies is likely to be considerable. Thus, the probability-based samples - which aim to reach hidden MSM - may provide more reasonable and perhaps representative estimates of HIV prevalence of MSM in various regions of South Africa, notwithstanding the limitations of RDS sampling and small sample size of MSM recruited via the sole household study.

Heterogeneity in populations sampled and differences in ways investigators implemented a sampling design are likely sources of variability in HIV prevalence estimates. For instance, while both Lane et al., (55) and Rispell et al., (57) sampled MSM from Johannesburg via the RDS method in 2008, the former sample drew men from a particular peri-urban township of that metropolis (The Soweto Men's Study), while the latter sampled MSM from unspecified locations in the city (The JEMS Study). It is unclear whether the networks of MSM that investigators accrued in their respective samples had any overlap. Finally, Rispel et al., did not weigh their HIV estimates according to RDS design, owning to difficulties they experienced in implementing RDS in their study. Hence, it is unsurprising that the estimates of HIV prevalence in the two samples differed significantly, with the estimate from the peri-urban township (13.2%, 95% CI: 12.4-13.9%) much lower than the sample drawn from the wider city (49.5%, 95% CI: 42.5-56.5%). Differences therefore in the way sampling occurred may have magnified possible geographic heterogeneities in HIV prevalence among MSM in Johannesburg.

The evidence suggests the fraction of MSM who are bisexual depends on the eligibility criteria for sampling, as MSM with less recent sexual contact with men may tend to have a higher rate of contact with women. In particular, there is evidence that men who ever have ever had sexual contact with other men in the general population in South Africa do not correspond to MSM sampled through studies targeting men with recent sexual contact with other men.

Qualitative evidence (62) and anecdotes from clinical practice (K. Rebe, personal communication) suggest that MSM who identify as bisexual may often refer to sex with feminine identifying men as sex with women, because the bisexual men regard themselves as “men” and feminine men identify as “ladies”. Additional qualitative evidence suggests designations of one partner being masculine, insertive and assertive with the other being feminine, receptive and submissive hold traction in same-sex relationships among MSM in Cape Town, across the socio-demographic spectrum (63) None of the present studies accounted for whether participants understood the terms of bisexuality and sex with women as sex with female-born individuals. This is in spite of reported preponderance of bisexual men identifying as the masculine - insertive – partners (55), which may mean at least some participants understood the term “bisexual” to designate their role in anal sex. Hence there is potential for over-estimation of bisexuality, in the case some MSM had only sex with male partners and the term “bisexual” merely designated their role in sex. In the final analysis, the estimation of bisexuality among MSM presents is challenging, because of the lack of uniformity in measure of bisexuality within and across studies and differences between populations from where investigators drew samples. At present, there is no evidence of a reliable estimate of the fraction of bisexual activity among MSM in South Africa.

In conclusion, we have found a considerable amount of data on the HIV prevalence and bisexuality among MSM in South Africa for use in the calibration of a mathematical model.

4.2.5 Tables of studies among MSM in South Africa

Acronyms listed in tables

BI: bisexual self-identified men

HETER: heterosexual or straight self-identified men

FTF: Face to Face Interview between field worked and MSM respondent

SAQ: Self-administered questionnaire where MSM respondent enters information alone

Table 4 a Studies employing non-probability sampling methods to estimate HIV prevalence in MSM

First author and date published (Reference No.)	**Eligibility criteria for MSM**	**Location (year sampled)**	**Design**	**HIV prevalence estimates (n)**
Sher 1985 (52)	Not stated (men described as homosexual)	Johannesburg (1983-1985)	Health-facility based sample	20.5% (n=375)
Sher 1986 (64)	Not stated (men described as homosexual)	Cape Town (not stated)	Not stated	10.0% (n=222)
Becker 1986 (53)	Not stated (men described as homosexual)	Cape-Town (not stated)	Health-facility based sample	10.5% (n=268)
Becker 1986 (53)	Not stated (men described as homosexual)	Durban (not stated)	Not Stated	10.7% (n=56)
Becker 1986 (53)	Not stated (men described as homosexual)	Bloemfontein (not stated)	Not Stated	0% (n=15)

Martin 1990 (65)	Not stated (men described as homosexual)	Johannesburg (1988-89)	Health-facility based sample	20.4% (n=49)
Sandfort 2008 *, (66)	Same-sex attraction	Three provinces in South Africa (2003-2005)	Venue based, snowball sampling and internet user samples	14.1% (n=728)*
Burrell 2011 (67)	self-identified as man who has a sex with men	Greater Cape Town (2008)	Venue-based sampling	10.4% (n=539)
Baral 2011(24)	lifetime history of sex with men	Peri-urban Cape Town (2009)	Venue-based snowball sampling	25.5% (n=200)
Eaton 2013* (68)	reported male sex partner in past 4 months	Peri-urban Cape Town (2009-2011)	Venue-based sampling	9.9% (n=143)*

* denotes HIV status ascertained by self-report instead of HIV test

Table 4 b Studies employing non-probability sampling methods to estimate bisexuality in MSM

First author and date published (Reference No.)	Eligibility criteria for MSM	Sample and Location (year of sampling)	Measure	Definition of bisexual men	Proportion bisexual
Heusser 2013 (69)	Men on gay/bisexual social networking website	Convenience sample from South African internet users (not stated)	Online survey	BI, HETERO or Other	10.7 % (n=230)
Stephenson 2011 (70)	Men who reported residing in South Africa and sex with men in past year	Convenience sample from South African internet users (not stated)	Online survey	BI or HETERO	13.3% (n=517)
Wagenaar 2012 (71)	Men who reported residing in South Africa and sex with men in past year	South African users of the internet (June-July 2010)	Online survey	i)BI, HETERO or unstated ii) Ever had sex with a woman (behaviour)	(n=439) i) 3.6% ii) 39.3 %
Stephenson 2014 (72)	Men who reported residing in South Africa and sex with men in past year	South African users of the internet (September 2011)	Online survey	BI	3.0% (n=521)

Eaton 2013 (68)	Men attending shebeens	Venue based sample from peri-urban Cape Town (2009-2011)	SAQ	Report both male and female partners	87.7% (n=143/163)
Pitpitan 2014 (73)	Men attending shebeens	Venue based sample from peri-urban Cape Town (2012)	SAQ	Report both male and female partners	80.9% (n=245/303)
Batist 2013 (74)	Ever reported sex with another man	Venue based and chain referral sample from peri-urban Cape Town (2012)	SAQ	i) BI or HETERO ii) reported at least one female partner in past 6 months	(n=98) i) 17.7% ii)75%
Burrell 2010 (67)	Ever reported sex with another man	venue based sample from Cape Town (2008)	SAQ	BI, HETRO or Other	15.2% (n=537)

Baral , 2011 (24)	Ever reported anal sex with another man	Venue based and snowball sample from peri-urban Cape Town (2009)	FTF	i)BI or HETERO ii) has concurrent male and female partners iii) had a female partner in last 6 months	(n=200) i)19.0 % ii) 3.0% ii) 17.1%
Sandfort 2008 (66)	Same-sex attraction	Venue based, snowball sampling and internet user samples. Three South African provinces (2003-2005)	FTF, SAQ , Online survey	Attracted to both males and females	12.7% (n=1045)

Table 4 c Studies employing probability sampling methods to estimate HIV prevalence in MSM

First author and date published (Ref. No.)	Eligibility criteria for MSM	Sample and Location (year of sampling)	HIV+ estimates (95% CI or n)
Lane 2011 (55)	Oral/anal sex with a man in past 6 months	RDS, Soweto (2008)	RDS weighted: 13.2% (12.4-13.9 %)
Rispel 2011(57)	Sex with another man in past 12 months	RDS,Durban (2008)	Unweighted estimates: 27.5% (17.0-38.1%)
Rispel 2011(57)	Sex with another man in past 12 months	RDS, Johannesburg (2008)	Unweighted estimates: 49.5% (42.5-56.5%)
Cloete 2014 (56)	Oral/anal sex with a man in past 6 months	RDS, Johannesburg (2012-13)	RDS weighted: 26.8% (20.4-35.6%)
Cloete 2014 (56)	Oral/anal sex with a man in past 6 months	RDS, Cape Town (2012-13)	RDS weighted: 22.3% (14.7-30.1%)
Cloete 2014 (56)	Oral/anal sex with a man in past 6 months	RDS,Durban (2012-13)	RDS weighted: 48.2% (37.9-55.4%)
Lane 2014 (59)	Oral/anal sex with a man in past 6 months	RDS,Gert Sibande (2012-13)	RDS weighted: 28.3% (21.1–35.3%)
Lanel 2014 (59)	Oral/anal sex with a man in past 6 months	RDS,Ehlanzeni (2012-13)	RDS weighted: 13.7% (9.1–19.6%)
Sandfort 2015 (37)	Oral/anal/masturbatory sex with a man in past year	RDS, Pretoria (2011-13)	RDS weighted: 30.1% (n=480)
Dunkle 2013 (75)	Ever had sex with another man	Multistage cluster sample of households. Eastern Cape,	27.4% (17.6-40.0%)

		KwaZulu/ Natal (2008)			

Table 4 d Studies employing probability sampling methods to estimate bisexuality in MSM

First author and date published (Ref. No.)	**Eligibility criteria for MSM**	**Sample and Location (year of sampling)**	**Measure**	**Definition of bisexual**	**Proportion bisexual (n)**
Lane (55)2011 , Arnold 2013 (76)	Oral/anal sex with a man in past 6 months	RDS, Soweto (2008)	Computerised SAQ with interviewer assistance	i)BI or HETERO ii)ever vaginal sex iii)regular female partner	RDS weighted (n = 363) i) 76.8% ii) 86.5% iii) 63.4%
Rispel 2011 (57)	Sex with another man in past 12 months	RDS, Durban and Johannesburg (2008)	Participant chose SAQ or FTF	i)BI or HETERO ii)Ever sex with a woman	Unweighted estimates (n=285) i) 23.1% ii) 64.4%

Vu 2012 (58)	Oral/anal sex with a man in past 6 months	RDS, Pretoria (2009)	Not stated	BI or HETERO	RDS weighted (n=307) 42.0%
Cloete 2014 (56)	Oral/anal sex with a man in past 6 months	RDS ,Johannesburg (2012-13)	Computerized SAQ with option of assistance.	i) Ever vaginal sex ii) Vaginal sex in past 6 months given lifetime experience	(n=349) i) 67.6% RDS weighted ii) 23.0% (unweighted)
Cloete 2014 (56)	Oral/anal sex with a man in past 6 months	RDS,Cape Town (2012-13)	Computerized SAQ with option of assistance.	i) Ever vaginal sex ii) vaginal sex in past 6 months given lifetime experience	(n=286) i) 69.7% (RDS weighted) ii) 28.4% (unweighted)
Cloete 2014 (56)	Oral/anal sex with a man in past 6 months	RDS,Durban (2012-13)	Computerized SAQ with option of assistance.	i) Ever vaginal sex i) Vaginal sex in past 6 months given lifetime experience	(n=349) i) 40.1% (RDS weighted) ii) 8.0% (unweighted)

Lane et al 2014 (59)	Oral/anal sex with a man in past 6 months	RDS,Gert Sibande (2012-13)	Computerised SAQ with interviewer assistance	i)BI or HETERO identity ii) Current regular female partner iii) Past female partners iv) At least one female partner in past 6 months	RDS weighted (n=307) i) 52.7% ii) 40.6% iii) 32.3% iv) 8.1%

Lane 2014 (59)	Oral/anal sex with a man in past 6 months	RDS, Ehlanzeni (2012-13)	Computerised SAQ with interviewer assistance	i)BI or HETERO identity ii) Current regular female partner iii) Past female partners iv) At least one female partner in past 6 months	RDS weighted: (n=298) i) 39.7% ii) 25.7% iii) 23.2% iv) 2.3%
Sandfort 2015 (37)	Oral/anal/ manual sex with a man in past year	RDS,Pretoria (2011-13)	Computerised SAQ with interviewer assistance	i) BI, HETERO or other ii)Lifetime sexual experience with women iii)Sexual attraction to women	RDS weighted: i) 30.4% (n=479) ii) 44.3% (n=479) iii) 34.0% (n=480)
Dunkle 2013 (75)	Ever had sex with another man	Multistage cluster sample of households. Eastern, Cape Kwazulu Natal (2008)	Computerised SAQ with audio guidelines	i) Ever had sex with a woman ii) Concurrent female partners iii) Attracted to women or unsure of whether attracted to women	(n=79): i) 98.9% ii) 85.0% iii) 100%

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Part C

Running head title:

Modelling HIV transmission among MSM in the generalized epidemic of South Africa

Full title: The contribution of heterosexual HIV transmission to the spread of HIV among men who have sex with men in South Africa

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ABSTRACT

Men who have sex with men (MSM) have disproportionately high HIV prevalence in nearly all settings. While computational modelling has aided in ascertaining factors that heighten the risk of HIV among MSM, few modelling studies have investigated this question in the African context. We sought to understand the impact the heterosexual spread of HIV has on the spread of HIV among MSM in South Africa. We extended an agent-based model of heterosexual HIV transmission to include MSM and allow for bisexual activity. The model was calibrated to South African data sources. Simulations demonstrated that HIV incidence for MSM over the period 1990-2010 fell by a median of 56.0% (IQR: 29.8-88.0%), in a counterfactual scenario that assumed no HIV transmission via the heterosexual route. Thus, high HIV prevalence among South African MSM may be attributable to HIV transmission from women to bisexual men, who in turn infect other MSM.

KEYWORDS: HIV, bisexual, MSM, Africa, modelling

RESUMEN

Los hombres que tienen sexo con hombres (HSH) tienen una prevalencia del VIH desproporcionadamente elevada en casi todas partes del mundo. Aunque modelos computacionales han desarrollado métodos para destacar factores que aumentan el riesgo de contagio del VIH entre HSH, muy pocos estudios se han enfocado en África. Se analiza el impacto de la transmisión del VIH entre heterosexuales en la transmisión del VIH entre HSH en Sudáfrica. Para ello, se extiende un modelo, basado en agentes, de la transmisión heterosexual del VIH en Sudáfrica para incluir HSH y la conducta bisexual. El modelo se calibra con datos de Sudáfrica. Simulaciones demuestran que, a lo largo de 1990-2010, la incidencia del VIH entre HSH cae en una mediana del 56.0% (rango intercuartil: 29.8-88.0%), en un escenario contrafactual bajo el cual no hay transmisión heterosexual del virus. Entonces,

puede que la prevalencia alta del VIH entre HSH en Sudáfrica se deba a la transmisión del VIH de mujeres a hombres bisexuales, quienes contagian a otros HSH.

