Mathematical Models of HIV: Methodologies and Applications

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Abstract. HIV is one of the significant public health threats globally, with approximately 36.9 million people living with HIV and 1.8 million people becoming newly infected in 2017 (WHO fact sheet). To prevent HIV, to decrease its impact and to eventually eliminate this infectious disease; clinical, medical, epidemiological, economic, and modeling studies have been conducted in the last 30 years. In this study, we explore the mathematical modeling studies where HIV has been examined to understand the dynamics and spread of the disease as well as to improve HIV prevention. We surveyed HIV modeling literature, summarized primary modeling methodologies, and briefly discussed relevant studies. For each study included in this paper, we presented their modeling method, interventions included, target populations, implementation process, key results, and insights. Two most widely used modeling methodologies for HIV are Bernoulli process models and dynamic compartmental models similar to other infectious diseases. These methodologies have been discussed in detail in this paper. Other modeling methodologies included Markov models, agent-based simulation models, and discrete-event simulation models. Many studies focused on risk populations such as heterosexual (HET), men who have sex with men (MSM), people who inject drugs (PWID) and jail inmates. We included the cost-effectiveness studies where HIV prevention and treatment interventions and strategies are compared concerning their costs and benefits. In this survey, we provided a summary of existing modeling literature as well as suggestions for future studies. We concluded that application of modeling tools for HIV presents excellent opportunities for both decision-makers and public health policymakers while predicting the future of this disease, establishing the most cost-effective prevention strategies and evaluating possibilities for the elimination of HIV.

Keywords: Mathematical Modeling · Infectious Disease · HIV · AIDS · Bernoulli Model · Compartmental Model · Markov Model · Agent-Based Simulation

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1 Introduction

HIV is one of the leading causes of death globally, and it is a significant public health challenge for all around the world (Joint United Nations Programme on HIV/AIDS 2012). In 2017, approximately 37 million people were living with HIV (PLWH), and this number is increasing with 5,000 new infections every day. To decrease the number of new infections and eventually eliminate HIV as a public health threat, the Joint United Nations Programme on HIV/AIDS (UNAIDS) prepared a new strategy intending to eliminate HIV by 2030. Although some targets such as the number of AIDS-related deaths and the number of new infections have fallen from their peaks, there is still a gap between targets to accomplish this goal and global realities (UNAIDS 2018). Moreover, significant variation exists for these statistics among regions. For example, Sub-Saharan Africa is the most severely affected region by HIV epidemic, and it has the most robust reductions in the AIDS-related mortality and the new infections while HIV epidemic is expanding in the Eastern Europe and several countries of Asia. (UNAIDS 2018; UNAIDS 2012; Piot and Quinn 2013). Overall, there is a need for further research and better strategies in the area of HIV prevention to reach UNAIDS goals and eliminate HIV.

HIV risk groups can be defined as subpopulations that have a higher risk for transmission and/or acquisition of HIV. In the low prevalence countries, risk groups are responsible for the majority of HIV infections. People who inject drugs (PWID, also known as IDU), sex workers (SW), transgender people, prisoners, and gay men and other men who have sex with men (MSM) and their sexual partners are among these key populations (UNAIDS 2017). The HIV prevalence among MSM in capital cities is 27 times higher than that in the general population, and recent data show that there is a rising trend in MSM HIV prevalence. PWIDs are among the population groups that are most severely affected by HIV, and the risk for acquiring HIV is 23 times higher for this group (UNAIDS 2012; UNAIDS 2018).

The recommended treatment for HIV is known as antiretroviral therapy (ART). In 2017, around 22 million, which is 59% of PLWH have access to ART globally (UNAIDS 2018; UNAIDS 2018). Health care organizations and governments have been endeavoring to fight against the disease, and there are some promising signs like advancing ART coverage in recent years. However, considering years of significant efforts, a large percentage of PLWH or people at risk for HIV have yet to have access to prevention, care, and treatment, and there is still no cure (UNAIDS 2018).

