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HIV/AIDS Modeling, a two-angle-retrospective.

**Toward a generic deterministic model for pattern II
countries?**

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Abstract

Over the past twenty years, several models have been developed in an attempt to understand the HIV/AIDS transmission dynamics. The first part of this article reviews the mathematical concepts describing the transmission of infectious diseases with a focus on HIV/AIDS epidemiological models. The second part reviews the major policy models with a focus on deterministic models, which have been developed to assess the impact of HIV/AIDS prevention and biomedical interventions in developed and developing countries. In the discussion section we emphasize the need for a generic model, and make recommendations on the structure of a generic deterministic HIV policy model applicable to pattern II countries.

Key words

HIV-AIDS-Modeling-Policy models-mathematical models-pattern II countries

Introduction

Numerous mathematical models have been developed to describe infectious disease transmission dynamics, understand the mechanisms of epidemic propagation, assess the impact of interventions on public health or forecast the future of epidemics.

The two types of models we are focusing on here are, on the one hand, the mathematical models and, on the other hand, the policy models. Although both mathematical models and policy models can be developed by the same scholars, the objectives of the two model types are different. The former aims at supporting the comprehension of the mechanisms driving the HIV/AIDS epidemic, while the latter mainly intends to support policy decision making,

Most of the theories behind HIV/AIDS transmission modeling were initially developed to describe the transmission of various pathological agents (3-22). However, there are specificities attached to the HIV transmission such as the sexual mode of contamination, the no-recovery/ no-immunization aspects of HIV/AIDS contamination and the world-wide span of the epidemic. Those specificities led to extensive modeling soon after the first publication identifying the cause of AIDS (historically named HTLV-III) [1,2]. Both mathematicians in biological sciences and policy modelers use deterministic and/or stochastic models. In deterministic models the events are not subject to chance, two model runs using the same equations and the same parameters will give the same results. In stochastic models, variability is taken into consideration. The most commonly used method is Monte Carlo simulation where a set of possible events is defined with a certain probability attached to each [3].

Deterministic models describe the dynamics of populations or sub-groups of a population (susceptible individuals, infected individuals). They use average contact rates and average transmission risk between the various groups. Population groups can be sub-divided into smaller groups and ultimately into individuals. Modeling the dynamics at the individual level allows for the representation of dynamic partnerships between individuals. Between those two extremes, the various population groups can be divided into classes of similar age, sex and sexual activity [4]. Models designed with sub groups of the population allow to take into consideration who acquires the infection from whom and help to understand the rate and pattern of infection among a given community [5].

Mathematical models simulating disease transmissions vary in complexity [5]. Simplicity allows a better understanding of the intrinsic properties of the models, however, oversimplified models may not be able to capture the reality of epidemiological disease transmission such as the heterogeneity of human sexual relationships. More complex models may be necessary to capture the finest details of disease transmission. The origins of the different orientations in modeling infectious diseases can be explained in part by the differences in objectives pursued by the two above mentioned disciplines more than by differences between model structures. For instance, although collaboration exists between mathematicians and policy model developers, the mathematical approach preferably takes into consideration the impact of individual aspects in the epidemics through a stochastic approach. Policy models usually consider aggregate views and use deterministic and/or stochastic approaches.

The aim of this review is to illustrate the evolution of the comprehension in HIV transmission mechanisms resulting from the two approaches. The first part reviews the mathematical concepts describing the transmission of infectious agents in general with a focus on HIV transmission. The second part describes the contribution of policy modeling, with a focus on deterministic models, in assessing action against HIV/AIDS. In the discussion section, we envision the need for a generic deterministic HIV policy model and briefly describe the structure of such a generic model applicable to pattern II countries.

Mathematical concepts in infectious disease transmission

In this section, we will first review the early history of mathematical modeling in infectious disease transmission and its main concepts, and secondly move to modeling applied to sexually transmitted diseases and more specifically to HIV/AIDS transmission. Although the HIV infection can be transmitted through infective sexual contacts and contaminated blood transfusion, the latter is nowadays minimized in industrialized countries and even in several developing countries, due to the improved use of pre-transfusion screening systems. In addition, HIV transmission through transfusion does not follow the general rules of infectious disease transmission (e.g. epidemic spread). Consequently, we will restrict the scope of the present work to contamination through sexual intercourse.