INTRODUCTION

In the fourth decade of the HIV pandemic, there is growing appreciation that a nuanced approach is needed to understand the distribution and risk of HIV across different sub-populations. To facilitate an evidence-based understanding of how to respond to epidemics, the Joint United Nations Programme on HIV/AIDS (UNAIDS) provides a framework of HIV epidemic settings (1). Under this schema, concentrated epidemics are defined as settings in which HIV transmission is largely confined to specific sub-populations. Generalized epidemics, in contrast, are settings where the sexual contact within the wider population permits the emergence and persistence of the HIV epidemic, above and beyond the sexual behaviours of sub-populations (2). Yet even in these settings, certain sub-populations have elevated burden and thus risk of HIV infection, compared to the general population (3). Notwithstanding the gains in prevention and treatment since the early years of the epidemic, men who have sex with men (MSM) remain one of populations most at risk of infection. Despite denial of their vulnerability to HIV infection by politicians from several countries in sub-Saharan Africa (4), these men have an estimated three-fold greater burden of HIV when compared with men in the general population(5).

It is commonly assumed that HIV epidemics among MSM within generalized HIV settings grow due to male-male sexual contact (3), with female-male transmission only incrementing infections in the non-MSM male population (6) . Modellers of HIV in MSM populations in South Africa, for example, have assumed heterosexual contact to be irrelevant to the epidemiology of HIV in MSM, as their models allow for HIV to spread in exclusively male sexual networks (7-9). By contrast, available data from South Africa casts doubt over the notion that male-male transmission of HIV in MSM is the sole driver of the epidemic in this sub-population. Importantly, various studies(10-13) report high proportions of MSM in South Africa who have both male and female sexual contacts, while molecular phylogeny reveals that HIV-1 subtype C, previously believed to typify the epidemic among heterosexuals, (14) has spread to MSM (15).

Studies on MSM in Africa, whose practices are illicit in much of the continent, have been fraught with obstacles, not least socio-legal contexts that criminalize and vilify MSM (4). In spite of these challenges, epidemiologic research has advanced considerably in South Africa, where MSM are afforded legal protection. Hence, a considerable amount of behavioural and HIV prevalence data has accumulated upon which investigators can build a mathematical model that assesses how much heterosexual transmission of HIV leads to infections in MSM. In resource-scarce settings, the modelling alternative is preferable to the resource-intensive molecular phylogenetic studies on nationwide HIV surveillance data, which have been used to understand HIV epidemiology (16).

Building on findings of Respondent Driven Sampling (RDS) studies on MSM in South Africa, we extend an earlier model of heterosexual transmission of HIV in South Africa (17). In our MSM-inclusive model, we allow for a sexual network where MSM are connected to women and, albeit indirectly, to heterosexual men. We also allow for changes in the network over time, unlike previous models that assume a static network (8). To our knowledge, the current study represents the first attempt at employing a model to quantify the extent to which MSM within a sub-Saharan African country acquire HIV due to their contacts with the general heterosexual population.

METHODS

Briefly, the model is an agent-based simulation (18) of an epidemic with a starting population size of 20 000 individuals. Agent-based simulations are amenable to constructing sexual networks between individuals and so are optimal for our investigation into putative network-level effects on HIV spread in MSM. The supplementary materials detail the model assumptions and structure. Here the focus is to describe how the model simulates sexual contact between men, as the modelling of heterosexual behaviour, where vaginal sex is the only route of HIV transmission, is detailed elsewhere (17).

Prior distributions are set to represent uncertainty around key input parameters (Table I). A review of the primary literature identified probability-based samples of MSM in South Africa as data sources for parameters.

The formation and dissolution of sexual partnerships and casual (once-off) sex allows for dynamic sexual networks between individuals to form. Simulation of sexual contact begins in 1985 and is updated at weekly time steps. To minimize the stochastic variation in modelled HIV prevalence, we chose 1990 as the initial date of HIV infection in the population, even though HIV had entered South Africa's MSM population by 1982 (19).

Partnerships were modelled as short-term or long-term (cohabitation), where a fraction of the former progress to the latter. Individuals fall into one of two sexual risk groups. Those with a propensity for concurrency (up to two regular partners at time) are in the high risk group, with the remaining individuals falling in the serially-monogamous low risk group. MSM are assumed to go through intermittent periods of engagement in casual sex. The partnership status, extent of preference for male partners, age and risk group determine the rate at which MSM enter and exit the casual sex state.

Unlike low risk MSM who engage in casual sex only when not in a regular partnership, high risk MSM can engage in casual sex at any time.

5% of the male population was assumed to have a propensity for sex with other men at some point in their life-course (11). Here we define MSM as men who have had sex with other men in the last 6 months.

Bisexual men are defined in the model as those men who ever have a propensity for male and female partners; relative preferences for male and female partners can change over the life-course. Gay men are defined as those men who only ever have a propensity for male partners**.** The male preference parameter (the probability a man chooses a male partner instead of a female partner) was differentially assigned to men over the life-course: for bisexual men the parameter varied by age over the life course (between 0 and 1.0), while for gay and heterosexual men it remained constant at unity and zero respectively. Each gay or bisexual man is assigned a fixed role preference, either an exclusive insertive, exclusive receptive or a versatile preference. Role preference is assigned differentially for gay and bisexual men, with gay men tending to be assigned the receptive role and bisexual men tending to the insertive role, with the versatile role randomly assigned to 30% of all MSM (20-22). MSM engage in anal sex in the event role preferences are compatible. Otherwise non-anal sex is assumed i.e. when two men have the same exclusive role preference, for instance when both partners have the receptive preference, they opt for sex that carries negligible risk of HIV transmission, such as mutual masturbation. The partnership type and age of MSM determine the rate of condom use in anal sex, and condom use is assumed to change over time in response to social marketing programmes.

To generate plausible model estimates of HIV prevalence in MSM, we identified the most reliable HIV prevalence and sexual behaviour data reported on MSM, from the most robust studies published on South African MSM cohorts, in both peer reviewed and gray literature (details of the studies are found in Supplementary Materials). Sexual behaviour parameters for which there was a great deal of uncertainty were given prior distributions (Table I). A likelihood function was defined using sexual behaviour estimates identified from probability-based samples of MSM. Then, 20 000 parameter sets were drawn from the prior distributions for use in generating the likelihood of observing the sexual behaviour data of MSM from the literature, given a set of parameters. The 100 best fitting sets of parameters (sets that maximized the likelihood function) were then chosen as most plausible values for each parameter; analogous to a posterior distribution. After fitting the model to the sexual behaviour data, a similar procedure was followed in calibrating the model to the HIV prevalence data. The sexual behaviour parameters were set at the means of the values in the 100 best-fitting parameter set. Prior distributions were specified to represent the uncertainty around the HIV transmission parameters (Table I), and a likelihood function was specified to represent the goodness of model fit to HIV prevalence from probability-based samples of MSM. As before, a sample of 20 000 parameter combinations was drawn from the prior distributions, the HIV likelihood was calculated for each, and the 100 parameter combinations with the highest likelihood values were selected. Model outputs are presented as median and inter-quartile range (IQR) of the 100 simulations corresponding to the best fitting parameter sets.

To assess the effect of heterosexual transmission on the HIV epidemic in MSM, the model was used to simulate a counterfactual scenario, in which it was assumed that HIV cannot be transmitted via vaginal intercourse (between men and women), but only via anal sex (between men). The contribution of heterosexual transmission to HIV incidence in MSM was quantified as a population attributable fraction (PAF) (2), which was calculated as 1 minus the ratio of cumulative incidence under the counterfactual scenario to the cumulative incidence in the main scenario, where both vaginal and anal transmission are possible routes of transmission (Cumulative incidence was calculated up to 2010.)

RESULTS

Model outputs of HIV prevalence in the general population were consistent with observed estimates of annual South African HIV prevalence between 1990 and 2012 (Fig 1A). For MSM, the model estimated trajectory of HIV prevalence followed that of heterosexuals, with a plateau reached during 2008-2012 (prevalence of 28.7 % (IQR 27.4-28.9%) in 2010). A comparison of the mean prevalence over 2008-2012 in MSM to estimates reported in respondent driven sampling (RDS) studies illustrates reasonable consistency of outputs to observed data (Fig 1B).

Although we fixed 5% as the fraction of men who could ever choose male partners, there was variability in the fraction of these men who could ever have sex with women, with a median of 83.5% (IQR: 80.6-86.35) across the best-fitting simulations. The best-fitting parameter combinations also suggested a decline in the extent of same-sex preference with respect to age in these bisexual men; the fraction of men with recent sexual contact with other men (MSM) decreased steadily with increasing age in the simulation (Fig 2A). The model estimates of the fraction of MSM with recent or lifetime sexual contact with women were in reasonable agreement with those reported in RDS studies (Supplementary Materials Figure S3). Prevalence of HIV in MSM was consistently greater than in other men at all ages (Fig 2B).

In terms of men who acquired HIV and who had sex with men at least once in the life-course, 43% of these men, across all ages, acquired HIV from women. The proportion who acquired HIV from women peaked once men passed the age of 20 (Table II). In the counterfactual scenario, the median HIV prevalence among men who had recent sex with other men (MSM) in 2010 was 10.0%(IQR: 2.8-17.4%); a decline relative to the median HIV prevalence of 28.2% (IQR 27.4-28.9%) in the main scenario (where both heterosexual and male-male transmission of HIV was possible). This drop in prevalence under the counterfactual scenario was largest among men with changing sexual preference for other men (bisexual men), compared to men who are always homosexual (gay men) (Figure 3). The population attributable fraction for the proportion of HIV incidence in MSM, over 1990 to 2010, that was attributable to heterosexually-transmitted HIV, was 56.0% (IQR: 29.8%-88.0%).

DISCUSSION

Although some dynamic models of HIV have allowed for women to infect MSM, as part of a generalized epidemic (23,24), most investigators have overlooked the extent to which MSM acquire infection via this route. In the present study, we specifically quantify the extent to which HIV infection in MSM is a function of transmission within the larger heterosexual population.

Our approach is built on previous reviews of evidence. Beyrer et al. have previously situated the HIV epidemics of MSM within the generalized, heterosexual driven epidemics of sub-Saharan African countries (5,25). However, little focus has been given to the HIV risk MSM incur as a result of their sexual contact with the heterosexual population.

Similarly, previous mathematical models of HIV epidemics have tacitly assumed exclusive male-male sex as the sole route of infection. A case in point is the UNAIDS Modes of Transmission model (MoT) espoused for use in generalized epidemics of sub-Saharan Africa. This model estimates the fraction of HIV infections among sub-populations and assumes that MSM can only transmit HIV to women in the general population, with all infections in MSM being due to male-male contact (26).

Our present modelling study, however, suggests that a substantial fraction of HIV infections in MSM could result from sexual contact with women in the heterosexual population. Hence, earlier modelling studies have potentially overlooked an important source of infection for MSM.

We have demonstrated that being part of a heterosexual network is a non-trivial risk factor for HIV acquisition among MSM, in settings where there is a high prevalence of HIV in the general population. That MSM have a 56% drop in cumulative incidence, under the assumption of no heterosexual transmission, implies overlap between heterosexual and MSM transmission networks. Hence, it is likely the high HIV prevalence observed in MSM over the 2008-2012 period, reported in RDS studies (10,20,22,27,28) is driven by high-levels of transmission between heterosexual and MSM networks in South Africa. This conclusion is premised upon the agreement between our model estimate of HIV prevalence among MSM with estimates of HIV prevalence reported in the RDS studies. Our model also captures the overlap of heterosexual and MSM sexual networks in South Africa, because it was calibrated to data indicative of bisexual activity among MSM. Our results therefore imply that HIV transmission from women to bisexual men, who in turn infect their male partners, is responsible for roughly half of the HIV transmission among MSM.

The present findings are consistent with other studies of MSM that have identified a network-level risk factor for high levels of HIV prevalence**.** Studies on cohorts of MSM from the US have shown that network-level risk, such as having a same-race partner, mediates the association between African-American race and HIV high prevalence (29). In that context, HIV prevalence is disproportionately higher in African-American MSM compared to white MSM, rendering the risk of HIV acquisition higher for a man who has African American partners. A reasonable explanation for our findings is that bisexual men in South Africa are likely to come into sexual contact with an HIV positive partner, given the high burden of HIV in the general population. Sexual acquisition is especially likely from women, as they bear the brunt of the HIV epidemic in South Africa (30). Onward transmission from these bisexual men - within the MSM sexual networks - then contributes to the high HIV prevalence in MSM.

Our results further clarify an earlier hypothesis regarding the relationship between the sexual-gender identities MSM in South Africa report and the spread of HIV (22). The hypothesis advances the notion that bisexual identified MSM are at centre of sexual networks, whose epidemiological endpoints are gay identified MSM. Our findings show that men who have both male and female partners may mediate the onward transmission of HIV from women to MSM networks. Importantly, as our model assumptions regarding the behaviour of bisexual men correspond to reported sexual behaviour of bisexual identified men, such as role preference and frequency with sex with women, our study expands the evidence base for bisexual men as drivers of high HIV prevalence among MSM in South Africa.

Our model results are contingent upon the way we assumed sex occurs between men. Importantly, we observed the estimated fraction of HIV infections acquired from women increased as men aged, because we assumed their opportunity for sexual contact and thus HIV acquisition from women, relative to men, increased. This is because we assumed men chose male partners based on their male preference parameter, which represents the frequency at which men chose other men as partners, relative to women. In our model, the majority of MSM experienced a decline in male preference over the life course, because we found the decline in the male preference, as a man ages, to be most consistent with the young age profile of MSM in the empirical data – the RDS studies report that the median fraction of MSM aged younger than 25 years was 69.7**%** (Supplementary Materials Table S12).

There are several possible explanations for the young age profile of MSM recruited via RDS. Firstly, this could be due to selection bias towards younger men, as MSM recruited via other methods, such as online surveys**,** venue-based sampling or snowball had either an older-age profile (31-34) or comparable proportions (35,36) of younger and older MSM. Secondly, there may be fewer older MSM in the population, as the RDS studies suggest; there is, evidence suggesting increasing age accompanies a decline in MSM behaviour within the context of transactional sex among men in South Africa (13) Lastly, societal empowerment for same-sex practises is a recent development, following the adoption of South African constitution in 1996 (42). Consequently, younger men grew up in a more accepting socio-political climate compared to those older men. Hence, this would exert a cohort effect on the population, resulting in a youthful age-profile of the sexually active population of gay, bisexual and other men who have sex with men. Further research, however, is required to clarify the reasons for an apparent decline in MSM behaviour with age. In addition, it is unclear whether this decline in MSM behaviour translates into a fall in the opportunity for HIV acquisition from male partners, as there is at present limited evidence on how risk behaviour varies by age.

Notwithstanding, our finding that 84% of men who ever have same-sex preference also have preference for women, at some point in their life course, is consistent with findings from the only known sample of men surveyed for lifetime sexual activity with other men on the African continent (11). Unlike the RDS studies, which excluded MSM who at the time of sampling had no recent male partners, this study ascertained the occurrence of bisexual activity over the life-course. That nearly all (99%) of MSM reported lifetime sex with women in that study implies the RDS studies may under-estimate the extent of bisexual activity.

