**MATHEMATICAL MODELS OF SUBPOPULATION-SPECIFIC SEXUAL INTERACTIONS FOR HIV TRANSMISSION AND CONTROL**

by

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Lisa M. Bodnar, PhD

**MATHEMATICAL MODELS OF SUBPOPULATION-SPECIFIC SEXUAL INTERACTIONS FOR HIV TRANSMISSION AND CONTROL**

Yuruo Li, MPH

University of Pittsburgh, 2016**ABSTRACT**

**Background:** The HIV epidemic has become the most serious health burden in the world. The primary mode of HIV transmission is unprotected sexual intercourse. It has been pointed out that human sexual behavior is one of the main drivers of the HIV epidemic. Modified compartmental models are mathematical models that divide the population into two or more subgroups according to various sexual behaviors. Modified compartmental models have been proven to be useful in describing the heterogeneity of the HIV-related sexual behaviors. Therefore, a review of current modified compartmental models of HIV behavior is necessary and important for public health research in further understanding and controlling the HIV epidemic.

**Method:** I searched PubMed and EMBASE for modified compartmental models published from 2000 to 2015. Eighteen articles that contained fourteen unique models were included in the final review. These models described the heterogeneity of HIV-related sexual behaviors and assessed the potential intervention strategies based on the behavioral assumptions. I summarized and analyzed the distribution of study populations, subpopulation composition, key methodologies used in the models and the predicted impact of selected intervention strategies that were examined by the models.

**Conclusion**: My results showed that high-risk individuals and steady sexual partnerships are more likely to transmit the infection compared to individuals in the general population and casual sexual partnerships. Intervention strategies focusing on the general population prevent more people from getting HIV, but more costly compared to the intervention strategies focusing on the high-risk individuals.

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# Introduction

In 1981, Human Immunodeficiency Virus (HIV) and Acquired Immunodeficiency Syndrome (AIDS) were first identified among homosexual men19. Today, 36.9 million people are still living with HIV worldwide20. In 2012, HIV/AIDS has become the 6th leading cause of death in the world, taking 1.5 million lives 21. In the United States alone, over 1.2 million people are living with HIV22. Over 80% of the infections have been attributed to sexual contact23. In response to the HIV pandemic, a reduction of risky sexual behaviors has been observed in many populations24 and has become an important focus in the prevention of HIV and other sexually transmitted diseases (STD).

Since the late 1980s, mathematical modeling technique has become a valuable tool in understanding the behavioral components of the HIV epidemic25 26. Such a technique provides insights about the social mechanism of HIV transmission and evaluates the potential intervention strategies. Researchers usually use the compartmental mathematical model to study the infectious disease dynamic27,28. The compartmental model is defined as the mathematical model abstracting the study population into compartments and assuming individuals in each compartment transfer from one to another at a certain rate29,30. The simplest compartmental model, known as the homogenous model, assumes that every individual in the population has an equal chance of being infected27. The homogeneous model divides the study population only according to the natural history of infection with no specifications on their health-related behaviors. Unfortunately, the actual spread of infections occurs in a diverse population. The homogenous compartmental model fails to capture the behavioral heterogeneity in the HIV epidemic.

The heterogeneity of sexual behaviors could be described by the modified compartmental model. Different from the homogeneous model, the modified compartmental model divides the study population into subpopulations according to various sexual behaviors. Subpopulations are the relative disjoint fractions of a population. An individual can be grouped into a subpopulation according to his/her frequency of sexual activities, occupations, relationship status, sexual partner preference, etc28,31. Individuals in different subpopulation classes have different risks of being infected and probabilities of transmitting HIV. Subpopulations differ by their choice of sexual partners and population sizes as well. Although these subpopulations are disjoint, the individuals in each subpopulation would have sexual contacts within and outside their subpopulation class. The process of an individual selecting a new partner is the partner formation or mixing process. Individuals in the same subpopulation class have similar partner formation preference. In the language of mathematical models, a subpopulation is represented by a compartment and the partner formation pattern is represented by the contact matrices, which map the probability of contact between two compartments. Contact matrices can determine the movements and interactions of individuals among subpopulations. The simplest assumption of the contact matrices is proportionate mixing, defined by Hethcote et al., as “the number of adequate contacts between two subpopulations is proportional to the relative activity levels of the two subpopulations” 28. In later developments of modified compartmental models, two more types of contact matrices, the assortative (i.e. Prefer mixing within the subpopulation) and the disassortative (i.e. Prefer mixing outside the subpopulation), are used to describe the preferences of individual’s choice of sexual partners. The subpopulation classifications and the mixing patterns outline the social and behavioral patterns of HIV transmission. Compared to the homogeneous model, the modified compartmental model can account for certain levels of behavioral heterogeneity. This essay will review the current literature on the use of modified compartmental models in studying the HIV epidemic.

Before this review, two similar systematic reviews were published in 2011 and 2012. The 2011 review systematically summarized all the mathematical models used in studying HIV spread and control among men who have sex with men (MSM) 32. The 2012 article is a more target review which focused on the impact of high-risk core-groups on HIV transmission among the heterosexual population33. The core-group theory claims that there is a subpopulation with a relatively small number of individuals that are more susceptible to HIV and more likely to spread the infection33. My essay is a target review which interested in looking at the mathematical models used to understand the links between subpopulations across sexual orientations from 2000 to 2015. Different from the previous reviews, this essay will focus on the modified compartmental models of all subpopulation structures, including core-groups and non-core-groups. This essay will include the following discussions: where the data were collected, how the subpopulations were defined, what the mixing patterns were used, and which intervention strategies were simulated in the models.