The foundations of infection transmission modeling

The foundations of mathematical modeling applied to infectious disease transmission were laid in the early 20th century. In 1906, Hamer [7] pointed out that the transmission dynamics of viral or bacterial infections is compartmental in structure; individuals can be grouped in classes according to their health status (e.g. susceptible, infected, immunized). While Hamer's theory was based on a discrete time frame to determine the transitions from one class to another, Ross [8] assumed continuous flows between the various compartments and proposed a set of differential equations to describe the flows between compartments. Another key concept in the mathematical modeling of epidemics, first introduced by Kermack and McKendrick [9], is the fact that the fraction of infected individuals increases exponentially in the early stage of the epidemic. Later, Mc Donald [10] called the number of secondary cases that one infected case can generate during the infection period, R_0 , the basic reproductive rate, which has, since, become a standard concept in epidemiology. In spite of these early efforts, significant mathematical modeling of infectious diseases only occurred in the 70's [11-16]). The modeling of sexually transmitted diseases was laid out in the seminal work by Yorke et al. on gonorrhea transmission [17].

The basis of HIV epidemic modeling

May and Anderson [18] described R_0 in HIV transmission as directly proportional to the rate at which new sexual partners are acquired, c , the average probability that infection is transmitted from an infected to a susceptible individual during the entire partnership, β and the average duration of infectiousness, D . Jacquez et al. [19], defined the reproductive rate as being proportional to the mean infectious period, D ; the number of contacts per unit of time, c ; the probability of transmission during a contact, β and the fraction of susceptible individuals, S . Considering that one infected individual has $\gamma = \beta c$ contacts per time unit, the number of susceptible individuals contacted during D is equal to $\beta c S D$, which is defined as the reproductive rate, R . If one admits that one infectious person is introduced into a large susceptible population ($S=1$) then the initial reproductive rate is:

$$R_0 = \beta c D. \quad (1)$$

R_0 applies to an initial population where all individuals are susceptible. R applies to the fraction of susceptible individuals within a global population. May and Anderson [18] also emphasized the importance of using the rate c at which new partners are acquired instead of only focusing on the total number of partners per year. The authors define c as:

$$c = m + \sigma^2/m \quad (2)$$

where m is the mean and σ^2 the variance of the distribution of the number of new sexual partners per unit of time. c represents *de facto* the number of sequentially monogamous partnerships.

May and Anderson were the first to mention the limitation of mathematical models in making accurate predictions of AIDS incidence. However, they pointed out the role that mathematical models can play in making predictions about disease incidence (new cases occurring in a given period of time) and prevalence (number of infected individuals in a population) under various specific assumptions and in clarifying which data are required to calculate those predictions. They describe the characteristics of HIV transmission such as the non-dependence of the incidence rate on the host density, the length of the asymptomatic phase, the absence of acquired immunity and the importance of the degree of heterogeneity in sexual activity. Although May and Anderson [18] initially focused on the groups at higher risk (e.g. men having sex with men), they also brought the heterosexual transmission in perspective by defining R_0' :

$$R_0' = (\beta_1\beta_2c_1c_2)^{1/2} D \quad (3)$$

where β_1 and β_2 are the probability of infection between infected females and susceptible males and between infected males and susceptible females respectively and c_1 and c_2 are the rate of acquiring new partners of the opposite sex by females and males, respectively. However, equation (3) does not take into account the duration of partnerships which has been shown to dramatically affect the spread of infection [20].

The importance of heterogeneous sexual relationships in HIV transmission

Jacquez et al. [19] point out the importance of contact patterns and depart from the generally accepted view that contacts in a given population take place at random. If the population is homogeneous, random mixing means homogenous mixing. For a heterogeneous population divided into groups that have different contact rates, random mixing equals proportional mixing. Jacquez et al. also extend the notion of the basic reproductive rate, R_0 , to the infection rate matrix \mathbf{R} , in which the element R_{ij} is the number of cases generated in group i by one case from group j :

$$R_{ij} = c_j \rho_{ji} S_i \beta_{ji} D_j \quad (4)$$

with

c_i , the number of sex acts per person per unit of time;

ρ_{ij} , the proportion of sex acts of a person from group i with individuals from group j ;

S_i , the fraction of susceptible individuals in group i ;

β_{ij} , the fraction of those contacts that result in transmission;

D_j , the mean duration of infectiousness for a person in group j .

The matrix $\mathbf{P} = [\rho_{ij}]$ is called the mixing matrix. \mathbf{P} is time homogeneous. This is a limitation as the nature (regular, concurrent, casual) and the number of relationships between the two groups of individuals can evolve over time, based on intrinsic causes (population aging) and extrinsic causes (campaigns aimed at reducing risky relationships and/or at reducing infection transmission during risky relationships).