A limitation of our study is our preference for RDS studies as sources of model parameters. While the RDS design is known to be well suited to surveying hidden populations (37) and has been advanced as less prone to selection bias than snowball sampling and convenience sampling of MSM (5), it remains unclear whether it is able to surmount difficulties in sampling MSM in South Africa. For RDS studies to be representative of MSM populations, the assumption that all MSM belong to one social network must hold true (38)**.** While this may be true for certain communities, it is unclear whether RDS sampling can enlist MSM across apartheid-era racial categories (39,40) . Clearly, uncertainty exists regarding the extent to which the parameters derived from RDS studies are representative of MSM in South Africa.

Furthermore, RDS studies lack detail on the context of MSM partnerships or casual encounters. In many cases, our assumptions pertaining to sexual behaviour were highly uncertain and we thus several parameters were set to be the same value as for heterosexual men due to lack of MSM specific data.

Since there is a paucity of data on the frequency of risk behaviours that MSM engage in within same-sex and opposite sex partnerships, the model may have overlooked risk behaviours that drive HIV incidence in this population (41). For example, qualitative evidence from a socio-demographically diverse sample of MSM highlighted how partners in the receptive role of same-sex partnerships are especially vulnerable to HIV infection, as being a receptive partner appears to go in tandem with sexual coercion and an inability to negotiate risk reduction strategies(42)

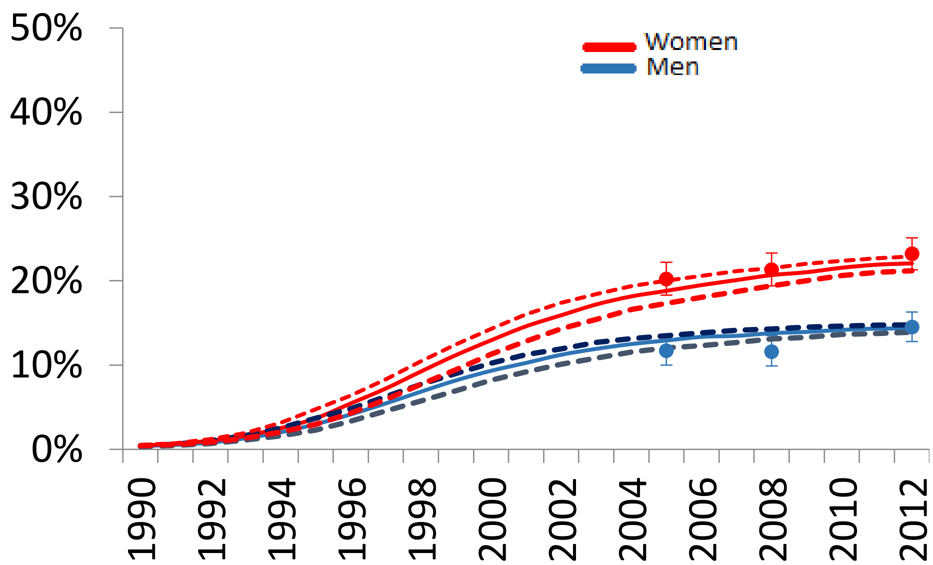
Despite these shortcomings, our study uncovers the possibility of a network-level risk factor – overlap of MSM and heterosexual HIV transmission chains – as a driver of the HIV epidemic among MSM in the sub-Saharan African context.

CONCLUSION

The use of computational models to assess factors explaining the disproportionate prevalence of HIV in MSM has recently emerged (5). Our study adds to this research by identifying how HIV infections in MSM can occur as result of direct or indirect sexual exposure to the HIV epidemic among heterosexuals. Interventions that adopt a multi-pronged approach to reduce infections between women and MSM, in addition to the prevention of sexual transmission between men, may hold the greatest promise for eliminating HIV infection among MSM.

Figure 1

A: Model HIV prevalence in heterosexuals compared to survey estimates



B: The mean of model HIV prevalence in MSM during 2008-2012 (median solid line, dashed line IQR) relative to HIV prevalence estimates (error bar: 95% CI) from RDS studies

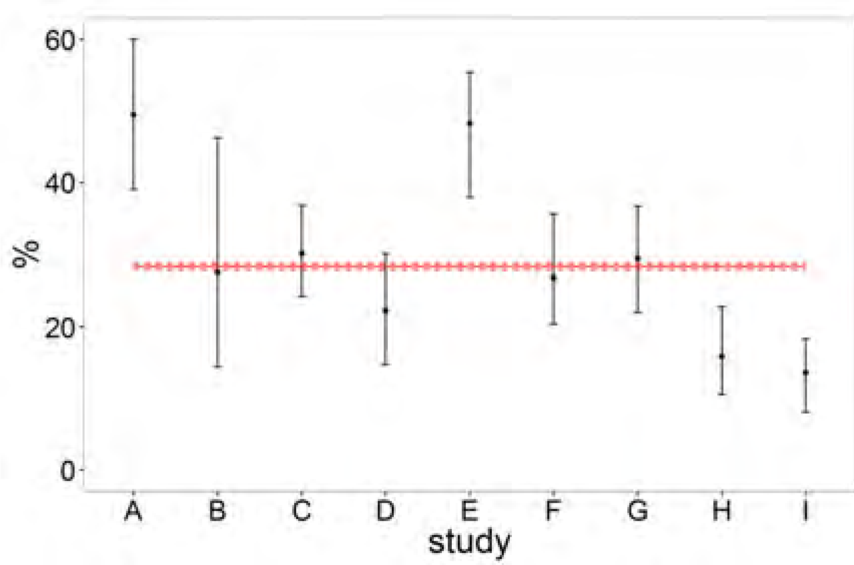


Figure 1 HIV prevalence estimates from model and comparison with observed data. (A) Model HIV prevalence for adults aged 15-49 years compared to point estimates of HIV prevalence from household surveys in the general population. (B) The model estimates of HIV prevalence in MSM (mean over the period 2008-2012) is compared to nine HIV prevalence point estimates from RDS samples conducted over the same time period. The Supplementary Material provides a full listing of RDS studies to which model was fitted. In all panels, the median (solid line), lower and upper quartiles (dotted lines) of the model HIV prevalence are shown. Observed estimates are denoted by points with 95% confidence intervals (error bars)

Figure 2

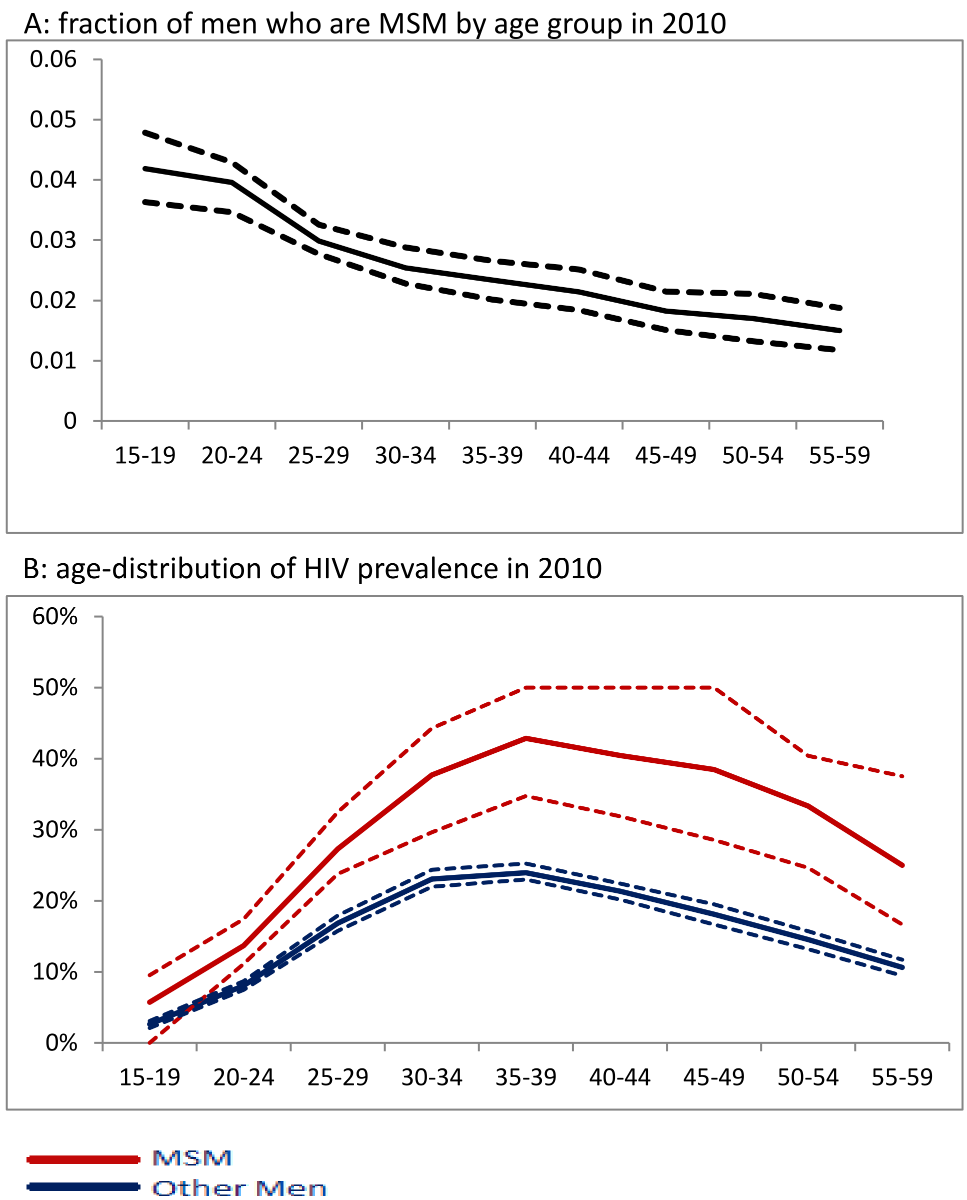

A: fraction of men who are MSM by age group in 2010
0.06
0.05
0.04
0.03
0.02
0.01
0
15-19
20-24
25-29
30-34
35-39
40-44
45-49
50-54
55-59
B: age-distribution of HIV prevalence in 2010
60%
50%
40%
30%
20%
10%
0%
15-19
20-24
25-29
30-34
35-39
40-44
45-49
50-54
55-59
MSM
Other Men

Figure 2 Age distribution of male sexual contact and HIV prevalence in MSM and all other men from model simulations: A) Proportion of men who are MSM (men who had sex with other men in the last 6 months) by age group. B) Comparison of age-specific prevalence of HIV among MSM and other men (heterosexual men and gay or bisexual men who have not had sex with other men in past 6 months). Solid and dashed lines denote the median and upper/lower quartiles of model output, respectively.

Figure 3

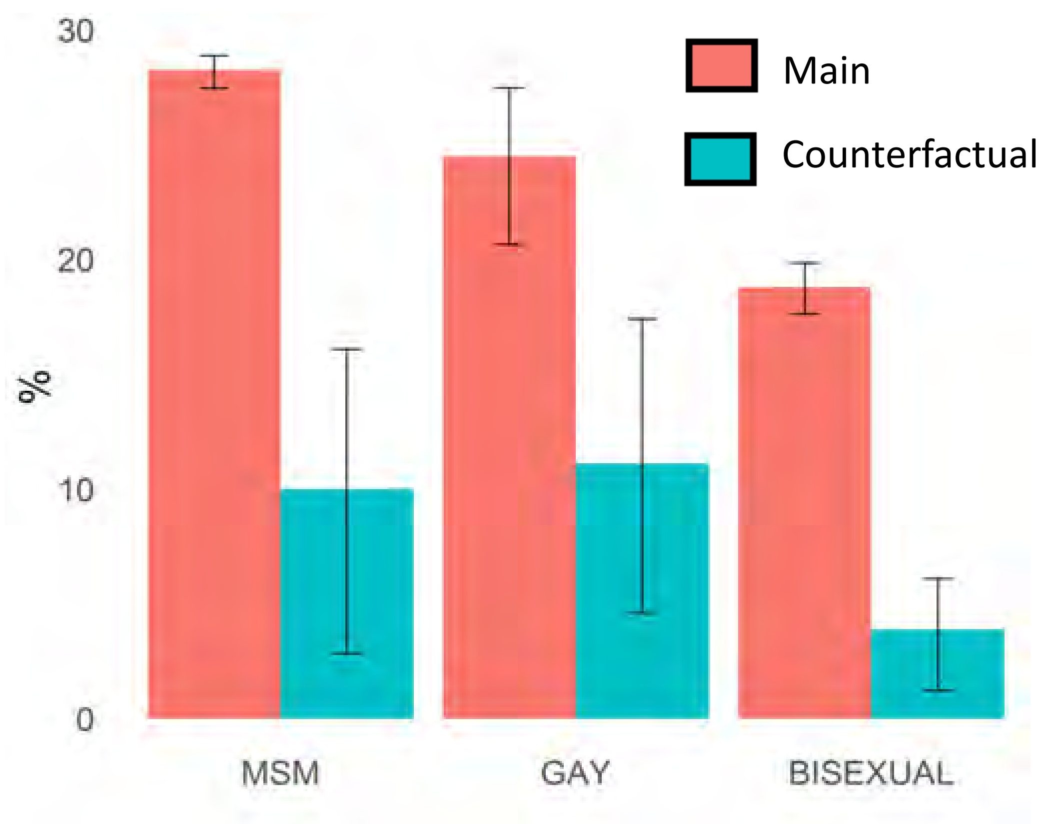


Figure 3 Comparison of HIV prevalence (median and IQR) between main (red) and counterfactual (blue) scenarios in 2010. MSM refers to men who have had male-male sexual contact at in the last 6 months; Gay refers to men with a propensity for only male partners; Bisexual refers to men who have propensity for partners of both sexes.

Table I Prior distributions for select model parameters

Parameter	Prior	Mean	SD†	Source
1.Proportion of gay/bisexual men who ever have a propensity for sex with women	Beta(12,3)	80.0%	10.0%	(20,22,27,28,43)
2.Mean initial male preference, in bisexual men	U(0,1)	50.0%	28.9%	Vague prior
3. Mean of annual average change in male preference	N(0,0.05)	0	5.0%	(44-46)
4. Risk of HIV acquisition per act of receptive anal sex in a ST# partnership %	Beta(3.945,354.7)	1.10%	0.55%	(47-50)
5. Risk of HIV acquisition per act of insertive anal sex in a ST partnership %	Beta(3.984,1241)	0.32%	0.16%	(49,50)
6. Risk of HIV acquisition per act of receptive anal sex in a LT# †partnership %	Beta(3.99,1991)	0.20%	0.10%	(47-51)
7. Risk of HIV acquisition per act of insertive anal sex in a LT partnership %	Beta(3.997,5705.3)	0.07%	0.04%	(49-51)
8. Odds ratio of condom use in casual sex relative to short-term relationships	Gamma(16,8.889)	1.8	0.45	(52)
9. Ratio of HIV prevalence in gay/bisexual men to that in heterosexual men in 1990	Gamma(5.325,1.775)	3.0	1.30	(53)

#LT = long-term. ST = short-term. †SD = standard deviation

Table II Traits of new HIV infections in men who ever have a propensity for same-sex relationships over the life course

	Total HIV infections	Fraction of HIV infections acquired from women
	N	**%**
Age at HIV acquisition		
<20	1643	35.2%
20-24	3365	45.0%
25-29	2779	47.2%
30-34	1975	47.3%
35-39	1463	46.4%
40-44	991	45.5%
Year of HIV acquisition		
1990-1994	1185	45.2%
1995-1999	3566	44.0%
2000-2004	4582	44.2%
2005-2009	3781	42.6%
2010-2011	1159	36.8%
Sexual history		
Ever had sex with women	10834	56.9%
Never had sex with women	3439	0%
Total	**14273**	**43.2%**

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Part D Appendix

1. Structure of sexual behaviour model and partnership types

1.1 Overview

The MSM inclusive model is based on a novel agent-based version of the STI/HIV interaction model. Briefly, this model is of a population of individual agents who are born, age to sexual maturity, form sexual partnerships and eventually die. Each simulated run of the model was based on a starting population of 20 000 persons who interact in a dynamic sexual network over the course of 1985 to 2012, allowing for population growth. The model assumptions pertaining to heterosexual contacts have been described elsewhere (1).