A reduction in HIV incidence has been a top priority to control the disease (Piot and Quinn 2013). It requires both to keep tracking of data available and use them in estimations for the future of the epidemic. In addition to this, we need to understand HIV behavior over time and evaluate the prevention efforts in a way that make the outcomes as useful as possible. With the significant increase in the modeling studies about HIV prevention in the last decade, it is apparent that mathematical models have become valuable and vital tools in analyzing the spread of infectious diseases, prevent and control these diseases. Models can be used for analyzing and testing theories, answering specific questions, figuring out the transmission characteristics, and key parameters from data for many infectious diseases (Hethcote 2000). Similarly, there has been a wide variety of mathematical models of HIV to understand disease dynamics and offer better prevention strategies.

In this study, we briefly discussed key methods of mathematical modeling for infectious diseases that included both deterministic and stochastic models. We described and focused on mainly three modeling techniques: (i) Bernoulli process models, (ii) dynamic compartmental models, and (iii) Markov models. We conducted a thorough literature search and summarized critical examples for each model. Although we have not included agent-based simulation in the modeling methods section, we included studies applied agent-based simulation in the literature review table. Our goal is to summarize main infectious disease modeling methods, to list HIV-related modeling studies chronologically, and then for each selected study, to present the study objectives, the model type, populations and interventions included in the study as well as critical insights. Although this list of studies is not comprehensive, it provides a summary of significant studies, and it covers the majority of high-impact research on HIV prevention.

The remainder of this paper is organized as follows. In Sect. 2, we present three main types of modeling methods which are often employed for infectious diseases. In Sect. 3, we present a table of HIV-related mathematical modeling studies.

2 Modeling Methods

Models reduce the complexity of a system to its essential elements; in other words, they represent a simplification of reality at a sufficient level of detail. From the health care perspective, models create mathematical frameworks that are used for the estimation of the consequences for health care decisions (Caro et al. 2012). Therefore, they are essential tools to utilize in exploring the dynamics of HIV infection. Many mathematical models developed for HIV use individual-level data to attain population-level outcomes such as incidence and prevalence of infection (Sayan et al. 2017).

There are many different modeling approaches in the literature. However, three most widely used methods are included in this review, and these methods are Bernoulli process model, dynamic compartmental model, and the Markov model. Other methodologies, such as agent-based simulation models, stochastic models, and system dynamics, are also employed to analyze and project the dissemination of HIV (Akpinar 2012). While we have not included these techniques in this paper, we included studies that used them in Sect. 3. We conducted a search of 3 electronic databases, including PubMed, Web of Science, and Google Scholar for relevant studies published in English from the earliest data available for the database to January 2019. We used a broad search strategy with appropriate keywords and Medical Subject Heading (MeSH) terms to identify HIV mathematical modeling studies. We included the keywords "HIV," "AIDS," "Mathematical Modeling," "Bernoulli Model," "Compartmental Model," "Markov Model," "Agent-Based Simulation" with Boolean operators 'OR' and 'AND.' From the articles and conference papers obtained through the electronic search, we screened based on the abstracts and titles, and we included HIV studies if they were original analyses; included a mathematical model as its main methodology and reported the model results. When we encountered two similar studies, we preferred to include more recent study. We summarized the selected studies in Table 1, where they are grouped based on the modeling technique, and they are ordered chronologically within each group.

2.1 Bernoulli Process Model

Bernoulli process model is based on the assumption that there is a certain probability of transmission each time an HIV infected person engages in some of HIV risk behaviors such as unprotected sex while each type of behavior is considered an independent event. Each event has a small fixed probability of transmission, which is called HIV infectivity, and it accumulates with the repetition of the related risk behavior (Pinkerton and Abramson 1998).

The cumulative probability of transmission for multiple contacts with an infected person is calculated using the following equation. In this equation, α represents infectivity, while n is the number of contacts (Pinkerton and Abramson 1998).

$$P = 1 - (1 - \alpha)^n \tag{1}$$

Today, among people living with HIV, about 9.4 million people do not know their HIV status (UNAIDS 2018). HIV may not show any symptoms for several years. Thus, in many cases, people do not know whether their partner is HIV infected or not. To include this uncertainty to the model, the following equation is proposed and the prevalence of infection, denoted with π, is added as a coefficient that reflects the probability of selecting an infected partner (Pinkerton and Abramson 1998).