Jacquez et al. propose to consider general heterosexual populations as pairs in a number of low-activity groups. Highly sexually active groups, such as active homosexuals or sex workers, form a bridge of contacts with the low-activity groups and, therefore, are referred to as bridge groups. These bridge groups significantly contribute to the spread of the epidemic.

Anderson et al. [21] also emphasize the heterogeneity in virus transmission resulting from contacts between urban and rural centers, various age classes or social classes and the rate of sexual partner change. They particularly point out the trend in Africa for men to form sexual partnerships with women at least 5 years younger than themselves. Following an article by Dietz and Hadelar [22], Watts and May [23] examined the effect of sexual pair formation and separation rates on HIV transmission and point out the concurrent partnerships as an important component of the HIV spread within populations.

The role of sexual partnership concurrency and sexual networks

Potterat et al. [24], in an empirical study on sexually transmitted Chlamydia infections, find that the best predictor of R_0 is the number of concurrent contacts and not the number of sequential contacts. Therefore, they argue against the validity of equation (1) which is commonly used since the mid-80's to predict the magnitude and direction of HIV and other sexually transmitted diseases (STDs). In their opinion, the main weakness of this equation resides in the fact that the contact number c does not take into account the network effect in infection transmission.

Chick et al. [25], elaborating on the limitations of R_0 , state that a dissociation between the individual-level and the population-level definitions of R_0 occurs when the partnerships are lasting instead of being point-in-time random events. They suggest a model development

process going from deterministic stages allowing exploration of high-level issues to a more detailed analysis through stochastic stages. In an attempt to bridge the gap between the deterministic and stochastic discrete-individual simulation approaches, they show that large-scale approximations are useful for populations over five hundred individuals. Koopman et al. [26] also emphasize the failure of deterministic compartmental models to capture the refinements of individual characteristics and network relationships.

Several authors have studied the role of sexual networks in STD transmission [27-30]. Ferguson and Garnett [30] argue that micro simulation models, although including all relevant details of networks, fail to capture all the events that take place in large, interconnected populations and often render the disentanglement of important factors in disease transmission impossible. They develop a model in which concurrent sexual partnerships are included with sexual pair formation and dissolution. They conclude that concurrency, even in moderate amounts, has a significant impact on disease prevalence and persistence, confirming the earlier study by Potterat et al. [24].

Following earlier work by Kaplan [31] who reported a weak correlation between HIV transmission probability and the number of sex acts, Rottingen and Garnett [32] examine the relationship between the per-act and per-partnership transmission probability. They study several models linking per-partnership and per-act probabilities, including the following non-linear relation:

$$\beta_p = 1 - (1 - \beta_a)^n \quad (5)$$

where β_p is the transmission probability per-partnership; β_a is the transmission probability per act and n is the number of acts per partnership.

The authors report no empirical evidence that this binomial relation represents an adequate description of the disease transmission and propose two hypotheses to explain this inadequacy:

- 1) The susceptibility and the infectiousness vary from partner to partner and this may be explained by genetic variations from one individual to another. Variations in infectiousness may also depend on the type of virus strain.
- 2) The infectiousness varies during the course of an HIV infection due to the variation of virus loads in the bloodstream and semen during the course of the infection [33,34].

Moreover, the binomial model, with constant per-act transmission probability, underestimates transmission in partnerships with a low number of sex acts and overestimates the transmission when a high number of sex acts occurs. They suggest separating the partnerships into two groups with respectively low and high per-act transmission probabilities and propose the following model:

$$\beta_p = f(1 - (1 - \beta_a^h)^n) + (1 - f)(1 - (1 - \beta_a^l)^n) \quad (6)$$

where f is the fraction of individuals in the high-risk group and β_a^h and β_a^l represent the transmission probabilities in the high-risk and low-risk groups, respectively.

Impact of other STDs in HIV transmission

Rottingen and Garnett [32] also explore the impact of the other sexually transmitted diseases (STD) on HIV transmission as there is evidence in the literature that the presence of STD such as syphilis and herpes increases the probability of HIV transmission [35]. Following the work by Cameron et al [36], Rottingen and Garnett [32] show a large impact of STDs during the early sex acts in a new partnership. Another important point in STD transmission is that the probability of male-to-female transmission is greater than female-to-male transmission. This has been reported for HIV as well as for other STDs, in various contexts including African countries [37-39].