Here we describe the components of the model relevant to MSM, including the choice of model parameters and their justification. The defining difference between our model and the previous agent-based version the allowance made for a fraction of the male population to engage in sex with other men. The purpose of this appendix is to describe how sex between men is simulated in this model.

1. 2. State Variables

1.2.1 Individual level states

The risk group state – high risk (HR) or low risk (LR) – is common to all individuals. Risk group membership is assumed to be immutable for any individual in the simulation. HR individuals have a propensity for concurrent partnerships. For the sake of simplicity, HR individuals can have up to two concurrent partners, while LR individuals are assumed to be monogamous (i.e. never having more than one partner at a given time).

There is insufficient data to estimate the proportion of MSM who are high risk. The Soweto Men's study (2) for instance, measured the prevalence of concurrency in its sample of MSM, but this is likely an underestimate, as the measure may have overlooked MSM who did not have concurrent partners at time of the survey, but had a propensity for concurrency nonetheless. As 35% is the assumed fraction of HR heterosexual men (1) and evidence from the Soweto Men's suggests that 35% of partnerships had a high degree of overlap, there was no reason for us to assume the propensity for concurrency needs be different for MSM relative to heterosexual men in the model. Hence, we assign 35% of MSM to the HR state.

1.2.2 Partnership level states

Individuals can either have no partners, thus effectively being celibate, have a single partner or, in the event they are HR individuals, two partners. Individuals can enter into either short-term (ST) or cohabitating/long-term (LT) partnerships. These relationships differ in rate of occurrence within the population and duration. The partnerships also differ with respect to the average frequency of sex within the partnership and the probability of HIV transmission per act of sex.

Men can also have once-off (casual) sexual contacts with other men. While the female sex worker-male client interaction has been described previously (1), the MSM inclusive model does not model male sex workers but instead allows men to have casual sex with other men. While sexual contact between sex-workers and clients is limited to HR men and HR women in the model, all men, who have a propensity for sex with other men, can have casual sex. However, while HR men can have casual sex regardless of whether or not they are in partnerships, LR MSM only have casual sex when they are not in a partnership.

1.3. Specifications of the sexual contact between men

We formed sexual networks where men and women are interconnected, via male with male and female with male sexual contacts. These sexual networks were dynamic – allowing for formation and dissolution of partnerships. The various states that describe partnership formation are described below (Figure S1). Men can either be gay (they have propensity for sex exclusively with men) or bisexual (they have propensity for sex with both men and women). Heterosexual men, therefore, comprise the remaining men in the model (men who only ever have propensity for sex with women).

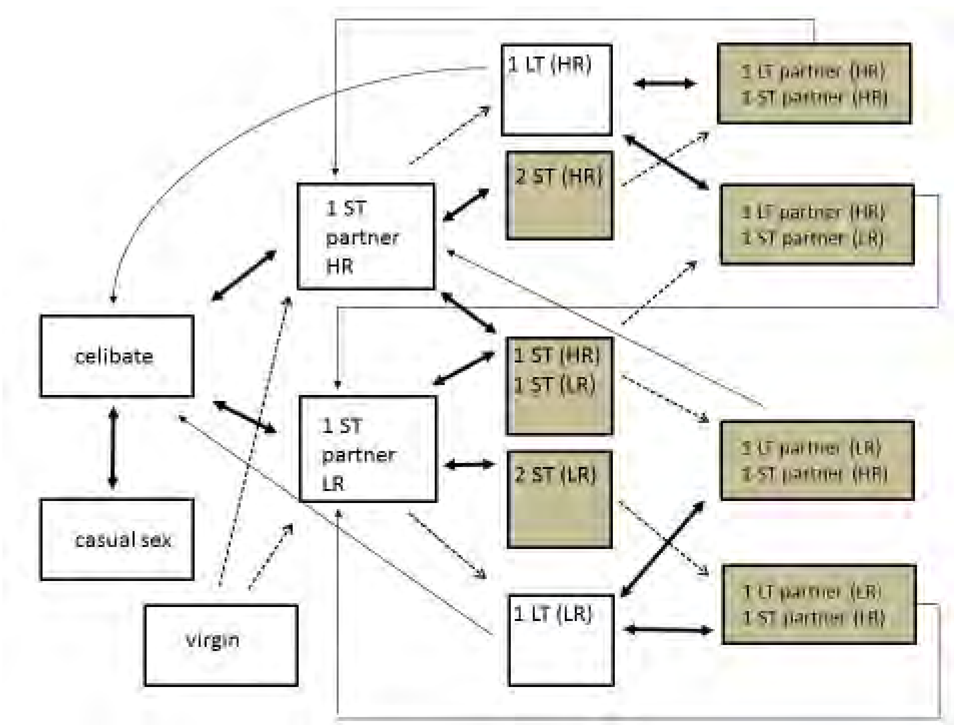

Figure S1 Sexual activity states for gay and bisexual men. Note that bisexual men can choose partners of either sex, while gay men choose only male partners. Arrows with dotted line denote change in partnership type with the same partner, except for the transition from virgin state (when the first male partner is acquired). Partners are either long term (LT) or short-term (ST), partners can be either "high-risk" (HR) or "low-risk" (LR). White boxes refer to sexual activity states occupied by LR or HR men, while shaded boxes are states exclusive to HR men. Note that casual sex is a state that HR men can enter while being in a partnership, while LR men are assumed to enter the casual sex state only when they have no regular partner.

1.4. Specification of partnerships for MSM

1.4.1. Sexual preference

We allowed 5% of the male population to have male sexual partners, as a population based survey by Dunkle et al., of sexual behaviour in South Africa (a household survey of two provinces (3)), reported this as the fraction of MSM in the male population.

Recognising that this survey benefited both from a representative sample of the households in the districts sampled and a measure that allowed respondents to confidentially report stigmatizing sexual behaviours (reducing the possibility of response biases), we considered this estimate to be most reliable out various studies that estimated the fraction of MSM in the male population. Hence, we chose the 5% reported in this study, of men who ever had sex with other men, as the fraction of men who ever have propensity for sex with other men in the model, for lack of a gold standard for the occurrence of MSM behaviour in a population.

The probability that the *ith* male individual aged *x* years chooses a male sexual partner is $m_i(x)$, the male preference parameter. We defined three different classes of men via this parameter.

4. Heterosexual men – have a male preference set to zero. These men can only choose female partners. These men are identical to those in the STI/HIV interaction model (1).
5. Gay men – men who can only ever have sex with other men. For these MSM, $m_i(x)$ remains constant: $m_i(x)$ =1.0, denoting choice of male partners 100% of the time.
6. Bisexual men who have propensities for sex with both men and women over their life course. The fraction of bisexual men (as a fraction of all men who ever have propensity for sex with other men), η, is determined by a prior distribution

$$\eta \sim Beta(12,3)$$

   The choice of prior distribution assumes that reported estimates for η from Respondent Driven Sampling (RDS) studies (a median of 58.3%, ranging between 35.6% and 86.5%, Table S7) are underestimates, since these studies exclude occasional MSM - MSM who have current female partners but have not had any male partners in the past 6 months**.**

The prior assumed 100% to be an upper bound for η, since Dunkle et al., reported close to 99.0% of MSM reporting having had lifetime sexual contact with women in their survey of two South African provinces.

Therefore, we chose η = 80% as the mean – the value roughly halfway between the lower and upper bounds (60% and 100% respectively). In addition, the standard deviation of the prior distribution was chosen at 10%, so that the 2.5th and 97.5th percentiles of the prior would be roughly consistent with the lower and upper bounds.

Prior distributions account for the uncertainty in what the male preference parameter – μ_m – for bisexual men would be on average. Given the absence of reliable estimates of the relative preference for male partners among MSM who also have sex with women, we used a vague prior distribution – one without any knowledge of reasonable upper or lower bounds – for μ_m.

$$\mu_m \sim U(0,1)$$

We assumed σ_m to be a function of μ_m

$$\sigma_m = \begin{cases} 0.4\mu_m \text{ , } if \ \mu_m < 0.5 \\ 0.4(1-\mu_m), \ if \ \mu_m \geq 0.5 \end{cases}$$

We assume bisexual male preference for men remains constant up until age twenty and thereafter allowed the possibility of change in male preference. We assign each bisexual man an initial, at age twenty, male preference parameter m_{i0}, where 0< m_{i0} <1. For each bisexual man, the constant m_{i0} is sampled from a Beta distribution to allow for heterogeneity in male preference between individuals. The shape parameters of the Beta distribution – *a* and *b* – are chosen such that mean and standard deviation of the distribution are given by μ_m, the mean male preference among bisexual men and σ_m, the standard deviation about the mean male preference:

The change of male preference allows us to capture changes in sexual behaviour that may accompany age, such as social sanction favouring marriage to women, which may limit the frequency with which MSM sexually contact other men. For the sake of model simplicity we consider only a linear change. $m_i(x)$ is assumed to vary according to following function:

$$m_i(x) = \begin{cases} \mathrm{m_{i0}} & for \ x \leq 20 \\ \mathrm{m_{i0}} + \Delta_i(x-20) & \text{for } x > 20 \end{cases}$$

As x increases beyond 20, we allow for an annual Δ_i change in male preference. Similarly to assigning initial male preference, we introduced individual level heterogeneity in Δ_i by sampling values of this parameter from a normal distribution.

$$\Delta_i \sim N(\mu_\Delta, \sigma_\Delta)$$

In order to account for uncertainty in the average annual change in male preference, we assigned prior distributions to the mean annual change, μ_Δ, and the corresponding standard deviation, σ_Δ.

With priors $\mu_\Delta \sim N(0, 0.05)$, $\sigma_\Delta \sim \text{Beta}(7.5, 42.5)$

A mean of zero for the prior of μ_Δ assumes there is, on average, no change in sexual preference over the life course, since cross-sectional and cohort studies from high-income settings suggest that although sexual orientation is far from stable over the life-course, there is no clear trend in preference for male or female partners in men (4-7). The prior distribution for the standard deviation of annual change in male preference, σ_Δ, is highly uncertain, as we identified only one prospective study from a high-income setting reporting on stability of same-sex attraction and behaviour (7). Data from that prospective study suggests 0.19 is an estimate for the standard deviation for the proportion of male adolescents who undergo a change in same-sex attraction. Yet since this study followed adolescent males from age 16 to age 22 – when sexual identity formation occurs in MSM (8) – the estimate of 0.19 is likely greater than which would be expected for men over the age of 20, who comprise the majority of sexually active males in our model.

1.4.2 Short term Male partner acquisition

The way MSM acquire ST male partners is similar to the way in which heterosexual men and women acquire ST partners (1). The rate of primary, ST, partner acquisition is the inverse of the average time (in years) a man spends without a male partner. Similarly, the rate of secondary partner acquisition is the inverse of the average time from acquiring a primary partner to acquiring a secondary partner.

We found no studies reporting on the duration before primary or secondary partner acquisition. Hence, we assumed the rates of short-term partner acquisition in gay and bisexual men are the same as those in heterosexual men, as described previously (1).

Briefly, the parameter *c(i,j,l,s,x)* is the rate of short-term partner acquisition for man with HIV disease stage *s*, aged *x* years, in risk group *i,* who already has a partner in risk group *j* of partnership type *l* (if the individual is not in a partnership, j = 0 and l =0) (1) . The age-specific rates are determined by a gamma function with parameters α and λ. The baseline rate of partnership acquisition is denoted by c, while adjustments for risk group and partnership status ,$\Omega_{i,j,l}$, and HIV status , $\Phi(s)$, also impact on the rate of partnership acquisition.

$$c(i,j,l,s,x), = c(x - 17.5)^{\alpha-1}\exp\big(-\lambda(x - 17.5)\big)\,\Omega_{i,j,l}\,\Phi(s)$$

The model projects the changes in relationship status at weekly time steps. At each time step, MSM acquire male partners in a three-step, random process:

1) The man acquires a new partner when his *c(i,j,l,s,x)* value, converted to a weekly rate, is greater than a random variable drawn from a uniform distribution (0,1).
2) If the man acquires a new partner, that partner is male when the male preference parameter, $m_i(x)$, is greater than a random variable drawn from a uniform distribution (0,1). Since $m_i(x)=1.0$ for gay men, these individuals will always choose male partners, while bisexual men will, on average, choose male partners 100 $m_i(x)$% of the time e.g. when $m_i(x)=0.70$, on average 7 out of ten partnerships formed by this man will be with men.
3) An individual partner is selected from the pool of potential partners of the chosen sex, in the same way as described previously (1).

1.4.3 Formation of Long-term partnerships

In the agent-based model, the rate at which heterosexual ST partnerships become LT partnerships – the inverse of the average duration partners are together before they decide to cohabit/marry – is assumed to vary by age and sex, based on rates of marriage in national censuses from 1996, 2001 and 2007, and is described in detail elsewhere (9) .

At present, there is no data on marriage rates among same-sex couples in South Africa, which by way of comparison with marriage rates in heterosexuals, could serve as a proxy for relative rate at which MSM couples enter into cohabitation. Yet the continued persistence of stigma surrounding homosexuality in South Africa (10) suggests that the ability of MSM to enter into cohabiting partnerships with other men remains constrained, relative to the ability of men to enter into cohabitation with women. Accordingly, suppose *n(i,x,t)* is the rate of transition from ST to LT heterosexual partnerships for men in risk group *i* aged *x* at time *t*. We then specify parameter ν, with range (0,1), as a multiplicative downward adjustment to *n(i,x,t),* with the assumption that the rate at which ST relationships between MSM become LT would not exceed that in heterosexual men. Hence the rate at which MSM in ST partnerships enter into LT partnerships is given by $\nu n(i, x, t)$.

The uncertainty surrounding the parameter ν is captured via a vague uniform prior distribution, as there is no available data to indicate plausible values of this parameter (Table S3). Hence, the uniform prior allows for all values in the range (0,1) to be sampled with equal probability.