$$P = \pi\left[1 - (1 - \alpha)^n\right] \tag{2}$$

Infectivity can be affected by various factors. Protected sexual intercourse is one of the prevention methods, and it reduces the infectivity of HIV. To provide a cumulative probability for a more complex situation, we can include m different sexual partners with k_i protected, and n_i unprotected sexual contacts, respectively. The model becomes following general form for the situation with multiple partners (Pinkerton and Abramson 1998).

$$P = 1 - \prod_{i=1}^{m} \left\{1 - \pi\left[1 - (1 - \alpha_n)^{n_i}(1 - \alpha_k)^{k_i}\right]\right\} \tag{3}$$

2.2 Dynamic Compartmental Model

Infectious diseases have been analyzed using dynamic compartmental models since 1927 (Akpinar 2012). In this type of models, populations divided into subgroups, which are called compartments. The main idea behind the construction of the model is that an infected person comes across with healthy individual and transmit the disease. There are many types of compartmental models such as SI, SIR, SIRS, SEIR, MSEIR, etc. selected based on different characteristics of infectious disease.

SIR compartmental model has three different compartments. In this model, S represents Susceptible, I represents Infected, and R shows the Recovered (or removed) (Fig. 1). For SIR model, we have transitions from S to I, which involves disease transmission and from I to R, which shows that infected patients recover from the disease. These movements occur at some defined rates known as infection rate and recovery or removal rate. To define the model with differential equations, a closed population that has no births and deaths, no migration is taken into account (Keeling and Rohani 2011).

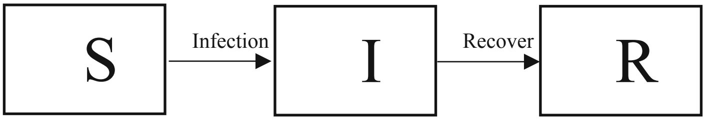

Fig. 1. SIR model diagram (Keeling and Rohani 2011).

SIR model is mathematically defined in the following equations where β is the transmission rate, and γ is removal or recovery rate (Keeling and Rohani 2011).

$$\frac{dS}{dt} = -\beta SI \tag{5}$$

$$\frac{dI}{dt} = -\beta SI - \gamma I \tag{6}$$

$$\frac{dR}{dt} = \gamma I \tag{7}$$

2.3 Markov Model

Markov model is known as a stochastic process that has Markovian property. Markovian property is based on the assumption that the conditional distribution of any future state depends only on the present, and it is shown in the equation as follows (Ross 2007).

$$P\{X_{n+1} = j | X_n = i, X_{n-1} = i_{n-1}, .., X_1 = i_1, X_0 = i_0\} = P\{X_{n+1} = j | X_n = i\} = P_{ij}$$

We assume that X_n is state i at time n and P_{ij} represents the probability that process will move from state i to state j then, this equation defines a model for all states i, j and all n that are greater or equal to 0. (Ross 2007).

Many clinical situations can be described in terms of the conditions that individuals can be in, how they can move among such states, and how likely such moves are (Fig. 2). These correspond to states, transitions, and transition probabilities, respectively. State transition models (STM) are well suited to the decision problems in these situations, and they are found reasonable when the decision problem can be described in terms of states and interactions between individuals are not necessary. Markov models are one of the STM modeling approaches, and they are based on cohort level. Thus, Markov modeling approach presents transparency, efficiency, and ease of debugging. They are recommended if a manageable number of health states are sufficient to describe all relevant characteristics of the problem. These states help biological/theoretical understanding of the disease and reflect the disease process with transitions. Interventions such as screening, diagnostics, and treatment can be included in the model to evaluate their effects (Siebert et al. 2012).

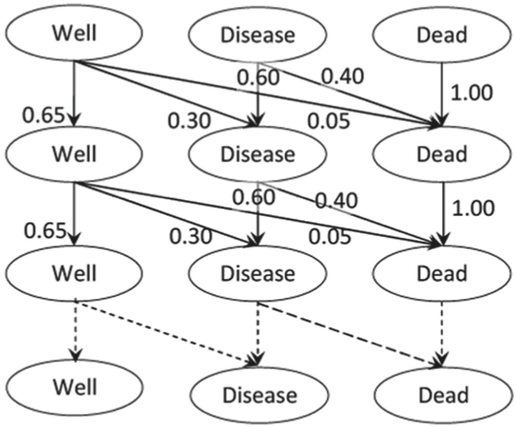

Fig. 2. Markov model diagram (Siebert et al. 2012)