# METHOD

## Searching Strategy

I searched PubMed and EMBASE for relevant studies using the following keywords: (“HIV”[Majr] or ’hiv’/exp or ’hiv’) and ((”Models, Biological”[Mesh:NoExp]) or “Models, Theoretical”[Mesh:NoExp] or “mathematical model”) and (”sexual Behavior”[Mesh] or “sexual behavior’[humans]/lim or ”Sex Factors”[Mesh] or “sex factors” or “network” or “network model”). The detailed search results are presented in Table 1: Searching Results. A total of 282 articles were identified, 16 articles were found to be duplicates and a total of 266 articles were included for selection.

## Selection Criteria

Studies were included if they were published between 2000 and 2015, were written in English, used compartmental models and divided the study population into two or more subpopulations according to their HIV-related sexual behaviors. Social network models were initially included in the search. When a network model assumes a group of individuals to be a node in the network, the math is similar to a modified compartmental model34. However, in the actual search, no social network model with a major focus on HIV transmission meets the inclusion criteria.

The models were excluded if they only divided the study population according to the natural history of infection progression (i.e. stages of HIV infection) or if they failed to capture the behavioral dynamic of subpopulation interaction. For example, models were excluded if they divided the study population into discrete age sets, assigned different probabilities of infection for each age set, but did not use any contact matrix to describe the sexual interactions between age sets. Non-dynamic mathematical models, mostly statistical models were excluded from the review. I also excluded any non-original research article and articles that only proposed a conceptual mathematical model without doing the actual math. Since the primary interest of this article is to look at the subpopulation composition and mixing patterns of the modeled population, no outcome variable was specified for exclusion. Compared to earlier studies, four homosexual articles2,6,7,17, and seven heterosexual articles3-5,9,12,14,18 were included in addition to the 2012 and 2011 review. The four homosexual articles were all published after the original review. The seven heterosexual articles were excluded from the 2012 review because they did not meet one of the inclusion criteria, which was using the population attributable fraction as an outcome of interest. Eventually, only 18 articles were reviewed for further analysis. The detailed selection process was presented at Figure 1: Selection Flow Chart.

Table : Searching Results

|  |  |  |
| --- | --- | --- |
|  | **PubMed** | **EMBASE** |
| Steps | Term | Results | Term | Results |
| 1 | ”HIV”[Majr] | 66518 |  ’hiv’/sup OR ’hiv’ | 342228 |
| 2 | (”Models,Biological”[Mesh:NoExp]) OR ”Models, Theoretical”[Mesh:NoExp] | 406309 | ’mathematical model’ | 103801 |
| 3 | ”Sexual Behavior”[Mesh] | 85262 | #1 AND #2 | 1938 |
| 4 | #1 AND #2 | 1243 | “sexual behavior’ | 93982 |
| 5 | **#4 AND #3** | **50** | **#4 AND #3 AND****[humans]/lam** | **190** |
| 6 | ”Sex Factors”[Mesh] | 222611 | ’sex factors’ | 323 |
| 7 | **#4 AND #6** | **5** | **#3 AND #6** | **0** |
| 8 | **#4AND network** | **29** | ’network model’ | 5368 |
| 9 |  |  | **#3 AND #8** | **8** |
|   Highlighted columns were the articles that entered the selection process. 50+190+5+0+29+8 = 282. 16 of them were found to be duplicates and removed before the further review, so a total of 266 articles were in the selection flow chart (see figure 1).  |

Figure : Selection Flow Chart

266 abstracts identified from EMBASE and PubMed database; abstracts examined

54 excluded due to published before 2000

212 abstracts examined

* 18 excluded due to being cost-effective analysis;
* 25 excluded due to being molecular model;
* 13 excluded due to being non-original research;
* 6 excluded due to being vaccination related model;
* 1 excluded due to being non-HIV paper;
* 3 excluded due to being Spanish papers.

146 assessed in more detail

* 43 excluded because these models were designed to assess the treatment efficacy or diagnostic strategy;
* 24 excluded due to non-mathematical model;
* 23 excluded because these models were designed at individual level.

54 received full-text review

* 31 excluded because these models were non-sexual transmission models;
* 7 excluded because these models not described the sexual interaction between population;

18 included in review

# MODEL DescrIption

## Characteristics of Study population

Table 5: Model Summary in the appendix has the full summary of the model characteristics. Among the eighteen articles, three models have been used twice under different circumstances3, 4,6,7,10,11. The repeated models were identified as dividing the study population into the same subpopulation class, using the same contact matrices and the same data set for model parameterization. Repeated models were also developed by the same team of authors and the earlier articles were cited as the source for the model development in the later articles. Repeated models will be discussed as separate models in the flowing analysis.