1.4.5 Mixing between risk groups

Reports concerning partnership formation across risk group for MSM in the Global South are scarce. Nevertheless, there is evidence from a study on MSM in South Africa that selection of regular partners depends on the extent to which a potential partner can perform masculinity (11). However this study does not report on whether the propensity for concurrency affects choice of partner and thus is of limited applicability to understanding mixing between risk groups.

Given the absence of applicable data, the degree to which men in the HR group acquire partners from the LR group is assumed to follow the same mixing pattern between the two risk groups as in the heterosexuals (9). The assortative mixing parameter ε, with range (0,1), specifies the degree to which individuals in a risk group form partnerships with individuals in the other risk group, with 0 specifying completely assortative mixing (HR individuals always partner HR individuals). For heterosexuals, the choice of ε was 0.56, based on fitting the previous frequency-dependent version of this model to data on the sexual behaviour of heterosexuals and prevalence of HIV. In the absence of data that would suggest that the processes determining partner selection differ substantially when men seek male partners, we assumed the same value of this parameter for MSM partner selection.

1.4.6 Age-mixing

To simulate the manner in which MSM choose the age of their male partners, we took the mean age and standard deviations thereof reported in the literature (2), where investigators reported on average age difference between partners. Though this study reported there was on average no difference (mean=0) between the ages of partners, they found that there was substantial variability in partner age differences (standard deviation 5.8 years). We assumed that the average age difference is linearly related to age, with younger MSM choosing older partners and older MSM choosing younger partners.

We obtained the distribution of ages for MSM – *g(x)* – from studies reporting on the age distribution of participants in RDS studies (Table S12).

Suppose f(y|x) represents the probability that an individual aged x chooses a partner who is aged y. In a single sex population, it is reasonable to assume that the age distribution of individuals in relationships will be the same as the age distribution of their partners. Thus the f(y|x) values need to be chosen in such a way that

$$g(y) \approx \sum_x g(x) f(y|x)$$

for all x. The conditional distribution of *y* given a specific *x* is represented in Table S1 where the rows represent *x* (index case) ages. These distributions were chosen such that the overall standard deviation of partner age differences was close to the 5.8 years noted previously.

Table S1 Proportion of male partners of MSM in each age group

	Age of partner															
Age of index	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+
10-14	0.09	0.48	0.25	0.11	0.04	0.02	0.01	0	0	0	0	0	0	0	0	0
15-19	0.03	0.42	0.31	0.15	0.06	0.02	0.01	0	0	0	0	0	0	0	0	0
20-24	0.01	0.29	0.36	0.21	0.09	0.03	0.01	0	0	0	0	0	0	0	0	0
25-29	0	0.15	0.36	0.28	0.13	0.05	0.02	0	0	0	0	0	0	0	0	0
30-34	0	0.06	0.30	0.33	0.19	0.08	0.02	0.01	0	0	0	0	0	0	0	0
35-39	0	0.02	0.20	0.35	0.26	0.12	0.04	0.01	0	0	0	0	0	0	0	0
40-44	0	0	0.10	0.30	0.32	0.18	0.07	0.02	0	0	0	0	0	0	0	0
45-49	0	0	0.01	0.11	0.29	0.31	0.18	0.07	0.02	0	0	0	0	0	0	0
50-54	0	0	0	0.01	0.11	0.29	0.31	0.18	0.07	0.02	0	0	0	0	0	0

55-59	0	0	0	0	0.02	0.11	0.28	0.31	0.19	0.07	0.02	0	0	0	0	0
60-64	0	0	0	0	0	0.02	0.11	0.28	0.32	0.19	0.07	0.02	0	0	0	0
65-69	0	0	0	0	0	0	0.02	0.11	0.28	0.32	0.19	0.07	0.02	0	0	0
70-74	0	0	0	0	0	0	0	0.02	0.11	0.28	0.32	0.19	0.07	0.01	0	0
75-79	0	0	0	0	0	0	0	0	0.02	0.11	0.27	0.32	0.19	0.07	0.01	0
80-84	0	0	0	0	0	0	0	0	0	0.02	0.11	0.27	0.32	0.19	0.07	0.02
85+	0	0	0	0	0	0	0	0	0	0	0.01	0.08	0.21	0.29	0.23	0.17

1.4.7 Dissolution of partnerships

The average duration of ST same-sex partnership for South African MSM remains highly uncertain. The Soweto Men's study reported on the average duration of same-sex partnerships for MSM, estimated at 2.5 months (standard deviation of 1.7 months) (2). That study did not define a partnership according to our definition of ST a partnership, as the study counted casual sexual encounters as partnerships. In addition, the measure for partnership duration was constrained to a maximum of half a year. Therefore these data are likely to under-estimate the average duration of a ST partnership between two men in South Africa. A gamma prior distribution was thus specified to represent the uncertainty surrounding the average ST partnership duration (Table S3). Given the limitations of the available data, the mean of this gamma distribution is the same as the assumed average duration of heterosexual ST partnerships (6 months) (1). The standard deviation (0.18 years) of the gamma prior was chosen in such a way that the 2.5^{th} percentile of the distribution corresponds to the average partnership duration reported in the Soweto Men's Study, thus including the existing data while recognizing that it is probably an under-estimate.

In absence of data on the rate at which cohabitating MSM terminate their partnerships, the rates of dissolution of LT same-sex partnerships were assumed to be the same as the rates set for heterosexual LT partnerships, which are based upon 2004 divorce rates (9).

1.4.8 Casual sex

The rate of entry into the casual sex state, λ_0 for a gay man, aged 20 in the HR sexual activity class, is calculated as a function of his corresponding rate of exit, μ_0 ,from this casual sex state and the prevalence of casual sex, π:

$$\lambda_0 = \frac{\pi \mu_0}{1 - \pi}$$

To represent the uncertainty regarding the prevalence of casual sex among MSM, we set a beta prior distribution on π, the lower bound of which is the reported fraction of MSM who had at least 3 partners in the past six months in the Marang Men's study (12). We specify a prior distribution for π with a 2.5th percentile to correspond to the estimated 56% of MSM in Cape Town and Johannesburg with at least 3 male partners in the past 6 months. We chose this as a proxy, as there is no specific measure of the occurrence of casual sex among MSM in the literature.

The inverse of μ_0 is the average duration in the casual sex state for a gay man, aged 20 in the HR group. Owing to the lack of literature regarding how long MSM typically spend having casual sex before they either enter celibacy or only have sex within partnerships, we set a gamma prior distribution for the $1/\mu_0$ parameter, with a mean of 1 year and a relatively large standard deviation of half a year to reflect uncertainty.

Age-dependence of entry into casual sex is modelled assuming exponential decline in the rate of entry with respect to age x_i and age adjustment factor τ for each *ith* gay or bisexual man:

$$\lambda(x_i) = \lambda_0 \tau^{x_i - 20},$$

We represent the uncertainty regarding the τ parameter by specifying a gamma prior distribution with a mean of 0.8 and a standard deviation of 0.2 and thus consider it most likely that there is a decreasing rate of entry into casual sex as MSM age. Though there is no literature to justify this choice of prior explicitly, the literature has found that transactional sex within informal drinking establishments is negatively correlated with age (13). As transactional sex at drinking establishments may be a proxy of one instance of casual sex, there is evidence that casual sex occurrence decreases with age. For this reason, we believe the proxy estimate of π, 56% of MSM with at least 3 partners, to be an underestimate – the sample of men in Cape Town, from which the estimate came from, was comprised of a preponderance of men older than the age of 25 years (Table S12). Since these older men are likely to engage in casual sex less often than men aged 20 – the age on which we base parameter λ_0 – we set the 56% estimate as a lower bound (2.5th percentile) for π.

MSM are assumed to go through phases of engagement in casual sex with other men, depending on their age, risk group and relationship status. The annual entry rate into casual sex ,ω_i, is determined by the product of the entry rate at age x_i, $\lambda(x_i)$, the male preference $m_i(\mathrm{x_i})$ parameter and the risk group adjustment factor θ_i

$$\omega_i = \theta_i \lambda(x_i) m_i(\mathrm{x_i})$$

For HR men, we assume the annual rate of entry into casual sex for those in partnerships scales by a factor of θ_{HR}, relative to those HR men with no partners i.e. θ_i is 1 if the individual is a HR man with no partners and θ_{HR} if the individuals is a HR man that has one or two partners. For LR men, the risk group factor θ_i is θ_{LR} regardless of partnership status.

$$\omega_i = \theta_i \lambda(x_i) m_i(\mathrm{x_i})$$

The uncertainty regarding the θ_{HR} , θ_{LR} parameters is represented by a uniform (0, 1) prior, assuming that HR men in regular partnerships and LR men, respectively, would engage in casual sex at a lower rate than HR men who are not in regular partnerships. The uniform prior distribution (0,1) was chosen owing to the absence of data to specify these parameters in the literature.

The rate of exit from casual sex state for each individual μ_i is given by:

$$\mu_i. = \frac{\mu_0}{\mathrm{m_i}(x_i)}$$

thus assuming that men with lower propensity for same-sex activity will remain in the casual sex state for a shorter period on average.

1.4.9 Role preference

Men can engage in either anal or non-penetrative sex, the former, we assume, has zero risk of HIV transmission between two men. For anal sex, the transmission of HIV from one man to another varies substantially by whether the susceptible man engages in the insertive or the receptive role. The model assigns role preference to MSM as a function of their sexual preference, where men exclusively take on one role or have equal preference for either role (versatile).

The model randomly allocates gay men into three groups with a ratio of 5:3:2 for exclusively receptive to versatile to exclusively insertive. Bisexual men are allocated into these three groups at ratio of 2:3:5. Hence, bisexual men tend to engage in more insertive sex relative to gay men, as the literature suggests (14-16).

1.4.10 Frequency of sex

We assume that men engage in anal sex only in the event their role preferences are compatible. Otherwise, we assume men engage in non-penetrative sex, such as manual-digital sex, that carries no risk of HIV transmission (17). The possible sexual role outcomes for two partners with all possible pairings of role preference are given in Table S2. For the sake of simplicity, the model assumes role preference does not impact on the choice of partner, although the literature suggests MSM with a receptive role preference preferentially seek out partners with the insertive role preference (11).

Table S2 Number of anal sex acts and roles performed, given role preferences of partners

Role preference partner 1	Role preference partner 2	Role partner 1	Role partner 2	Number of acts of anal sex per sexual episode
Receptive	Receptive	Non-anal role	Non-anal role	0
Insertive	Insertive	Non-anal role	Non-anal role	0
Versatile	Versatile	Receptive, Insertive	Receptive, Insertive	2
Insertive	Receptive	Insertive	Receptive	1
Insertive	Versatile	Insertive	Receptive	1
Versatile	Receptive	Insertive	Receptive	1

The frequency of sexual episodes between two male partners over a month is defined as f. In addition, we assume that each man has only a single episode of sexual contact with a specific man when in the casual sex state. Therefore, f_{ST} (frequency of sex in a ST partnership) and f_c ,the frequency of sex in the casual sex state) refer to the frequency of sexual episodes with short-term and casual male partners, respectively, in a given month.

The Soweto Men's Study (2) was the only study to report on sexual frequencies. To capture the uncertainty in the frequency of sex, gamma prior distributions were set for f_{ST} and f_c. For f_{ST} the mean of the prior distribution (5.5 acts per month) was set above the mean of frequency of sex reported in the Soweto Men's study (4.3 acts per month). We assumed this was an underestimate, because that study only measured episodes of anal sex over a period of 6 months and thus overlooked the contribution of non-penetrative sex episodes to the total frequency of sex, which according to a household sample of MSM, may account for at least half of sexual encounters between men who ever have sex with other men (3). The standard deviation of f_{ST} was set so the 2.5th percentile was 3.0 acts per month, the coital frequency in heterosexual partnerships, assuming frequency of sexual contact in same-sex ST partnerships is on average greater than the corresponding frequency for heterosexual partnerships. The mean of the prior distribution for f_c was set at 4 acts per month, assuming men who are not regular partnerships will have fewer sexual contacts with other men, on average, compared to men in regular same-sex partnerships.

As there are no data on the frequency of sex for cohabitating male couples, we assumed f_{LT} (the frequency of sex in a LT partnership) is the same as in heterosexual LT relationships, i.e. declining exponentially from a mean of 5 acts per month for MSM in the 20-24 age group, and halving every 20 years.

1.5. Prior distributions of sexual behaviour parameters

To account for uncertainty in specific assumptions regarding sexual behaviour, prior distributions have been specified for the corresponding sexual behaviour parameters (Table S3). Table S3 summarizes the information on the prior distributions specified in the previous sections.

Table S3 Prior distributions for sexual behaviour parameters

Parameter	Symbol	Prior distribution	Prior mean (std. dev.)	Source for prior
Proportion of MSM who have a propensity for sex with women	η	Beta(12,3)	0.8 (0.1)	RDS studies (15,18), (12), (19), (20)
Mean initial male preference for bisexual men	μ_m	Uniform(0,1)	0.5 (0.289)	Vague prior
Mean of annual average change in male preference	μ_Δ	Normal(0,0.05)	0 (0.05)	Data from high income countries (4-7)
Std. dev. of annual average change in male preference	σ_Δ	Beta(7.5,42.5)	0.15 (0.05)	Data from high income countries (4-7)
Casual sex adjustment factor for LR MSM relative to HR MSM	Θ_{LR}	Uniform(0,1)	0.5(0.289)	Model assumption of HR MSM having greater propensity for casual sex
Relative Risk of entry into casual sex for high risk MSM who have regular partner(s) (relative to HR MSM who do not have a regular partner)	Θ_{HR}	Uniform(0,1)	0.5(0.289)	Model assumption that HR MSM in a partnership will have less casual sexual encounters compared to single HR MSM

Age adjustment factor for entry into casual sex	τ	Gamma(16,20)	0.8 (0.2)	Convenience sample of MSM in Cape Town (13)
Average duration of casual sex among HR gay men, aged 20	1/μ	Gamma(4,4)	1.0 (0.5)	Gamma distribution reflects uncertainty in the parameter
Prevalence of casual sex among HR risk MSM, aged 20 and not in a partnership	π	Beta(12,3)	0.8 (0.1)	Marang Men's study (12)
Mean duration of ST partnerships (years)	ς	Gamma(7.716,15.4321)	0.5 (0.18)	Soweto Men's study (2) and assumptions for heterosexual partnerships (1)
Relative rate of entry into LT partnerships from ST for MSM (relative to heterosexual men)	ν	Uniform(0,1)	0.5 (0.289)	Vague prior, with assumed lower rate of entry into same-sex cohabitation relative to heterosexual cohabitation.