3 HIV Mathematical Modeling Studies

Table 1. Literature review

Authors	Year	Short summary	Model type	Country	Model objective	Interventions	Risk populations	Key results/Insights
Downs et al.	1996	Isotonic regression and Bernoulli Model were performed, and their results were compared	Bernoulli Process Model	Nine different countries involved in the European study	To evaluate the relationship between the number of heterosexual contacts and HIV transmission probability		Heterosexual (HET) couples	The relation between the number of contacts and transmission probability could be well designed by a more complex model approach instead of those with constant per-contact infectivity
Pinkerton and Abramson	1996	The probability of transmission for different infectivity levels with protected and unprotected intercourse and reproductive rate of HIV transmission was found	Bernoulli Process Model		To estimate the dependence of HIV infectivity based on disease stage			Infectivity of HIV and reproductive rates of infection are obtained for the initial period and asymptomatic period of HIV
Pinkerton, Holtgrave, and Valdisseri	1997	The number of HIV infections prevented is determined. Costs and cost-effectiveness of two interventions are compared	Bernoulli Process Model		To decide whether skills-training should be included among HIV interventions	A safer sex lecture and the same lecture with a 1.5-h skills-training group session	Men who have sex with men (MSM)	According to the model results, skills-training was found both cost-effective and cost-saving
Bos et al.	2001	Using total costs and the number of infections averted, the authors estimated costs per life-year gained	Bernoulli Process Model	Netherlands	To investigate the cost-effectiveness of HIV screening for a clinic	HIV screening of STD-clinic patients	STD clinic attendees	Screening of STD-clinic patients for HIV was found cost-effective
Wilson et al.	2003	The authors constructed a model which includes behaviors and estimates individual HIV infection probability by taking into account of sexual histories of partners. Sexual behaviors were obtained from interviews	Bernoulli Process Model	US	To analyze HIV risk behaviors and risky characteristics of Latino couples in California		Latino couples in California	Results indicated that HIV risk of women is higher than men. They also revealed demographic, behavioral, and psychosocial factors affecting HIV risk for both male and female partners
Pearson et al.	2007	The authors worked on a study group, and their model predicted HIV prevalence of unprotected sex, and they extrapolated the results to find the expected number of secondary infections annually. They later estimated the effect of interventions	Bernoulli Process Model	Mozambique	To predict the number of new HIV infections according to the sexual behaviors of a study group taking HAART treatment	Increased condom use and HAART along with syphilis and herpes simplex virus type 2 (HSV-2) treatment	Men and women initiating HAART	The number of HIV infections per year was estimated. HAART, along with syphilis and herpes simplex virus type 2 (HSV-2) treatment could reduce HIV transmission more than increasing condom use

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Table 1. *(continued)*

Authors	Year	Short summary	Model type	Country	Model objective	Interventions	Risk populations	Key results/Insights
Fox et al.	2011	From a literature search, the odds ratios of factors for HIV exposure risk scores are determined. A model framework which estimates the risk of HIV acquisition based on reported sexual practices, STI status, and partners' infectiousness is developed	Bernoulli Process Model		To generate HIV exposure risk between serodiscordant couples according to biological and behavioral factors		HIV serodiscordant couples	Risk estimates for scenarios concerning male-male, male-female, and female-male transmission were presented. Risk multipliers considered were viral load, stage of HIV infection, and the presence of genital ulcer disease, HSV-2, and type of sex acts
Wang et al.	2011	The authors included the effect of interventions as the change in the sexual behaviors and measured it by the number of infections averted. Then, they performed a cost-effectiveness analysis with disability-adjusted life years (DALY)	Bernoulli Process Model	China	To determine the cost-effectiveness of voluntary testing and counseling	Free HIV voluntary counseling and testing	General population and men who have sex with men (MSM)	Free HIV voluntary counseling and testing strategy were found to be cost-effective for high-risk populations such as MSM other than the general population
Lin et al.	2013	They measured the effectiveness of interventions with the reduction in risk of transmission under different budget allocation strategies	Bernoulli Process Model	California	To analyze how budget cuts on HIV interventions could affect the number of newly infected HIV patients	Testing and risk reduction programs	HET, IDU, and MSM	Budget cuts could result in additional new HIV patients while optimizing the budget effectively could avert these new infections. To achieve that, it was recommended to allocate the budget to cost-effective programs
Adams et al.	2013	By interviewing with jail inmates at different times (30 days before, six months after or 1 year) before incarceration and post-release, behavioral data have been collected and based on data, HIV risks were calculated	Bernoulli Process Model	Northern Virginia	To determine HIV risk behaviors of men and women jail inmates		Jail inmates	HIV risk was found to be decreasing in the inmates after release. Behavioral differences between men and women could be used to develop appropriate intervention programs