HIV policy models

The first policy models to support decision making relating to infectious disease transmission were developed by scholars from the Operations Research field in the late 60's [11]. Although several models are based on the theory of system dynamics [40], both deterministic and stochastic approaches are used in policy modeling. As we are interested in the macro-level aspects of HIV epidemics, the focus will mostly be on describing deterministic models as this type of model is convenient in representing the infection spread among general populations. Rauner and Brandeau [41] indicate that HIV/AIDS policy models are designed to evaluate the monetary and non-monetary consequences of decisions on HIV/AIDS intervention. Merson and Dayton [42] describe five uses of HIV models by policy makers: forecasting, estimating the importance of risk factors, predicting the impact of a preventive intervention, predicting the impact of biomedical intervention, predicting the impact of mixed intervention techniques. A supplementary usage has been added which consists in assessing specific transmission modes and subsequent preventive measures. We also discuss antiretroviral therapies.

Forecasting

Several models were developed in the 80s to assess the demographic impact of the HIV/AIDS epidemic. Eight models were presented in 1989 during the UN/WHO workshop [43], on modeling the demographic impact of AIDS in Pattern II countries. These models were developed using stochastic [44-47] or deterministic [48-50] approaches, or a combination of both [51]. All models were tested with the same initial conditions and showed significant variations in HIV prevalence on a 25 year projection. Bernstein et al. [52] compared two of these models, the US Interagency Working Group model (iwgAIDS), originally developed by Stanley et al. [50], and the SimulAIDS model developed by Auvert [46]. The iwgAIDS model is a compartmental deterministic model, which has three logical components: a set of differential equations designed to model the age-structured demographic process, a set of differential equations designed to model the age-structured HIV/AIDS epidemiologic process and a baseline data file designed to tailor parameter estimates for different socio-cultural contexts. SimulAIDS is a stochastic model where each individual is represented separately. Bernstein et al. used the two models to compare single and combined interventions in a severely affected East African city. Despite significant differences in projected baseline HIV incidence rates between the two models, they were able to replicate baseline prevalence curves in agreement with the patterns of surveillance data.

In parallel to sophisticated models such as those mentioned above, efforts were made to design simpler models such as AVERT, a stochastic model, which was proposed by Rehle et al. [53] based on a model previously developed by Weinstein et al. [54]. The AVERT model includes a simplified male-female and female-male contamination matrix. The interest of such a model is that it requires far less extensive data than more sophisticated models. However, AVERT cannot be used to assess long-term scenarios and does not take into consideration the heterogeneity in sexual mixing nor the impact of other STDs on HIV transmission.

Estimating the importance of risk factors

Van der Ploeg et al. [55] use a stochastic micro simulation model (STDSIM) to illustrate the impact of STDs on HIV transmission. An interesting aspect of this model is that it combines the transmission risks for HIV and for four other STDs. The impact of STDs on the transmission of HIV has recently been assessed for Botswana and India by means of a deterministic compartmental model by Nagalkerke et al. [56]. Their two-sex model includes

two groups for each sex, low-risk groups (general population) and high-risk groups (female sex workers and their clients). Each group is split into four stages: uninfected, infected with HAART sensitive strains but not receiving HAART, infected with drug-sensitive strains and receiving HAART, and infected with resistant strains irrespective of treatment. The authors compare the impact of the same interventions (e.g. increased use of condoms, interventions targeted at sexual workers, anti-viral drugs) for both countries. They report significant differences for similar interventions between these two countries. For instance, an intervention targeted toward sex workers in India would drive the prevalence to extinction after 30 years in that country, while a similar intervention in Botswana would have a more modest effect. This can be explained by the large difference in HIV prevalence between India and Botswana (2% and 25% in 2000, respectively) implying that the HIV epidemic in Botswana has reached all population groups, while the HIV epidemic is mainly limited to the riskier groups in India.

Predicting the impact of prevention interventions

Expanding on an earlier contribution from Lee and Pierskalla [57], Brandeau et al. [58] designed a general two-sex compartmental model to assess a wide range of interventions and used it to assess HIV screening policies in the United States. Their model incorporates four disease stages and seven population classes: low, medium and high risk men and women, and children. The high risk women are represented by women aged 13 to 44 who are injection drug users (IDUs), high risk men include men aged 13 to 64 who are IDUs or gay or bisexual. Medium risk women are women aged 13 to 44 having a male IDU partner or many sex partners. Medium risk men are men aged 13 to 64 who are sex partners of high risk women or have multiple partners. The medium risk groups represent the bridge groups between the high risk and low risk groups. The authors test five different screening policies aimed at reducing the cases of HIV infected newborns and based on data from the State of California, they show that under certain conditions, screening high-risk women significantly reduces the number of HIV infected infants.