### Population Distribution of the Selected Studies

Among all the selected models, twelve (67%) of them focused on the heterosexual population3-9,12-15,18, six (33%) of them focused on the homosexual population1,2,10,11,16,17, and no study focused on the bisexual population. Most of these models also focused on what were described as the socially vulnerable populations such as sex workers, drug users, widows and immigrant or mobile populations. Five articles (28%) incorporated sex workers into their model design or parameterization9,14-16,18. Two heterosexual models treated female sex workers (FSW) as a major subject of interest14, 18. One article considered the role of widows and FSWs in their model design15. One article treated injecting drug users (IDUs) as the major subject of interest and included a small proportion of IDUs who worked as commercial sex workers to support their drug habits9. One homosexual model considered the probability of male sex workers, known as the “money boy” in its model parametrization. Two models focused on migrants or mobile populations12, 13

Sixteen (89%) articles used the epidemiological and behavior data for model parameterization and data comparison1-11,13,15-18. Five of them (28%) used data from developed countries, including Amsterdam, Netherlands10,11,13, the United Kingdom2, and San Francisco, the United States14. Four out of five data sets from developed countries focused on the homosexual population. Among eleven articles (61%) using the data from developing countries, two homosexual studies were from Shanghai, China16 and Bangalore, India17. Nine of them studied the heterosexual population. Seven of them (39%) used the data from African countries3, 8, 6,7, 4,5, 15. The study focusing on the IDUs used the data from Odessa, Ukraine9. Another article used the data from Yunnan, China, focusing on the role of FSWs in the disease transmission dynamic18.

## Subpopulation composition

This section will discuss the composition of subpopulation for each selected model. The composition of subpopulation could determine the research data used in model parameterization and the partner formation patterns between two subpopulations. I identified three main criteria used in dividing the study population, which are sexual activity level, social position, and sex-role preference. The definition of three categories will be discussed in each subsection. Figure 2. Subpopulation Composition Diagram is a visualization of the model structure classification.

### Sexual Activity Level

56% of the studies grouped individuals based on their sexual activity levels1-8,14,15. The sexual activity level is important because individuals with higher sexual activity level are more likely to get and spread the infection. The criteria used to classify sexual activity level varied by studies. Seven articles stratified sexual activity level simply based on the number of sexual partners, the sexual partner turnover rate, defined as the frequency of partner change, or both. Among the above seven articles, six of them focused on the heterosexual population 3-8,and one of them focused on the homosexual population2; Beyond the above definition, three additional variations were found in defining the sexual activity level. One article incorporated the concept of safe sex in addition to the frequency of sexual intercourse1. The other two articles defined an individual’s sexual activity level based on the social characteristics of that person’s sexual partners. Bacaer et al. designated any male individual who has sexual intercourse with a female sex worker (FSW) as an individual with high sexual activity18. High sexual activity group in the other article was made of sex workers, widows and other individuals with high partner turnover rates 15.

### Social position

The last two models incorporated FSWs and widows into the design of subpopulation composition. Sex worker is an occupation and widow is a relationship status. They are both social positions. The social position of an individual is a person’s position, role or rank in a society and the expected behaviors based on it. The social position could be associated with individual’s occupation, relationship position, social class, religions etc. An individual’s social position is important because it could shape that person’s health behavior. Sex workers4,15,18, relationship status10,11, immigrants12,13 and injecting drug users9 were social positions identified in the selected models. One article divided the study population into commercial sex workers, unpartnered males, non-sex worker females, and long-term couples in the heterosexual population. This article discussed the role of a “bridge” population (i.e. unpartnered males) in the spread of HIV14. The “bridge” population served as a connection between the general female population and high-risk females (i.e. FSW). Two papers divided the homosexual population into singles and pairs10,11. Singles and pairs were defined as whether a man was in a long-term steady relationship. Singles were more likely to have casual sexual relationships with other people. Individuals in a casual relationship were more likely to use condoms compared to pairs in a steady relationship. Paired individuals could also have casual sexual relationships, but they formed less casual relationships than singles. Immigrants were also discussed as a social position using real world data13 and in a theoretical setting12.

All the subpopulation described above except singles and pairs also fall into the category of “core-group”. A core-group, as defined in the introduction, is a relatively small group of individuals that are more susceptible and likely to transmit HIV. In the 2012 review, they viewed the commercial sex workers, individuals in concurrent sexual partnerships and immigrants associated with high-risk behaviors as the core groups. These groups often are more sexually active and have high HIV prevalence. If the HIV epidemic only stayed within the core-groups, the epidemic would die out soon. The persistence of epidemic indicates that the infection constantly transmits from the core-groups to the general population. Core-groups are relatively small in size. Therefore, target interventions for the core-groups are usually more efficient in controlling the HIV epidemic33 .

### Sex-role Preference and HIV-transmission-related Characteristics

Sex-role preference was used in subpopulation classification as well, commonly among the homosexual population. Sex-role preference is important because the transmission probability of a single sex act is different depending on the sex-role. Two articles defined the sex-role specified subpopulations similarly. One divided homosexual population into “only top”. ”only bottom” or “versatile”16, and the other divided population into “predominantly insertive”,”predominantly receptive”, or “double decker” 17. Different from the core-group concept, the number of individuals in each sex-role preference group was more evenly distributed. From observational studies, 20% of the homosexual population were “only top”, 20% of the homosexual population were “only bottom” and 60% of them were “versatile”16. However, a typical core-group, using FSWs as an example, only composed less than 0.1% of the general population35.