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Table 1. (*continued*)

Authors	Year	Short summary	Model type	Country	Model objective	Interventions	Risk populations	Key results/Insights
Lin et al.	2016	The model was developed to estimate the reduced annual HIV risks due to interventions. Costs per averted HIV case and QALY's were also calculated	Bernoulli Process Model	US	To compare alternative preventions and target populations for HIV in terms of cost-effectiveness	HIV testing in clinical and non-clinical settings, partner services, improving linkage to care, retention in care, improving adherence to ART, behavioral interventions for HIV infected and uninfected persons, circumcision, Pre-exposure prophylaxis (PrEP)	MSM, IDU and sexually active heterosexuals	After the economic analysis, the most cost-effective combination of population and interventions were determined. HIV testing and providing care and treatment presented the lowest cost per prevented case and interventions targeting MSM was the most cost-effective
Yaylali et al.	2016	Combination of linear programming and Bernoulli model was used for a resource allocation model. First, the most cost-effective interventions were determined, then a fixed budget has been allocated from the most cost-effective intervention to the least one until it is exhausted. The model was implemented for four health departments in real life	Bernoulli Process Model	US (Philadelphia, Chicago, Alabama and Nebraska)	To maximize the number of new infections averted to find an optimal allocation strategy for a fixed HIV budget	Testing in clinical and non-clinical settings, partner services, continuum-of-care–related interventions designed to improve linkage to care, retention in care, and adherence to ART, and behavioral interventions for HIV-positive and HIV negative persons	MSM, IDU and sexually active HET	According to results, testing for MSM in non-clinical settings was found the most cost-effective intervention, and behavioral interventions were the least cost-effective. Practitioners implemented the model in real life and reported the model as helpful
Lasry et al.	2011	In this study, the authors created a national HIV resource allocation model with SUD compartmental model for various combinations of intervention and populations. They provided a case study of the model application	Compartmental Model	US	To minimize the number of infections over five years	HIV screening interventions and interventions to reduce HIV-related risk behaviors	High-risk heterosexuals, IDU and MSM	Focusing on HIV risk groups such as IDU and MSM improved the effectiveness of resource allocation model
Cipriano et al.	2012	The authors determined the number of infections averted by identifying the status and stages of infection with compartments. They conducted a cost-effectiveness analysis and determined costs, QALYs, and ICERs for each strategy	Compartmental Model	US	To assess the cost-effectiveness of HIV and HCV screening alternatives for IDU population in the US	Screening individuals in opioid replacement therapy for HIV, HCV, or both infections with different testing alternatives and time intervals	IDUs in opioid replacement therapy (ORT)	It was concluded that doing HIV screening with both antibody and viral RNA testing in every 3-6 months was the most cost-effective screening strategy