Bogart and Kunz [59] developed a deterministic model to determine the impact of a partially effective HIV vaccine among IDUs in Thailand. They include two groups: high and low risk, each divided into seven subgroups : HIV negative not vaccinated, HIV negative vaccinated not susceptible, HIV negative vaccinated susceptible, HIV positive asymptomatic unidentified, HIV positive asymptomatic identified, HIV positive symptomatic, AIDS. The

authors conclude that a partially efficient vaccine significantly reduces HIV prevalence over a 40 year period (from 50% without vaccine to 37% with a 75% efficient vaccine).

Condom use has been demonstrated to be an effective tool to reduce HIV transmission during homosexual and heterosexual acts [60] and Pinkerton and Abramson [61] quantified the protective effectiveness of condoms by means of a Bernoulli model. Van Vliet et al. [62] used the STDSIM model to evaluate the impact of three different strategies of condom uses in various settings and showed that targeting increased condom usage among FSW and their clients is more efficient than increasing the usage among females with steady relations. Dowdy et al. [63] showed a cost effectiveness of female nitrile condoms in Brazil and South Africa over a one year time period by using a simple stochastic model previously developed by Weinstein et al. [48].

Predicting the impact of biomedical interventions

Korenromp et al. [64] used the STDSIM model to assess the value of a single-round mass treatment to reduce STD prevalence and subsequently HIV incidence in African populations. Vickerman et al. [65] developed a deterministic compartmental model (POP 1.0) to assess the cost effectiveness of targeted preventive interventions on FSW in Johannesburg. The population is divided into sub-groups according to their sexual behaviour and HIV and STD status. The individuals form relationships of limited duration, and have various coital frequencies and level of condom usage. The per-capita HIV infection rate is fixed and determined by individual sexual behaviour. The authors showed that targeted interventions in FSW groups against STD can be cost effective. Vickerman et al. [66] used the same model to show that moderately sensitive point-of-care (POC) tests can reduce the spread of some STDs and HIV transmission in certain African countries.

Predicting the impact of a mixture of interventions

Intervention mix can be tested in simultaneous combinations: Bernstein et al. [52] in a comparative study of SimulAIDS and iwgAIDS, using data from Kampala, Uganda showed that combined interventions (e.g. reducing the number of casual partners, condom use and STD treatment) can slow down HIV transmission. However, the results from the combined intervention in both models were different from a linear combination of the component strategies used separately. The results from the stochastic model (SimulAIDS) were closer to

an additive result, while the results from the deterministic model (iwgAIDS) were far different.

Interventions can also be assessed in succession: Korenromp [64] showed that mass treatment of STD in rural Africa followed by sustained targeted treatment would be effective in the short and long run. Williams et al. [67] used the model previously developed by Vickerman et al. [65] to assess combinations of interventions targeted at FSW and their clients and at men having sex with men (MSM) in India and show the potential benefit and cost effectiveness of the combination of condom use and STD treatment. They also point to the importance of intervention duration for STD treatment.

Assessing the impact of specific transmission modes

Mother to child (MTC) transmission has been identified as an important cause of HIV transmission in sub Saharan countries due to the high prevalence levels among women in some of these countries [68]. Transmission can occur in utero, during parturition and during breast-feeding. Jacquez [69] emphasizes that the disease stage of the mother is an influential element in MTC transmission. Dunn [70] uses a stochastic model to show the importance of timing in HIV transmission risk during breast feeding due to variations in mother infectivity or stage of infant development. Decision models have been developed to assess the cost effectiveness of strategies to reduce MTC [71, 72].

Needle and syringe sharing among injection drug users (IDUs) are other important transmission modes. Since the pioneering work by Kaplan [73,74], deterministic models of various complexity have been developed to investigate HIV infection through heterosexual and IDU contact [75], to determine change in HIV and Hepatitis C (HCV) infection rates among IDUs [76] and to explore the relationship between HIV prevalence and the coverage of syringe distribution [77].