In heterosexual relationships, male-to-female and female-to-male contacts have different transmission probability as well. Seven articles divided the study population by gender and used different transmission probability for a single sex act for each gender in model parameterization6,7,9,12,14,15,18.

In addition to sex-role and genders, twelve (67%) articles divided HIV infective status into more than one category2-8,10,11,13,15,17. The importance of dividing the study population according to the HIV stages is that HIV stages are associated with HIV viral load and infected individuals with higher viral load are more likely to infect other people through sexual intercourse36. However, when an individual developed AIDS, although his/her viral load became very high, most articles excluded them from the transmission dynamic because the opportunist infections and other complications prevented them from staying sexually active. Only Lopman et al. included individuals with AIDS to be part of the transmission cycle15. In addition to the natural history of infection stages, the use of antiretroviral therapy (ART) was also incorporated into the classification of HIV status2,6,7, because ART could reduce an HIV-positive individuals’ probability to infect other people per sex act37.

In general, an increasing complexity of subpopulation composition was observed over time, especially in the classification of HIV stages. The first three articles from the beginning of the 21st century only had one infective stage, and most of the later studies, except the two 16,18 all had more than two infective stages. Later studies were also more likely to incorporate ART use into the infection stage specifications2,6,7.

## Characteristics of Intervention Strategies

Thirteen (72%) out of eighteen articles implemented intervention strategies into their model analysis1,2,4-6,8,10-13,15-17. Eight of them simulated some types of drug treatment, including highly active antiretroviral therapy (HAART) 2,6,10,11,13,16 and pre-exposure prophylaxis (PrEP)8,17. The simulations focused on the general coverage of the HAART, when to implement the intervention (early HAART treatment), or who to use the intervention programs on (provide treatment for core or bridge populations). Although no successful HIV vaccine has been invented yet, one study still looked into the theoretical effectiveness of the HIV vaccines16. Reverse behavioral changes, increasing risky sexual behaviors due to HAART and PrEP, were also considered in analyzing the impact of intervention strategies.

Behavioral interventions were examined in the mathematical models as well. Two articles took condom use as their primary intervention strategy. They studied the relationship between the population condom coverage and the HIV prevalence 1,5. Four studies examined the behavioral intervention more closely related to the subpopulation composition, including delaying the age of first sex, changing partner formation patterns such as reducing cross-generational dating, and reducing the partner turnover rate4,6,7,15. One study did not examine any specific intervention strategy but built an optimal control function to examine when a fixed budget intervention program should be implemented to achieve the most optimal benefits12. An increasing complexity of intervention strategies being examined has also been observed over time.

## Characteristics of outcome of interest

Two major types of outcome variables were found in the selected models: 1) to test whether certain subpopulations or mixing patterns, with or without pre-existing intervention strategies, could explain the observed HIV prevalence/incidence, and 2) to predict the effectiveness of target intervention strategies. Six articles reported the type 1 outcome variable, six articles reported the type 2 outcome variable, and five of them reported both. Among the six articles used the type 1 outcome, four of them reported HIV prevalence/incidence3,5,7,13 and two of them reported the basic reproductive number in their result sections9,18. All six articles with type 2 outcome, reported HIV prevalence/incidence in their result sections1,4,6,10,11,14.Among five articles using both outcomes, two of them reported HIV incidence averted by the target interventions8,15, two of them reported the basic reproductive number and HIV prevalence16,17, and one article reported the percentage of total infections attributed to subpopulation2. Sani et al. used optimal control function to assess when to implement a generic fixed budget intervention program could have the most benefits. The outcome was different from the above two types of outcome12.

|  |
| --- |
| Sexual Orientation |
| Homosexual(N=2) |
| Heterosexual(N=12) |
| Homosexual(N=4) |

Figure . Subpopulation Composition Diagram

21,2

63-8

**Non-Core-Group**

8

By # of sex partners

By partner turnover rate

3

2

Sexual Activity Level

8

Social Position

6

Sexual activity & FSWs18

Sexual activity & Widows15

3

Relationship

Other

IDUs9

2

Mobile population12,13

Singles, Pairs10,11

2

Singles, pairs, FSW14

7

Sex-Role Preference

Only Top or bottom, versatile16

Predominantly top or bottom, versatile1,17

2

**Core-Group**

10\*

Subpopulations

\*Number of articles identified

Non-core group

Core-group

Overlapped articles

# Key Methods

Almost all models were generally established by sets of differential equations. Twelve out of eighteen articles proposed the equations using ordinary differential equations, three articles using partial differential equations and two articles using integro-differential equations. These methods were consistent with the methods used in previous reviews. The detailed list of the model methods was given by Table 5: Model Summary.

Among seventeen models constructed by differential equations, all the investigators provided numerical solutions for the models. Most of the authors only provided numerical solutions, and only three papers provided analytical solutions. Numerical solutions could provide more information and be more useful in public health research. In the 2012 review, close to 70% of the reviewed studies used real data in model paratermization33. In the 2011 review, this number was 22%32. In this study, the result is closer to the 2012 review. This result is expected because this review only included the articles after 2000 and there was more epidemiological data available compared to the pre-2000 era. The 2012 review contained nineteen post-2000 studies and only three pre-2000 studies. But the 2011 review contained much more pre-2000 studies. Another possible explanation is that more heterosexual data were available than homosexual data.