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Authors	Year	Short summary	Model type	Country	Model objective	Interventions	Risk populations	Key results/Insights
Juusola et al.	2012	The authors developed a mathematical model for estimating the cost-effectiveness of PrEP. The model included awareness of HIV, HIV status, and PrEP use as treatment factor. Outcomes such as HIV incidence and prevalence, costs, and QALY's were calculated	Compartmental Model	US	To investigate the cost-effectiveness of PrEP and its implementation in the high risk and general MSM population	Pre-exposure prophylaxis (PrEP)	MSM	The model suggested that QALYs gained PrEP were cost-effective for high-risk MSM
Lasry et al.	2012	Different allocation scenarios of a fixed HIV budget were assessed by using an optimization model combined with an epidemic model. While the optimization model allocated funds to interventions and subpopulations, the epidemic model calculated the number of new infections	Compartmental Model	US	To develop an optimal resource allocation scenario which minimizes the number of new infections	HIV testing, individual and group-level counseling & education	High-risk heterosexuals, IDU and MSM	The authors suggested that funds for testing MSM and IDU should be increased and interventions should be developed for the high-risk individuals of HIV
Gilmour, Li, and Shibuya	2012	The authors developed a model that consisted of 10 compartments to generate projections of HIV prevalence. Two scenarios were defined according to varying parameter values, which represents the effect of interventions. The study also included a multivariate sensitivity analysis to measure the ranges of outcomes	Compartmental Model	Japan	To project the HIV infection in Japan for the next 30 years	Behavioral interventions such as higher rates of condom use amongst MSM, higher rates of HIV testing, and more effective passive case finding in PLWH	MSM, low-risk men, and low-risk women	When the current situation continued, HIV prevalence would be much higher by 2040 with a significant increase in MSM. Prevalence of HIV could be changed in a positive way with decreasing risky behaviors and increasing testing rates
Sorensen et al.	2012	The authors projected HIV infections among MSM and assessed the national HIV strategy. Model compartments were based on infection status, age groups, and sexual activity levels. They determined the number of HIV infections with the current situation and with different combinations of interventions	Compartmental Model	US	To estimate the potential benefit of interventions applied to decrease new HIV infections among MSM	Improvements in the annual HIV testing rate, notification of test results, linkage to care, earlier initiation of ART, and increase in HIV viral load suppression	MSM in urban population	Results showed that interventions related to test-and-treat could substantially decrease the number of new infections among MSM in New York City. Based on the model, five goals of the national HIV strategy could be achieved

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Table 1. *(continued)*

Authors	Year	Short summary	Model type	Country	Model objective	Interventions	Risk populations	Key results/Insights
Alistar et al.	2014	The authors applied an SIT compartmental model combined with a non-linear optimization model. The model utilized with a single population or multiple independent populations and then two interacting populations	Compartmental Model	Russia and Uganda	To minimize the reproductive rate of infection so that the resources could be allocated efficiently among the HIV prevention and treatment options	Investment in prevention (such as condom promotion and associated counseling) and treatment programs	General population and IDU	For Uganda, condom programs were found to be preferable, and for Russia, it was more efficient to focus on prevention strategies on IDU rather than other populations
Baggaley	2017	The author developed a model considering HIV progression, CD4 count, and diagnosis status. The model calculated HIV incidence and the effect of HIV screening. The study included QALY and ICER estimations for 30 years, 40 years, and 50 years	Compartmental Model	UK	To determine the cost-effectiveness of early HIV diagnosis using data from a randomized controlled trial	Rapid testing for HIV in primary care or called an RHIVA2 trial which is done by primary care physicians	MSM and HET	The results suggested that HIV screening in primary care was cost-effective in the medium-term (33 years)
Sayan et al.	2017	To analyze the dynamics of HIV, the number of HIV cases, and the basic reproduction ratios were calculated from a mathematical model that consisted of 3 compartments. Model results were compared with surveillance data	Compartmental Model	Turkey	To find HIV/AIDS cases and to calculate the reproduction ratios between 1985–2016	No interventions included in the model	General population	Results indicated that there is an increasing reproduction rate of HIV. Thus, the authors concluded that there is a need for more interventions from public health authorities
Longini et al.	1991	Authors developed a model with eight states based on CD4 count. Transitions were progression rates indexed with co-factors such as age, gender, etc. The model employed data from the US Army	Markov Model	US	To estimate HIV progression rates	No interventions included in the model	General population	The authors estimated the mean waiting times between HIV progression stages and the proportion of people with decreased CD4 count. Results showed that age was an essential factor in HIV progression
Sanders et al.	2005	The authors examined no screening, one-time screening, and recurrent screening strategies according to their costs and benefits. Model states defined by the history of disease, awareness, CD4, and viral load count and treatment status	Markov Model	USA	To evaluate the cost-effectiveness of screening for HIV	HIV Screening	MSM, IDU Heterosexual Men, and Women	HIV screening was found to be, and it could potentially provide significant benefits in improving HIV prevention

(continued)