2. HIV assumptions

2.1 Per-contact risk of transmission

Observational studies have consistently found diverse estimates of per-contact risk of HIV acquisition (21-24)**.** Receptive anal intercourse with an HIV-positive partner, for example, has been estimated to convey a per-contact risk of acquisition that varies between roughly 0.5% and 3.0% in North American (21) and Australian MSM cohorts (22). To account for this diversity in the estimates of per-contact risks, we set prior distributions for these HIV transmission risks, from HIV positive to HIV negative men (Table S4). A large coefficient of variation was set for all the prior distributions, to account for the absence of estimates the South African population and the consequent reliance on studies from high-income countries (21-24) , whose findings are of unknown external validity.

The per contact risk of HIV transmission varies according to partnership type, for heterosexual contact, in the model. The reasoning thereof stems from findings among cohorts of serodiscordant heterosexual partnerships. Data from these cohorts indicates an overall fall in the per-contact risk of transmission as the cumulative number of sex acts – and thus duration of sexual contact - increases in a serodiscordant partnership (25-27). However, as Bavinton et al., noted, results arrived at from observation studies of heterosexual partnerships cannot simply be extrapolated for same-sex male couples (28). Therefore, observational studies among serodiscordant same-sex couples are necessary to understand the way per-contact risk relates to partnership duration for MSM. This is necessary to estimate appropriate parameter values for per-contact risk of transmission, according to same-sex partnership type, for MSM in the model.

Hence, we identified two studies that report on the association between partnership duration and per-contact transmission risk, one a prospective study among Australian MSM (28) and the other a review of prospective studies among MSM in the US (23).The findings thereof imply that the fall in per-contact risk of transmission, that accompanies an increase in relationship duration among heterosexuals, is also valid for MSM. The reason for this is that infectivity – a function of viral load – of the HIV positive partner may decrease over time. The data from Australian cohort study suggests this, as the HIV incidence in serodiscordant couples fell with increased partnership duration(28). Furthermore, Scott et al., reported that among serodiscordant MSM in the US, per-contact risk estimates decreases as the number of sexual contacts increased, also corroborating the notion that HIV transmission is most probable early in the partnership, when the cumulative number of sex acts is still relatively low(23).

There are other reasons for which short term partnerships are more risk for seroconversion, relative to longer ones. For instance, given that STIs have been associated with high per-contact risks of transmission (23), it is reasonable to assume that in once-off, casual encounters the per-contact risk will be greater than in long-term, monogamous partnerships, because STI status is less likely to be known in the former compared to the latter. Another factor may be nature of the sex acts in short-term partnerships – Bavinton et al., suggest that the partnerships may terminate due to risky sexual practices. In fact, seroconversion of the formerly HIV negative partner may itself be the reason for the end of a partnership. In addition, data indicate frequency of sex is greatest early on in a partnership for heterosexuals (29) and this may also hold for same sex partnerships. Taken together, these phenomena may explain the finding of higher estimates of per-contact risk of HIV transmission (23) or HIV incidence after relatively short duration (28) (or relatively fewer sexual contacts) among MSM.

Accordingly our model permits greater per-contact risk of transmission in ST partnerships relative to LT partnerships for MSM. For simplicity, we assumed the per-contact risk for casual sex as the same as for ST partnerhsips, as the Australian cohort data suggest that partnerships of less than one year duration have similarly high per-contact risks of transmission (28). LT partnerships in the model thus correspond to real-world serodiscordant partnerships between MSM, in which HIV infection occurs relatively late in the partnerships, after the initial 6 months or so when the risk of transmission is greatest. A review on the reasons for which relationships may persist as serodiscordant for longer periods is given by Bavinton et al., (28). Suffice it to say that recent investigations among MSM in the US have identified that a specific genotype (heterozygous individuals for CCR5 delta 32 deletion) known to render individuals less susceptible to HIV infection may dampen the HIV incidence among individuals with the genotype (30).

We assume HIV treated MSM had 90% reduction in infectiousness, per sexual contact, relative to untreated HIV positive MSM, as assumed for heterosexuals ((31).

2.2 Condom usage

There are few studies that compare condom use among MSM and heterosexual men in South Africa. While two surveys have assessed condom use among youth in sexual minorities, including MSM, comparisons with youth in the general population are possibly confounded by gender and relationship type, as the results were not disaggregated for male and females or relationship status and so could not be used to inform our model. The findings from these surveys suggest that youth who either identified as sexual minorities (lesbian, gay or bisexual), had same-sex partners or had same-sex experience had lower rates of condom use, albeit not significantly so, compared to their heterosexual peers. These results are possibly chance findings, given that the sample sizes of non-heterosexual youth were an order of magnitude smaller than those of heterosexual youth (32,33) . It is therefore assumed that the rates of condom use in MSM in short-term and long-term relationships are the same as the corresponding rates among heterosexual men in short- and long-term relationships (31).

The rate of condom usage varies by age and the sexual activity state an individual occupies. The model assumes yearly rates of condom use for MSM, starting in 1985. To initialize age distribution of condom use, the rate of use among 15-19 year old MSM with male partners is assumed equal to that rate of condom use during vaginal intercourse among 15-19 year old men, and the odds of condom use is assumed to decrease by 2.5% with each year of age. Condom use with male partners is assumed to increase over time in response to behaviour change campaigns, in the same manner as it does for vaginal sex. Condom use is assumed to be lower in LT partnerships relative to ST partnerships for MSM, by the same factor assumed for heterosexual partnerships (9,31).

As casual sex is a sexual activity state specified only for MSM, the rate of condom use in this state (relative to the ST partnership state), ψ, is specified according to findings from the literature review.

Evidence suggests that as the degree of trust and intimacy of a partnership increases, MSM are less likely to use condoms (34). Investigations into patterns of condom use among MSM in South Africa, conducted among a diverse sample of MSM from two urban centres, uncovered that once MSM enter long-term partnerships, where there is perceived monogamy and a high degree of trust, they are less likely to use condoms than in relationships with less trust (35).

The corollary of this finding is that men who are engaging in casual sexual encounters – where there is likely less trust than in ST partnerships – are more likely to have protected sex. Partnership level data from an RDS study in Soweto indicated that the rate of unprotected anal intercourse during the six months prior to the study was nearly two fold larger for men who were in regular – trusting – partnerships relative to men who were not in such partnerships (IRR=1.8 , 95% CI:1.4-2.3) (2). However, it is unclear to what extent this incidence rate ratio represents the relative rate of unprotected sex in regular partnerships for MSM outside the peri-urban settings of Soweto. Hence, we specified a prior distribution for ψ: the odds ratio of condom use during casual sex relative to condom use in the context of ST partnerships. The standard deviation of the prior distribution was chosen such that the lower bound (2.5^{th} percentile) was 1.0, because it is unlikely condom use is more frequent in regular partnership than in casual sexual encounters. The mean of ψ was set at 1.8, to correspond to the finding from the Soweto Men's study (2).

Furthermore, a survey conducted on a convenience sample of MSM in Pretoria concluded that frequency of recent, unprotected anal intercourse increased with age of the MSM respondents, both as direct consequence of age and the impact of age on the attitudes MSM held towards condom use (36). Taken together, these findings suggest that the default assumption for heterosexuals – that condom usage is less frequent among older adults (37) – are applicable also to MSM relationships.

Condoms are assumed to provide a 90% reduction in the risk of HIV transmission per sex act (37).

2.3 HIV survival and ART assumptions

The manner in which the model assigns HIV infected individuals a disease stage variable, adjusts the per contact probabilities of HIV transmission (according to disease stage) and accounts for progression of HIV disease, has been described in detail previously. The age, HIV status and HIV disease stage (1=acute infection, 2=latent infection, 3=pre-AIDS symptoms, 4=full blown AIDS or 5=on ART) affects the rates at which individuals acquire partners, as described previously (37).

Given the paucity of literature on linkage to and retention in care for HIV positive MSM in South Africa, we assumed that HIV positive MSM received ART at the same rate as HIV positive heterosexual men, as described previously (37). Briefly, we assume individuals could begin ART once they enter the pre-AIDS symptomatic state, which assumes they passed through the acute and latent infection states untreated. The proportion of individuals who access ART is based on the fraction of HIV positive South Africans who accessed ART annually from the start of the South African ART rollout until mid-2011 (38).

2.4 Initial HIV prevalence among MSM

To set the initial HIV prevalence among MSM (in 1990), we sourced AIDS cases reported in South Africa from 1990 to 1995, as we did not find any estimate of HIV prevalence in MSM (from a probability-based sample) reported in the literature for this period.

We estimated the initial prevalence in MSM indirectly, by first estimating parameter ϖ – the ratio of the initial HIV prevalence in MSM to that in heterosexual men. To represent the uncertainty around ϖ, we specified a prior distribution. We estimated parameter ρ – the fraction of the 1990-95 AIDS cases that were among MSM We obtained an empirical estimate ($\rho_{empirical}$=0.0539) of this fraction by dividing the reported number of homosexual patients with AIDS by the number of homosexual and heterosexual

AIDS cases (excluding people infected via drug use, unknown exposure and paediatric cases) reported in 1990-95 period from routine surveillance (39). We also obtained a theoretical estimate of the fraction that would be expected if the HIV prevalence in 1990 were the same in heterosexual men and MSM ($\rho_{theoretical}$ =0.0185). This theoretical estimate was premised on the following assumptions: that 5% of the male population are MSM; and that the ratio of HIV prevalence in heterosexual men to women was 0.585 (40).

Then, we assume

$$E(\varpi) = \frac{\rho\ empirical}{\rho\ theoretical} = 3.0,\ \ \varpi \sim gamma(5.325, 1.755)$$

We set the standard deviation of the prior distribution on ϖ such that the lower bound of this distribution (2.5th percentile) was 1.0, as the burden of HIV in MSM is likely to have been at least equal in size to that in heterosexual men in 1990, in the context of high HIV prevalence among MSM in South Africa during the 1980s (41-43).

2.5 Prior distributions of HIV transmission parameters

To account for uncertainty in assumptions regarding sexual transmission of HIV from one man to another, HIV transmission parameters were given prior distributions (Table S4).

Table S4 Prior distributions of HIV transmission parameters

Parameter	Symbol	Prior distribution	Prior mean (standard deviation)	Source for prior
Risk of acquisition per act for receptive partner in anal sex (ST or casual partnership) %	$\beta_{R,ST}$	Beta(3.945,354.7)	1.10% (0.55%)	Observational studies from high income countries (22,23)
Risk of acquisition per act for insertive partner in anal sex (ST or casual partnership) %	$\beta_{I,ST}$	Beta(3.984,1241)	0.32% (0.16%)	Observational studies from high income countries (21-24)
Risk of acquisition per act for receptive partner in anal sex (LT partnership) %	$\beta_{R,LT}$	Beta(3.99,1991)	0.2% (0.1%)	Observational studies from high income countries (22,23,28)

Risk of acquisition per act for insertive partner in anal sex (LT partnership) %	$B_{I,LT}$	Beta(3.997,5705.3)	0.07% (0.04%)	Observational studies from high income countries (21-24,28)
Odds ratio of condom use in casual sex relative to ST partnership	ψ	Gamma(16,8.889)	1.8 (0.45)	Soweto Men' Study (2)
HIV prevalence in gay/bisexual men relative to heterosexual men in 1990	ϖ	Gamma(5.32,1.755)	3.0 (1.3)	AIDS surveillance from 1990s in South Africa (39)
frequency of sexual episodes (per month) in ST partnerships	f_{ST}	Gamma(13.44, 2.44)	5.4 (1.5)	Soweto Men's Study (2)
Frequency of sexual episodes per month for men with only casual partners	f_C	Gamma(16,4)	4.0 (1.0)	Assumed : $f_C < f_{ST}$

3. Calibration

3.1. Accounting for heterogeneity in calibration data

Studies on HIV prevalence and sexual behaviour among MSM in South Africa show a wide range of estimates for these outcomes. This heterogeneity in estimates is likely a consequence of the recruitment of MSM from diverse communities and the observed geographical clustering of HIV burden in "risk spaces" (44). Moreover, while the study design of choice for our calibration was RDS, the studies reviewed varied substantially in their sample sizes and in the extent to which they obtain generalizable samples of the MSM communities. Hence, it is important to account for this heterogeneity in attempting to estimate a national average for levels of sexual risk behaviour and HIV prevalence in MSM. Similar to our previous work (45), we chose to use random effects when specifying the likelihood function, to account for the observed heterogeneity in the HIV prevalence and sexual behaviour for MSM in South Africa..

3.2 Definition of the Likelihood

Suppose in the *kth* study, investigators found proportion p_k of MSM tested HIV positive. We define a likelihood function to represent the goodness of model fit to the HIV prevalence data. More specifically we relate, p_k to the model predicted HIV prevalence, $C(\phi)$ (given parameter set ϕ), a random effect ,r_k and random error ε_k. $C(\phi)$ represents the model estimate of the average HIV prevalence among South African MSM, over the 2008-2012 period. The equation on which the likelihood function is based is

$$log\left(\frac{p_k}{1-p_k}\right) = log\left(\frac{C(\phi)}{1-C(\phi)}\right) + r_k + \varepsilon_k$$

where $r \sim N(0, \sigma_r^2)$ and $\varepsilon_k \sim N(0, \sigma_k^2)$.

The random effect is a term that attempts to account for variability in the HIV prevalence between the various studies, due to unmeasured factors such as geographical differences in the burden of HIV and the way sampling took place (for instance, one RDS study explicitly reported that they failed to achieve the minimum requirements of a RDS sample (20)). The random error term accounts for differences in HIV prevalence due to random chance, i.e. as a result of limited sample sizes and the uncertainty due to the RDS weights. To ensure that the random effect and random error terms are approximately normally distributed, we apply a logit transformation to the observed and modelled HIV prevalence levels.

It is evident that all of the HIV prevalence calibration data are from the 2008-2013 period (Table S5) and there is no temporal trend in the HIV prevalence for studies between 2008 and 2013. Preliminary model fits to the data also suggest no strong time trend over the 2008-2013 period. We therefore calculate *C(Φ)* as the average model estimate of HIV prevalence over the 2008-2012 period and ignore time dependency in the modelled estimates of prevalence; the averaging of the results over the 2008-2012 period has the additional advantage of reducing stochastic variation in model outputs.
The variance due to random error – uncertainty due to small sample size and uncertainty due to sampling design effects – σ_k^2 is estimated from the published 95% confidence intervals around p_k. The variance of the random effect σ_r^2 is approximated using the maximum likelihood estimate of the total variance and subtracting the variance due to random error from the total variance, i.e.:

$$\widehat{\sigma_r^2} = \frac{1}{n}\sum_{k=1}^{n}\left(log\left(\frac{p_k}{1-p_k}\right) - log\left(\frac{C(\phi)}{1-C(\phi)}\right)\right)^2 - \widehat{\sigma_k^2}$$

where n is the number of HIV prevalence measurements to which the model is calibrated. The likelihood of observing *n* HIV prevalence estimates (represented by vector **p**) given a set of model parameters ϕ is then:

$$L(\mathbf{p}|\phi) = \prod_{k=1}^{n}\frac{\exp\left[\frac{-(logit(p_k) - logit(C(\phi)))^2}{2\left(\widehat{\sigma_r^2}+\widehat{\sigma_k^2}\right)}\right]}{\sqrt{2\pi\left(\widehat{\sigma_r^2}+\widehat{\sigma_k^2}\right)}}$$

3.3 Obtaining best fitting parameter values

Here we elaborate on the procedure for obtaining the parameter sets that best fit the HIV prevalence and sexual behavioural data, in terms of the likelihood:

For the sake of simplicity, we explain how calibration took place using HIV prevalence data:

- We drew 20 000 samples from the prior distributions for the HIV transmission parameters (Table S4). Based on this we formed 20 000 parameter combinations, Φ_i, i = 1, …, 20 000.