## Partner Formation

Partner formation or subpopulation mixing pattern is the most important part of the model methods and closely related to the subpopulation composition. Partner formation pattern is represented mathematically by contact matrices. As I stated in the introduction, three general types: assortative, disassortative and proportionate, are the basic mixing patterns. In model applications, five articles assumed that the subpopulations were mixed randomly (proportionate mixing). All five articles were published in the early 2000s. Three of them grouped the study population by their sexual activity level1,9,18, and two of them grouped the study population into singles and pairs10,11. Sexual activity specified subpopulations were more likely to be assumed having assortative or proportionate mixing3-5. Disassortative mixing is more commonly used when sex workers14, sex-role perference16 and cross-generational partnerships (i.e. older men dating younger women)6,7,17 were involved.

Besides the three basic partner formation patterns, newer studies with more complicated subpopulation composition were more likely to use “setting plausible” mixing. “Setting plausible” means the mixing patterns depended on the characteristics of the subpopulation. For example, the study of the mobile population assumed that the probability of individuals dating and infecting from one population to another depended on the HIV prevalence within the cluster12. The “setting plausible” scenario of the sex-role preference groups was that the versatile group could either have maximum assortative or disassortative mixing and the top and bottom groups always have maximum disassortative mixing17. Three studies did not make any assumption on their partner formation patterns, so they simulated all three basic patterns and compared the simulated results with the real world data to find the best match2,13,15. Matching mixing patterns with observed data could improve the validity of the models. After the partner formations, three articles further classified the partnerships to be casual or steady2,10,11. The casual partnerships only last for a short time and the frequency of sex acts in a casual relationship is low. The steady partnerships last for a longer time and have more sex acts compared to casual partnerships.

# Model Predictions

As stated before, since each model made different assumptions on subpopulation composition and partner formation patterns, they also measured different types of outcomes. For that reason, it was difficult to perform quantitative analysis on pooled estimates across the models. Therefore, this section partially grouped the studies with comparable outcomes and assessed the impact of subpopulation composition, partner formation patterns and intervention strategies on HIV transmission.

## impact of subpopulation

Five articles used comparable outcome variables in assessing the impact of each subpopulation to the overall HIV epidemic. The outcome variable was the percentage of HIV incidence that was attributed to subpopulations, which measured the number of new infections from each subpopulation over the total number of new infections. This outcome variable was also used in the 2012 review to assess the effectiveness of intervention strategy. From the Table 2: Impact of Subpopulations, we can observe that 80% of the HIV incidence was attributed to the high sexual activity MSM group. Female injecting drug users, combined with female sex workers were responsible for 77 new HIV infections per month with 1 million total population. 8-17% of the HIV incidence in Zimbabwe could be attributed to widows that only made up 1.2% of the total population. 53% of the HIV incidence in Netherland could be attributed to African immigrants. This finding further confirmed that the core-group have a high impact on the HIV epidemic.

Besides core-group, in homosexual population, the “top” subpopulation (made up 1.2%-30% of the total population, the number of tops was estimated depending on the number of bottoms and versatiles in that model) were responsible for more HIV incidence than versatile and bottom subpopulations. Therefore, target intervention strategies, not only for the high-risk group but for subpopulations with relatively large size are worth to explore.

Table : Impact of Subpopulations

|  |  |  |
| --- | --- | --- |
| Population | Subpopulation | Incidence attributed to subpopulation |
| Homosexual | India17 | Top | 41 %( CI: 13%-79%) |
| Versatile | 33% (CI: 7%-71%) |
| Bottom | 20% (CI: 5%-54%) |
| The UK2 | Low sexual activity | 23.3% (CI: 15.8%-32.7%) |
| High sexual activity | 79.6% (CI: 70%-86.9%) |
| Age 15-34 | 62% (CI: 46.7%-74.0%) |
| Age 35-64 | 44.3% (31.8%-59.5%) |
| Heterosexual | Zimbabwe15 | Widows | 8%-17% |
| Netherlands13 | Immigrants from high HIV prevalence countries | African migrants: 53%;Caribbean migrants: 26%Dutch local: 22% |
| Ukraine9 | IDUs to General population | Male: 19 new infections per monthFemale:77 new infections per month |

## impact of Partner Formation Pattern

Two studies assessed the impact of partner formation on HIV transmission in the homosexual population. On contrary to the common perception, which casual sex was the main driver of sexually transmitted diseases. Table 3: Impact of Partner Formation Pattern showed that more HIV incidence could be attributed to steady relationships. Among homosexual men in the UK, the one-off partnership, which an individual only has one single sex act with one random partner, is only responsible for 16.5% of the HIV incidence, but the steady sexual partnership is responsible for 20%-90% of the new infections. Findings from Netherlands confirmed the above conclusion. Less than 20% of the HIV incidence were attributed to casual relationships but more than 80% of the HIV incidence was attributed to steady relationships.

Two Zimbabwe studies suggested that cross-generational partnerships in the heterosexual population only have little contribution to the overall HIV prevalence. One article suggested that with 50% of the partnerships being cross-generational, the overall HIV prevalence only increases from a little over 12% to a little over 14%4. The other article did not quantify the impact of cross-generational partnerships but concluded that the HIV incidence was similar with or without the cross-generational partnership between male widows and young females15.