Table 1. *(continued)*

Authors	Year	Short summary	Model type	Country	Model objective	Interventions	Risk populations	Key results/Insights
Xuan, Xu, and Li	2009	In this agent-based simulation model, new agents are included with infection and agents removed from the model with deaths. The model included six stages, which are healthy, dangerous, infected, infectious, symptomatic, and deceased	Cellular automata Simulation Model		To understand the dynamics of HIV/AIDS better		General population	The authors concluded that HIV could potentially end up with either extinction or persistence. The factors associated with the increase in the infection level were agents' mobility, population density, initial infection ratio, and the extent of neighborhood increasing
Hontelez et al.	2011	The authors presented a STDSIM, individual-based microsimulation model for a dynamic network of sexual contacts. They evaluated the impact of several re-vaccination strategies depending on coverage (30% and 60%) and time intervals (2 years and 5 years)	Microsimulation model	South Africa	To predict the impact and the cost-effectiveness of HIV vaccination	Vaccination		The authors mentioned that one-time vaccination had limited impact. Results suggested that re-vaccination strategies could be cost-effective for certain coverage and time interval strategies
Gopalappa et al.	2012	A Monte Carlo simulation model was developed to represent the interaction between HIV infected patients and healthy people and their transmission routes. Costs and QALY's under different linkage to care scenarios were assessed with the help of the model	Simulation Model		To find the maximum cost value that could be spent on linkage to care programs without losing the cost-effectiveness of this intervention and to analyze the cost-effectiveness of the national target of linking 85% of HIV infected patients to care	Antiretroviral Treatment Access Study (ARTAS) type intervention, an implementation designed to link people recently diagnosed with HIV to medical care		Increasing the rate of early linkage to care found to be, and the sensitivity analysis showed that CD4 level at the time of diagnosis has the most significant effect on the cost-effectiveness value
Beyrer et al.	2012	The authors defined key factors of HIV for MSM. Then, the importance of these factors was evaluated by calculating the reduction in the model outcomes of each counter-factual scenario based on varying factor values	Agent-Based Network Simulation Model	USA and Peru	To compute the cumulative number of infections over five years		MSM	Based on the results, key drivers of HIV among MSM were obtained. High probability of transmission per act through receptive anal intercourse was found to have an important role, and interventions focused on this factor could be crucial
Bristow et al.	2016	The authors defined four different combinations of HIV and syphilis screening strategies. A model for antenatal patients was developed, and the model outcomes included the expected costs and expected newborn DALY's for each strategy. One-way and Monte Carlo multi-way sensitivity analysis was conducted	Markov Model	Africa	To evaluate the cost-effectiveness of different screening strategies for HIV and syphilis	Screening		Results showed that dual HIV and rapid syphilis test was cost-effective and resulted in fewer DALY's. Based on the multivariate sensitivity analysis, dual HIV and rapid syphilis test was cost-saving for all iterations

4 Conclusion

Many mathematical models have been developed and implemented in estimating and controlling infectious diseases. HIV is one of such diseases with an extensive literature of modeling studies that aimed at the prediction of HIV in different countries and target populations, the evaluation of prevention and treatment strategies in terms of their cost-effectiveness, the optimal allocation of HIV budgets and other many applications. This study summarizes 28 papers about HIV modeling that covers between 1991 and 2018. Different modeling methodologies applied in these studies have been presented, and these methods included the three most common techniques, which are the Bernoulli model, a dynamic compartmental model, and the Markov model. The majority of the papers focus on the economic analysis of prevention strategies, and mathematical modeling is employed to estimate the number of infections averted under different prevention strategies. Determining the incidence and prevalence of the disease in a specific location or for a target population is another popular study objective through understanding the spread of HIV. These studies often analyzed risk groups and their risky behaviors and estimated the health and economic outcomes to inform the decision-makers about the future of epidemic, possible interventions, and their consequences. There are some advantages and limitations of modeling methods used in the studies. Bernoulli model is a static approach while estimations from a compartmental model continue over some time due to its dynamic nature. However, compartmental models assume people in the same compartments are acting and responding to the disease in the same way. Markov models complement the HIV progression process by adding the stochastic framework into the problem. Agent-based simulation systems are useful and displays system in a more realistic way, however, they are data-intensive and cannot be generalized to other regions or populations. Although each methodology has some advantages and disadvantages, they are essential to understand the disease dynamics, and they provide us the opportunity to predict the future of the disease and find appropriate prevention and intervention methods.

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