- We then ran 20 000 simulations of the model, one for each Φ_i to obtain 20 000 model estimates of HIV prevalence ,$C(\Phi_i)$, in MSM over the 2008-12 period.
- We then computed the likelihood associated with the estimates from the data, **p**, given each of the $C(\Phi_i)$.
- We took the 100 parameters sets with the highest likelihoods.
- For each of the 100 best-fitting parameter combinations we reran the model to generate more detailed model outputs. We report the median and inter-quartile range for each output, from the 100 simulations.

The procedure for calculating the likelihood with respect to behavioural and demographic outcomes listed in Tables S6-S12 is the same as that described above for HIV prevalence, except that likelihood is calculated separately for each behavioural outcome and the total likelihood is calculated as the product of these likelihoods. The random effect, r_k , is calculated separately for each outcome, since there are several behavioural outcomes to which the model is calibrated. The procedure for identifying the parameter combinations that best fit the behavioural data is the same as that described previously, except that we sample from the prior distributions in Table S3 (not those in Table S4).

Our calibration process occurred in two stages:

Stage 1: Fitting sexual behaviour parameter sets (Table S3) consistent with sexual behaviour data. The best 100 fitting parameter sets are obtained.

Stage 2: Fitting HIV parameters (transmission probabilities, coital frequencies and condom use, initial HIV prevalence,Table S4) to HIV prevalence data. For this analysis, the sexual behaviour parameters referred to in the previous step were fixed at the means of the 100 parameter combinations that yielded the best fit to the sexual behaviour data. Then, the 100 parameter sets that provide the best fit to the HIV prevalence data were obtained.

3.4 Data for calibration

The sources for the HIV prevalence and behavioural outcomes, listed below, are presented in the tables (Tables S5-S12) that follow.

D0: Estimates of HIV prevalence among MSM from studies with probability-sampling design (MSM are 18 years of age and had sex with other men either in past 6 months – RDS studies – or lifetime experience – household survey).

D1 Proportion of MSM (men who are at least 18 years of age, who report having sex with men in the past 6 months) who report having sex with women in past 6 months

D2 Proportion of MSM (men who are at least 18 years of age, who report having sex with men in the past 6 months) who report having ever had sex with women over the course of their lives

D3: Proportion of MSM (men who are at least 18 years of age, who report having sex with men in the past 6 months) who report being married or in a cohabiting relationship (regardless of the sex of the partner)

D4: Proportion of MSM (men who are at least 18 years of age, who ever had sex with another man) who report currently having a regular male partner

D5: Proportion of MSM (men who are at least 18 years of age, who report having sex with men in the past 6 months) who report currently having a regular male partner

D6: Proportion of MSM (men who are at least 18 years of age, who report having sex with men in the past 6 months) who report having at least two male partners in the last 6 months

D7: Proportion of MSM (men who are at least 18 years of age, who report having sex with men in the past 6 months) aged over 25 years

Table S5 Studies reporting on HIV prevalence.

Location of population	Study design (n)	Reported Prevalence among MSM(95% CI)	Year and Reference
Rural and urban districts in EC,KZN	Household survey (n=73)	27.4% (17.6-40.0%)	2008(3)
Johannesburg	RDS (n=202)	49.5% (39.0-60.0%)*	2008 (20)
Durban	RDS (n=69)	27.5% (14.4-46.2%)*	2008 (20)
Soweto	RDS (n=363)	13.6% (8.1-18.3%)	2008 (15)
Pretoria	RDS (n=480)	30.1% (24.2-36.8%)*	2013 (16)
Gert Sibande	RDS (n=307)	29.4% (22.0-36.7%)*	2012-2013(18)
Ehlanzeni	RDS (n=298)	15.9% (10.6-22.8%)*	2012-2013(18)
Cape Town	RDS (n=286)	22.3% (14.7%-30.1%)	2012-13 (12)
Johannesburg	RDS (n=349)	26.8% (20.4-35.6%)	2012-13 (12)
Durban	RDS (n=290)	48.2% (37.9-55.4%)	2012-13 (12)

*The 95% confidence intervals for these HIV prevalence estimates were either omitted or calculated including non-testers within the total sample (18). Hence we calculated these 95% confidence intervals by assuming the same RDS design effect as estimated for the remaining studies in the table. The design effect was calculated as the ratio of the variance calculated from the RDS weighted confidence interval to the variance that would have been obtained assuming simple random sampling (SRS). The average of these design effects was then multiplied by the SRS variance estimates for the RDS studies denoted with * in order to obtain the RDS-adjusted variance estimates for each of these studies.

Table S6 Data used in calibration of parameters for outcome D1: proportion of MSM (aged at least 18 years, who report anal sex with male partners in last 6 months) who report having sex with women in past 6 months

Location of population	Study design (n)	Reported prevalence among MSM (95% CI)	Year and Reference
Soweto	RDS (n=363)	23.0% (17.3-30.1%)	2008 (15)
Cape Town	RDS (n=286)	28.4% (21.6-35.9%)	2012-13 (12)
Johannesburg	RDS (n=349)	23.0% (17.3-30.1%)	2012-13 (12)
Durban	RDS (n=290)	8.0% (3.4-13.6%)	2012-13 (12)
Gert Sibande	RDS (n=307)	40.6% (32.2-48.9%)	2012-2013(18)
Ehlanzeni	RDS (n=298)	25.7% (18.1-33.2%)	2012-2013(18)

Table S7 Data used in calibration of parameters for outcome D2: proportion of MSM (aged at least 18 years, who report anal sex with male partners in last 6 months), who report having ever had sex with women over the course of their lives

Location of population	Study design (n)	Reported Prevalence among MSM(95% CI)	Year and Reference
Soweto	RDS (n=363)	86.5% (79.7-81.2%)	2008 (15)
Johannesburg and Durban	RDS (n=284)	35.6% (27.1-45.1)*	2008 (20)
Cape Town	RDS (n=286)	69.7% (61.7%-77.1%)	2012-13 (12)
Johannesburg	RDS (n=349)	67.6% (57.9-76.5%)	2012-13 (12)
Durban	RDS (n=290)	40.1 % (30.3-49.3%)	2012-13 (12)
Gert Sibande	RDS (n=307)	72.9% (64.3-80.6%)	2012-2013(18)
Ehlanzeni	RDS (n=298)	48.9% (41.8%-56.6%)	2012-2013(18)
Pretoria	RDS (n=480)	44.3% (37.2-51.6%)*	2011-2013(16)

* The 95% confidence intervals for these estimates were not reported. Hence we calculated these 95% confidence intervals by assuming the same RDS design effect as estimated for the remaining studies in the table. The design effect was calculated as the ratio of the variance calculated from the RDS weighted confidence interval to the variance that would have been obtained assuming simple random sampling (SRS). The average of these design effects was then multiplied by the SRS variance estimates for the RDS studies denoted with * in order to obtain the RDS-adjusted variance estimates for each of these studies.

Table S8 Data used in calibration of parameters for outcome D3: proportion of MSM (aged at least 18 years, who report anal sex with male partners in last 6 months) who report being in marriage or long-term, cohabiting relationships with a partner (regardless of the sex of the partner)

Location of population	Study design (n)	Reported Prevalence among MSM(95% CI)	Year and Reference
Pretoria	RDS (n=307)	12.6% (7.1%-17.8%)	2009 (46)
Cape Town	RDS (n=286)	28.8% (20.7-37.3%)	2012-13 (12)
Johannesburg	RDS (n=349)	21.6% (15.1-27.2%)	2012-13 (12)
Durban	RDS (n=290)	19.3% (12.6-29.5%)	2012-13 (12)

Table S9 Data used in calibration of parameters for outcome D4: proportion of MSM (aged at least 18 years, who report ever having sex with other men) who report having a regular male partner

Location of population	Study design (n)	Reported Prevalence among MSM(95% CI)	Year and Reference
Rural and urban districts in EC,KZN	Household survey (n=94)	27.7% (20.1-36.8%)	2008 (3)

Table S10 Data used in calibration of parameters for outcome D5: proportion of MSM (aged at least 18 years, who report anal sex with male partners in last 6 months) who report having a regular male partner

Location of population	Study design (n)	Reported Prevalence among MSM(95% CI)	Year and Reference
Gert Sibande	RDS (n=307)	66.0% (58.2-73.7%)	2012-2013(18)
Ehlanzeni	RDS (n=298)	74.2 % (65.9-79.9%)	2012-2013(18)
Soweto	RDS (n=363)	69.6% (64.7-76.7%)	2008 (15)

Table S11 Data used in calibration of parameters to outcome D6: proportion of MSM (aged at least 18 years, who report anal sex with male partners in last 6 months) who report having at least two male partners in the last 6 months

Location of population	Study design (n)	Reported Prevalence among MSM(95% CI)	Year and Reference
Gert Sibande	RDS (n=307)	29.7% (23.5-37.2%)	2012-2013(18)
Ehlanzeni	RDS (n=298)	37.8% (31.0-46.5%)	2012-2013(18)
Cape Town	RDS (n=286)	68.7% (60.9-75.6%)*	2012-13 (12)
Johannesburg	RDS (n=349)	71.0 % (64.1-77.1%)*	2012-13 (12)
Durban	RDS (n=290)	60.3% (52.4-67.7%)*	2012-13 (12)

* The 95% confidence intervals for these estimates were not reported. Hence we calculated these 95% confidence intervals by assuming the same RDS design effect as estimated for the remaining studies in the table. The design effect was calculated as the ratio of the variance calculated from the RDS weighted confidence interval to the variance that would have been obtained assuming simple random sampling (SRS). The average of these design effects was then multiplied by the SRS variance estimates for the RDS studies denoted with * in order to obtain the RDS-adjusted variance estimates for each of these studies.

Table S12 Data used in calibration of parameters to fraction of MSM who were older than the dividing age reported in the study (D7)

Location of population	Dividing age	Study design (n)	Proportion age ≥ dividing age	Year and Reference
Johannesburg and Durban	25	RDS (n=285)	33.3% (25.3-42.4%)*	2008 (20)
Johannesburg	25	RDS (n=363)	31.0% (24.4-39.4%)	2008 (15)
Pretoria	26†	RDS (n=307)	28.3% (21.0-37.9%)	2009, (46)
Gert Sibande	25	RDS (n=307)	29.6% (22.5-37.2%)	2012-2013(18)
Ehlanzeni	25	RDS (n=298)	28.0% (22.6-36.9%)	2012-2013(18)
Cape Town	25	RDS (n=286)	67.3% (57.0-74.9%)	2012-13 (12)
Johannesburg	25	RDS (n=349)	27.0% (19.2-36.2%)	2012-13 (12)
Durban	25	RDS (n=290)	52.1% (44.4-59.5%)	2012-13 (12)

†For the purposes of calibration, this age was set assumed as 25 years, so the outcome is consistent across studies.

* The 95% confidence intervals for these estimates were not reported. Hence we calculated these 95% confidence intervals by assuming the same RDS design effect as estimated for the remaining studies in the table. The design effect was calculated as the ratio of the variance calculated from the RDS weighted confidence interval to the variance that would have been obtained assuming simple random sampling (SRS). The average of these design effects was then multiplied by the SRS variance estimates for the RDS studies denoted with * in order to obtain the RDS-adjusted variance estimates for each of these studies.

4. Results of model fitting

4.1 Best fitting parameter estimates

4.1.1 Sexual behaviour parameters

The 100 best-fitting parameter estimates had smaller standard deviations about the mean compared to the prior distributions. All parameter estimates retained the same sign, except the mean annual change in male preference, which had a negative mean in the distribution of best fitting estimates, indicating a decrease in male preference with age (Table S13). In addition, the rate of entry into LT partnerships from ST partnerships for MSM, relative to heterosexual, was decreased by roughly 40% in the best fitting distribution compared to the prior distribution. This suggests that the model assumption that MSM are less likely to enter into co-habitation compared to the general population is reasonable, given the available data.

Table S13 Prior and best-fitting distributions of sexual behaviour parameters

Parameter	Symbol	Prior mean (std. dev.)	100 best fitting values mean (std. dev.)
Proportion of MSM who have a propensity for sex with women	η	0.80 (0.10)	0.84 (0.05)
Mean initial male preference for bisexual men	μ_m	0.5 (0.289)	0.48 (0.25)
Mean of annual average change in male preference	μ_Δ	0 (0.05)	-0.07 (0.04)
Std. dev. of annual average change in male preference	σ_Δ	0.15 (0.05)	0.13 (0.05)
Casual sex adjustment factor for LR MSM relative to HR MSM	Θ_{LR}	0.50(0.289)	0.60 (0.25)

Relative Risk of entry into casual sex for high risk MSM who have regular partner(s) (relative to HR MSM who do not have a regular partner)	Θ_{HR}	0.50(0.289)	0.58 (0.25)
Age adjustment factor for entry into casual sex	τ	0.80 (0.20)	0.82 (0.19)
Average duration of casual sex among HR gay men, aged 20	$1/\mu$	1.0 (0.50)	0.86 (0.47)
Prevalence of casual sex among HR risk MSM, aged 20 and not in a partnership	π	0.80 (0.10)	0.88 (0.06)
Mean duration of ST partnerships (years)	ς	0.5 (0.18)	0.40 (0.10)
Relative rate of entry into LT partnerships from ST for MSM (relative to heterosexual men)	ν	0.5 (0.289)	0.29 (0.15)

4.1.2 HIV transmission parameters

With the exception of the odds of condom use in casual sex, relative to ST partnerships, generally the best-fitting HIV transmission parameter estimates had mean values larger than those of the prior distribution (Table S14). The per contact risks of transmission in ST partnerships, in particular, were of substantially larger magnitude after fitting of the model, compared to the modest increase or stability in magnitude for the corresponding per contact risks for LT partnerships. In sum, these findings suggest the per-contact risk of HIV transmission between men in the South African context may be greater than estimated by studies conducted in high income countries.