Table : Impact of Partner Formation Pattern

|  |  |
| --- | --- |
| Partner Formation | Population attributable Fraction |
| One-off sexual partner (proportionate)2 | 16.5% (12.2%-23.9%) |
| Repeated low Sexual activity MSM assortative2 | 22.6% (18.6%-27.6%) |
| Repeated high Sexual activity MSM assortative2 | 70.1% (63.8% - 75.2%) |
| MSM casual partnership10(Proportionate) | 12%-20% (10%-26%) |
| MSM steady partnership10(Proportionate) | 80%-88% (74%-90%) |

## impact of Intervention strategy

Both behavioral and medical interventions were evaluated in the selected articles. Behavioral intervention was defined as the intervention strategies without using any medication or vaccine. Intervention strategies with medications and vaccines were classified as medical interventions. Since behavioral interventions were modeled based on the reduction in partner turnover rate or controlling the number of individuals in each subpopulation, they were difficult to be quantified and compared to. A conclusion drawn by both behavioral and medical intervention studies was that early intervention implementation is much more beneficial than late implementation. Examples of early intervention implementations included giving HAART at the early stage in HIV infection4, starting behavioral intervention programs at the beginning of the epidemic1, and allocating more money to the initiation stage of an intervention program12,14.

Results of medical intervention evaluations were found to be more comparable. In Table 4: Impact of Interventions, two models found that giving PrEP for all individuals in the study population could reduce more new infections than only giving PrEP to high-risk subpopulations. Giving PrEP to the general population is also much more expensive than giving PrEP to target subpopulations. If PrEP was only given to target groups, distributing PrEP to age groups with the highest HIV prevalence and the “tops” was more beneficial than giving PrEP to other subpopulations. The results also suggested that high coverage and early initiation of HAART could reduce HIV incidence by 28% to 40%, and the reduction is more significant in the basic reproductive number. All three articles also predicted that HAART initiation will increase the partner turnover rate and reduce the condom use. Even with these behavior changes, HAART could still significantly decrease the HIV incidence. With the same intervention enrollment rate, HIV vaccines can avert less new infections than HAART.

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| Intervention | Targeted Group Implementation | Results |
| PrEP8,17(core-group)For comparison, I only selected the result when PrEP is 92% effective(Non-core-Group) | Sexual activity | Decline Cumulative Incidence (%) 0.8-28.8Infections Averted per Person-Year of PrEP 0.07-0.33 |
| By Age group | Decline Cumulative Incidence (%) 2.0-45.5Infections Averted per Person-Year of PrEP 0.01-0.04 |
| None (for all individuals in population) | Decline Cumulative Incidence(%) 3.3-74Infections Averted per Person-Year of PrEP 0.01-0.03 |
| Top | Percentage of Infections Averted: 50.7%-63.9%o |
| Versatile | Percentage of Infections Averted: 28.3%-43.1%o |
| Bottom | Percentage of Infections Averted: 38.9%-44%o |
| None | Percentage of Infections Averted: 92.2%-92.3%o |
| HAARTEffeciveness>80% | HIV Stage 2\*6Enrollment rate: 0.9/yr | (Male) Decline Cumulative Incidence(%): 39.46%(Female) Decline Cumulative Incidence(%): 29.01% |
| Homosexual stage 210Enrollment %: 60-80 | Decline Cumulative Incidence(%): 28.91%(without condom use reduction and partner turnover rate increase) |
| Homosexual16Enrollment rate: 0.2/yrStarted stage unknown | Decline in basic reproductive number (%): 65%(without condom use reduction due to HARRT) |
| Vaccine16 | Susceptible; Efficacy: 30%Efficacy: 70%Enrollment rate: 0.2/yr | Decline in basic reproductive number (%): 27.6%Decline in basic reproductive number (%): 63.37% |

Table : Impact of Interventions

O: Differ by different mixing patterns: maximum assortative/disassortative and proportionate

\*: Stage 2: 5 month – 7years after initial infection, clinical latency, usually asymptomatic

# DISCUSSION

Different from the 2011 review, this essay provides quantitative results of the impact of subpopulations, partner formation patterns and intervention strategies on the HIV epidemics. Compared to the 2012 review, which only focused on the core-groups, this essay assessed the impact of all types of subpopulations on the HIV epidemic. The 2012 and this review supported the importance of controlling core-groups in HIV prevention. This review also suggested that interventions focusing on non-core-group subpopulations are more efficient than the interventions focusing on the general population. The 2011 review suggested that HIV education should focus on individuals in steady relationships and this review supported this finding as well. Neither of the previous reviews focused on the impact of mixing patterns on HIV incidence in the heterosexual population. This review found that different from the common perception that cross-generational dating drives the HIV epidemic in Africa38, cross-generational dating does not significantly increase the HIV incidence.

I agreed with the conclusion drawn by the 2012 review, which claimed that only limited scope of epidemic regions was explored by the current literature on mathematical modeling. Studies on homosexual populations were mostly limited to developed countries, sex-role preference and sexual activity levels. Some high-risk core-groups such as male and transgender sex workers were not included in the world of mathematical models. A more standardized guideline for outcome report should also be proposed so that more mathematical models could be analyzed together to implement policy making and contribute to the general knowledge.

Since there was no guideline for literature reviews of mathematical modeling studies, this essay used the previous two reviews as samples. I summarized and described the modeled population by narrative, listed the mathematical methods, assessed the intervention strategies and reported the model findings. In the result section, the 2011 review only qualitatively listed the model findings and the 2012 review provides a more detailed analysis on model findings. Since this essay did not put a restriction on the outcome of interest in article selections, some modeled results were not comparable. Therefore, I grouped the comparable results for quantitative analysis and reported the other results qualitatively. I did not select models based on their outcome variables. Exploration on subpopulation composition and the partner formation patterns of these models could provide useful insights into future model development.

 “All models are wrong, but some are useful”. All mathematical models have to make unrealistic assumptions in order to build equations and perform the model analysis. The validity of the model predictions completely depends on whether the models could adequately represent the entire population. More detailed and in-depth discussion on subpopulation composition and partner formation patterns is necessary to improve the validity and usefulness of the mathematical models. It will also require more communications between mathematicians and social science researchers to fill the gaps of knowledge.

Overall, mathematical modeling for sexual behavior required the collaboration among social scientists, epidemiologists, and mathematicians. With the development of computational algorithms, hardware computers, and epidemiological data, this method would be more broadly used in policy making and eventually help to eradicate HIV.

**APPENDIX: MODEL SUMMARY**

Table : Model Summary

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| Year | Population | Subpopulation Composition | Intervention | Method | Partnership Formation | Outcome of Interest | Validity |
| 200014 | HeterosexualNo real world data | Commercial sex workers, unpartnered males (bridge population), non-core group females and long-term unbreakable couples; HIV status: susceptible and infective. | No treatment/behavioral programs, program only for core group, only available for bridge group | Ordinary differential equations(ODE); Analytical solution and numerical examples | All unpartnered males could only form the sexual partnership with CSW or get married. No concurrent partnership. | HIV prevalence under different intervention scenarios; mathematical equilibrium | Strength: assess the effects of intervention on different target subgroups; sensitivity analysisLimitation: all single males were assumed to only have sexual contacts with FSW, no specific intervention proposed |
| 20011 | Homosexual San Francisco, USA | Risk level which is distinguished by the risk of getting disease (sexual activity and safe sex); HIV status: susceptible, infective | Condom | Integro-differential equations analytical and numerical solution | Proportionate | AIDS/HIV incidence | S: Performed sensitivity analysisL: proportionate mixing assumption, when assortative mixing is a more realistic assumption |
| 20039 | Heterosexual Odessa, Ukraine | Male IDUs, female IDUs, male general population and female general population. (considered some IDUs be FSWs); HIV status: susceptible and infective | No | Proposing the calculation of R0 but not in detail equations has been constructed | Proportionate | R0 | S: assessed the attribution of bridging population, locally uniqueL: No sensitivity analysis, no intervention implementation, did not specify HIV stages |
| 200310 | Homosexual Amsterdam, Netherlands | The population is divided into singles and pairs. Paired partners could be both negative, both positive(with the same stage or different stage) and discordantHIV status: susceptible, infected stage 1(more infective) and infected stage2 (less infective); | Uncertainty analysis of HAART | ODE; solve numerically | Proportionate but the nature of the partnership is defined as casual or steady. Men in the steady partnership will have less casual partnerships.Concurrency is not allowed. | HIV incidence contributed by steady or casual relationship | S: Performed uncertainty analysisL:Neglect types of partnership in between  |
| 200411 | Early HAART treatmentEarly HAART treatment | HIV incidence due to early treatment |

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| **Table 5 Continued** |
| Article | Population | Structure | Intervention | Method | Partnership Formation | Outcome of interest | Validity |
| 20063 | Heterosexual Uganda, urban Kenya, Zimbabwe and urban Haiti | 5 sexual activity groups, gender, age structureHIV status: 5 different disease stages: susceptible, acute infection, latent infection, pre-AIDS and full blown AIDS. | No | Partial differential equations, with parameters estimated from data;Runge-Kutta | Assortative to proportionate | HIV prevalence | S: Fit the model with different assumptions;L: Not counting on concurrent relationship; No sensitivity analysis (at least not mentioned) |
| 20074 | Zimbabwe | 1) Reduce cross-generational mixing. 2) Changes in age at first sex. 3) Changes in condom use  | HIV prevalence under different intervention scenarios; Lifetime probability of getting HIV |
| 20078 | Heterosexual Sub-Saharan Africa | Gender, age, sexual activity level, PrEP status, and HIV-1 drug resistance. HIV status: recent, chronic, AIDS. | PrEP | ODEs, numerical solution | Assortative to Proportionate | Cumulative HIV incidence averted because of PrEPEffectiveness of intervention/PrEP | S:Sensitivity analysis, Considered drug resistant mutationL: did not quantify the accuracy of model prediction; No impact of mixing pattern on PrEP |
| 200718 | HeterosexualYunnan, China | Sexual activity level which are, males who never have sexual contacts with FSWs (low) and males who have sexual contacts with FSWs; HIV status: susceptible and infective | No | Integro-differential equations; Analytical solutions based on parameters estimated from data | Proportionate | R0 | S: Include some uncertainty analysisL: one infective stage; Unrealistic assumption; size of sex workers assumed to be static; |
| 200812 | Heterosexual No Real World Data | By gender by population patches, individual could move between patches on certain rate (Each patch might keep constant population size; with varying population size; or constant mobility.)HIV status: Susceptible, Infected or AIDS | Generic control problem. No specific intervention strategies have been applied but consider how to distribute a fixed budget over time. | ODES, numerical solution, using cross entropy technique(Monte Carlo method) | Contact from one patch to another depending on the HIV prevalence within each patch | The control function which represents the amount of budget spent in each population per time unit | S: Fitted with different parameters and control strategies, uncertainty analysis. Useful in decision-makingL: Not validated by real world data.  |