Table S14 Prior and best-fitting distribution of HIV transmission parameters

Parameter	Symbol	Prior mean (std. dev.)	Best fitting mean (std. dev.)
Risk of transmission per act of receptive anal sex in a ST or casual partnership %	$\beta_{R,ST}$	1.10% (0.55%)	1.74% (0.61%)
Risk of transmission per act of insertive anal sex in a ST or casual partnership %	$\beta_{I,ST}$	0.32% (0.16%)	0.46% (0.18%)
Risk of transmission per act of receptive anal sex in a LT partnership %	$\beta_{R,LT}$	0.20% (0.1%)	0.21% (0.09%)
Risk of transmission per act of insertive anal sex in a LT partnership %	$\beta_{I,LT}$	0.07% (0.04%)	0.07% (0.03%)
Odds ratio of condom use in casual sex relative to ST partnership	ψ	1.80 (0.45)	1.77 (0.45)

HIV prevalence in gay/bisexual men relative to heterosexual men in 1990	ϖ	3.0 (1.3)	3.1 (1.5)
frequency of sexual episodes (per month) in ST partnerships	f_{ST}	5.5 (1.5)	6.68(1.71)
Frequency of sexual episodes per month for men with only casual partners	f_C	4.0 (1.0)	4.35 (1.12)

4.2 Comparison of HIV prevalence data to model output

The model output for HIV prevalence among MSM, averaged over 2008 and 2012, is consistent with the most of the observed prevalence estimates (Figure S2).

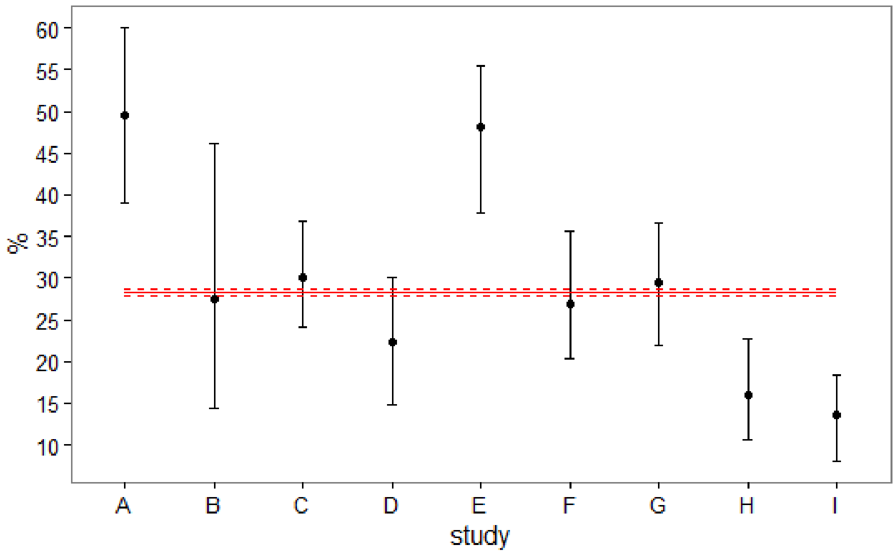

Figure S2 Comparison of model output to observed HIV prevalence in MSM. Point estimates are reported with error bars (Table S5) (95% confidence intervals). Estimates A and B are from 2008, Johannesburg and Durban respectively (20), C from 2013, Pretoria (16), D E and F from 2012-13, Cape Town, Durban and Johannesburg respectively (12), Gert Sibande (G) and Ehlanzeni (H) from 2012-13, districts in Mpumalanga (18), I is from Soweto in 2008 (15). The median (solid line) and IQR of HIV prevalence (dotted lines) are shown for 100 simulations, after the mean prevalence over the period 2008-2012 was computed.

4.3 Comparison of sexual behaviour indicators to model output

Analogously, we obtained the likelihood of observing the estimates of each of the sexual behaviour outcomes, D1-D7.

The model provides a reasonable fit to the observed data for outcomes D1 and D2 (Figure S3) – the proportion of bisexual MSM – and D3, D4 and D5 (Figure S4) – the proportion of MSM in LT or regular partnerships.

There is a modest fit of the model outputs to the sexual behaviour outcome D6, whilst there is a poor fit to outcome D7 (Figure S5). This indicates the model does not capture well the high proportion of MSM aged under the age of 25 years. By comparison, the model is in reasonable agreement with the estimates of the fraction MSM who had at least two partners in the past two months.

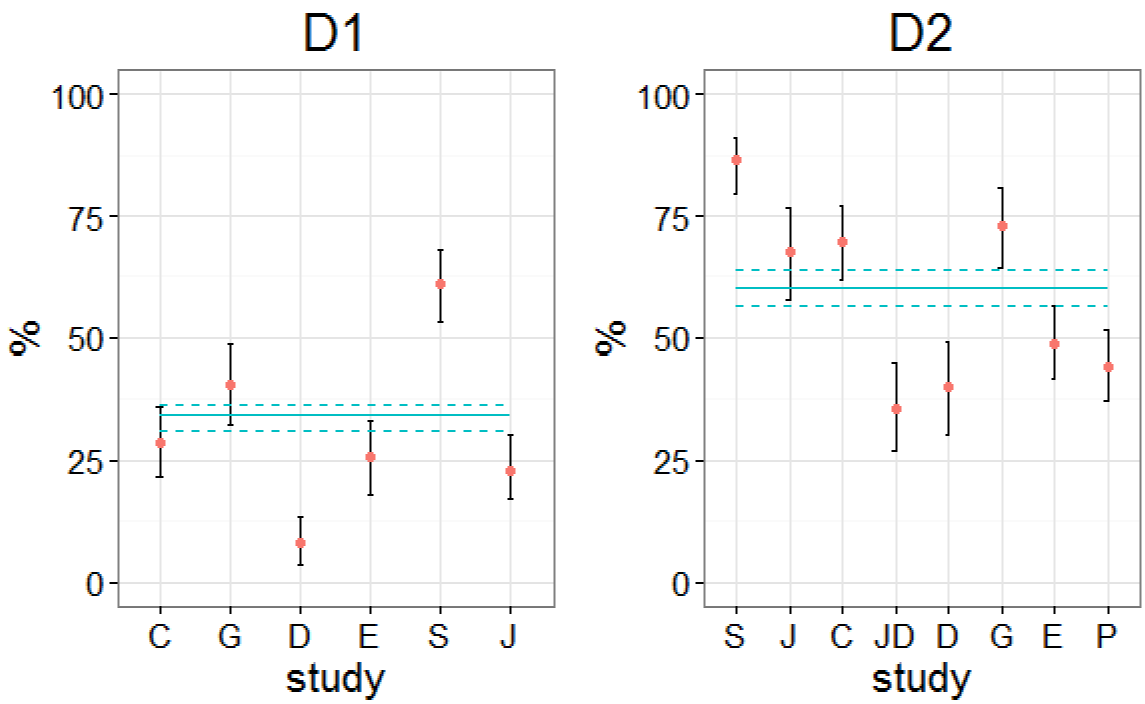

Figure S3 Comparison of model predictions for prevalence of sexual behaviour outcomes: D1 MSM who recently had female partners (Table S6) and D2 MSM who ever had female partners (Table S7). Estimates, C,D, J are from Cape Town, Johannesburg and Durban respectively (12), E and G are from Ehlanzeni and Gert Sibande in Mpumalanga (18), S form Soweto (15), P from Pretoria (16), JD from a pooled Durban and Johannesburg sample (20). The median (solid line) and IQR of the prevalence of D1 and D2 (dotted lines) are shown for 100 simulations, after the mean prevalence over the period 2008-2012 was computed. Empirical estimates are shown as points; the 95% confidence intervals are denoted as error bars, for those estimates where they were reported.

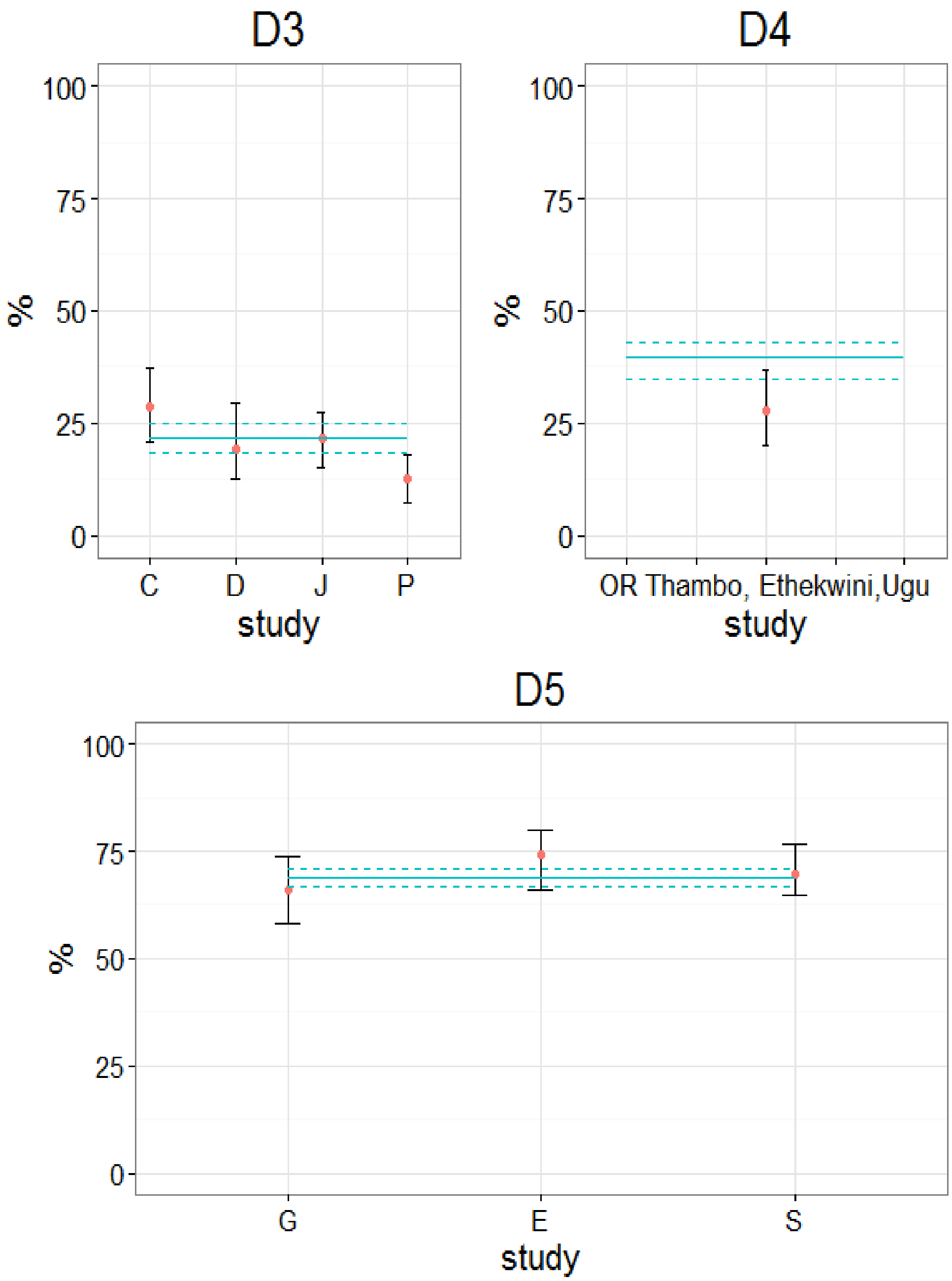

Figure S4 Comparison of model predictions for prevalence of sexual behaviour outcomes: D3 MSM who have LT partners (Table S8); D4 current regular male partners among all men who have ever had sex with other men) (Table S9); D5 current regular male partners among MSM sexually active with men in past 6 months (Table S10). Studies C, D, J are from Cape Town, Johannesburg and Durban respectively (12), P from Pretoria (16), E and G are from Ehlanzeni and Gert Sibande in Mpumalanga (18), S form Soweto (15), OR Thambo, Ethekwini and Ugu are the locations from which men where sampled in a household survey of male-male sexual behaviour (3) Median (solid line) and IQR of the prevalence of D3, D4 and D5 (dotted lines) are shown for 100 simulations, after the mean prevalence over the period 2008-2012 was computed. Empirical estimates are shown as points; the 95% confidence intervals are denoted as error bars.

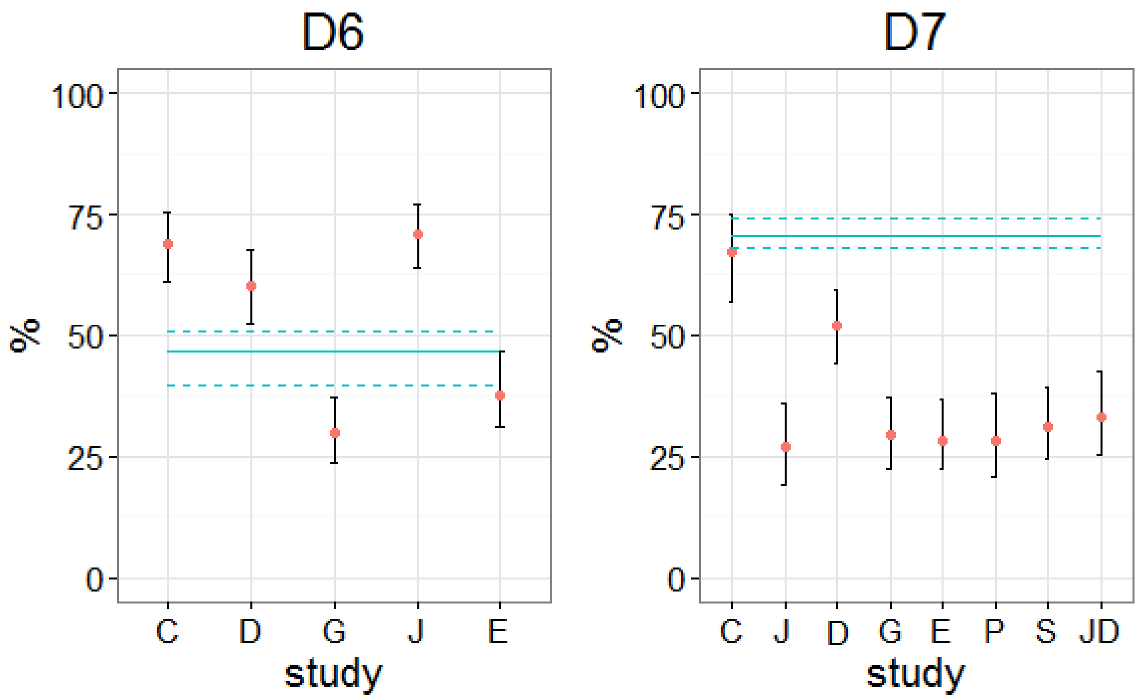

Figure S5 Comparison of model predictions for prevalence of sexual behaviour outcomes: D6 (Table S11) MSM who report at least two male partners in past 6 months); D7the proportion of MSM aged older than 25 years (Table S12) Studies C, J, D are from Cape Town, Johannesburg and Durban respectively (12), E and G are from Ehlanzeni and Gert Sibande in Mpumalanga (18), P from Pretoria (16) , JD from a pooled Durban and Johannesburg sample(20) and S form Soweto (15). The median (solid line) and IQR of the prevalence of D6 and D7 (dotted lines) are shown for 100 simulations, after the mean prevalence over the period 2008-2012 was computed. Empirical estimates are shown as points; the 95% confidence intervals are denoted as error bars.

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