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| **Table 5 Continued** |
| Year | Population | Structure | Intervention | Method | Partnership Formation | Outcome of Interest | Validity |
| 20095 | Heterosexual Zimbabwe | 3 sexual activity group, gender; HIV status: 5 different disease stages susceptible, acute infection, latent infection, pre-AIDS and full-blown AIDS. | Prefixed intervention from the survey: condom use rate, partnership turnover rate. Not testing new intervention strategies | Partial differential equations, with parameters, estimated from data | Partnerships formed from the two higher risk groups are classified as casual; Others are regular.The mixing pattern is either random or assortative. | HIV prevalence/incidence | Strength: Sensitivity analysis, uses the model to see whether behavior existed given the observational prevalence.Limitation: Not considering the duration of relationship and concurrency |
| 200915 | Heterosexual Manicaland, Zimbabwe | Marital status, age group, sexual activity group (sex worker, casual sex or spousal sex); HIV status: susceptible, primary, incubating, pre-AIDS, full-blown AIDS. | Reducing the number of sexual partnerships involving widows. | ODEs numerical solution using Runge-Kutta algorithm; | Widows prefer non-widows or random; widows date within their age groups VS. Older male widows prefer younger women compared to non-widows | Predicted case averted (the percentage fewer cases in the intervention compared to baseline) | Strength: Locally appropriate, unique target population. Targeted interventionLimitation: No sensitivity analysis, data only available for three years follow-up |
| 200916 | Homosexual Shanghai, China | Sex-role preference (only top, only bottom or versatile), money boy(male sex workers); HIV status: susceptible and infective | HAART; Vaccine | ODEs analytical solution/numerical analysis; | Disassortative | HIV prevalence | Strength: Considered vaccine effectivenessLimitation: Did not consider the impact of different HIV stages |
| 201013 | Heterosexual Amsterdam, Netherlands | By ethnic groups: Africans, Caribbean (countries with high HIV prevalence) and general Dutch people; By gender. 6 subpopulations in total. HIV status: susceptible, acute, chronic, and pre-AIDS. | HAART | ODE numerical solutions | Assortative, proportionate and disassortative are all considered as mixing patterns. Partnerships are formed as the main partnership (steady and long-term) and secondary partnership (casual or concurrent steady partnership). | HIV prevalence under different mixing pattern simulation | Strength: Model could apply to different countriesLimitation: Only considered immigrants and local people in the mixing, neglect the other common characteristics such as age,  |

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| **Table 5 Continued** |
| Year | Population | Structure | Intervention | Method | Partnership Formation | Outcome of Interest | Validity |
| 20117 | Heterosexual Uganda | Population is divided by sexual activity level, defined as the partner turnover rate and age mixing ;HIV state of the population: susceptible, 4 stages HIV without ART; 3 HIV stages with ART and one AIDS state | Behavioral (migration, partner turnover, cross-generational dating) | ODEs;Numerical solution | Partner mixing could be random, assortative and cross-generational mixing is also considered | HIV prevalence contributed by natural disease dynamic | Strength: Performed sensitivity analysisLimitation: Only two age groups and cross-generational fitting only account women dating within or older than 25 years old. |
| 20146 | ART and behavioral changes (increasing partner turnover rate as a result of ART introduction) | HIV prevalence under intervention |
| 201417 | Homosexual Bangalore, India | Sex-role preference predominantly top, versatile and predominantly bottom; HIV status: susceptible acute, chronic and pre-AIDS | PrEP | ODE, numerical solution | Maximum assortative, setting plausible (DD maximum assortative while other groups disassortative), proportionate, and disassortative | R0/ HIV prevalence | Strength: Different types of mixing patterns and targeted intervention were consideredLimitation: Did not consider the behavior intervention due to PrEP |
| 20152 | Homosexual United Kingdoms | Population are divided into 2 age groups (15-34and 35-64) and 2 sexual activity groups: high activity, low activity(¡=1 partners per year); HIV status: HIV progression is divided into 5 stages including ART use stage (by CD4 count) | HAART | ODEs Monte Carlo filtering method | Sexual partnership types: one-off or repeat sexual partnership; assortative, disassortative, proportionate are all assessed in the model; proportionate mixing by disease stages | Percentages of each subpopulation contributing to HIV prevalence | Strength: Sensitivity analysis was performed Limitation: Uncertain parameterization (the limited availability of data) |

 Highlighted articles were included in addition to the 2011 and 2012 reviews.

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