Zaric et al. have developed a deterministic model to study the effect of increased methadone maintenance on the spread of HIV among IDUs [78]. Their model includes nine population groups aged between 18 and 44, divided according to their infection status and risk. Infection transmission occurs through drug injection among IDUs and sexual contact between uninfected individuals and infected members of IDU groups. They show that methadone

maintenance program extension is cost effective among IDUs and beneficial to the non-IDU population.

Anti-retroviral therapies

Anti-retroviral treatments (ART) became available in developed countries in the early 90s and highly active antiretroviral therapy (HAART) became available in the late 90s. The introduction of these powerful drugs raised an interest in assessing their impact in developed countries by means of policy models. [79-83].

Blower et al. [79] developed a one sex compartmental model including 5 groups (susceptible, untreated infected with sensitive and with resistant strains, treated with sensitive and with resistant strains). Infection rates are a function of the number of infected individuals at any time. The model includes a proportion of individuals who give up on ART each year and a rate of resistance emergence. The model takes into account the emergence of resistance. Using data from the gay community in San Francisco, the authors conclude that over a limited period of time (10 years) antiretroviral therapy would reduce the AIDS death rate and substantially reduce the HIV incidence rate in the San Francisco gay community provided that a reduction in risky behavior takes place. Sensitivity analysis shows that even with a high incidence of infection by resistant virus strains, both death rates and total HIV incidence rates will not be significantly affected.

Goudsmit et al. [81] developed a simple deterministic model to identify the determinants of the resistance against the anti HIV drug zidovudine (ZDV) in the Amsterdam Cohort Study (ACS) population. The patients in the cohort originally received a ZDV mono-therapy and a few years later, the majority of patients were given a tri-therapy regimen (HAART). The model includes 3 groups: patients infected by resistant virus strains, patients infected by sensitive strains and patients with acquired resistance due to treatment (The ZDV resistance is acquired due to suboptimal treatment and is lost when ZDV is stopped). The model indicates that the incidence rate of infection by resistant virus strains reaches a plateau, the level of which only depends upon the treatment rate and the outflow rate of patients with resistant virus strains.

Dangerfield et al. [83] expanding on a previous model [84] developed a deterministic compartmental model to assess the impact of HAART in the United Kingdom. The model

includes 12 groups depending on their infectious status and their treatment history. The model incorporates the transition from mono-therapy to HAART but does not incorporate resistance rate. The authors conclude that new HIV infections will be considerably reduced providing that risky behavior remains at current level or lower.

Velasco-Hernandez [82], using the model previously developed by Blower et al. [79] to assess the long term effect of HAART, calculates R_0 with ARV use, assuming long-term use of ARV within the gay community of San Francisco. The author concludes that ART acts as an effective HIV-prevention tool and can lead to a value of R_0 below 1 if risky behavior decreases in conjunction with ART use.

Few models assess the impact of ART in developing countries. Blower and Farmer [85], using a previously developed model [79] estimate the impact of ART in developing countries taking into consideration the emergence of resistance. They conclude that 50% of infected individuals should receive ART in order to avert 10 to 30% of new HIV cases in the next decade. The authors express concerns about the overall impact of ART if risky behaviour is not reduced in parallel to ART diffusion. Over et al. [86] expand a previously developed epidemiological model to assess the cost effectiveness of three policies for ARV diffusion in India: increase adherence to treatment by enhancing unstructured private ART supply, provide ART to all infected women attending antenatal clinics and provide ART to all infected below the poverty line. They conclude that the first of these options is the most cost effective.

Discussion

The first part of this review illustrated how mathematical models have contributed to expanding the understanding of infection transmission and the important factors and structures that an HIV policy model must include. The second part described policy models which have contributed to support decisions and/or helped to understand the probable consequences of various interventions. The second part also revealed the large diversity of policy models. Some models have significantly contributed to support policy decisions in developed countries by pointing at risk groups [73,74] and by highlighting the impact of resistance in ART [87]. In developing countries, models helped to identify the role of MTC transmission and assess interventions to reduce MTC transmission [70-71]. However, it is

difficult to evaluate the real impact of models on final decisions, due to the complexity of policy decisions [88], and a lack of optimal policy model utilization due to perceptions and predetermined views from policy makers [89]. Evaluating this impact on a large scale would represent a research project in itself.

The need for model realism

Koopman mentions p. 304 that “too often modeling efforts stand alone in addressing the issues to which they are directed [90]. Indeed, most of the models are developed with a focus on specific aspects, and related interventions, such as behavioral changes [58, 91, 92], the number of sex acts [53], the migration process [52, 93], or the role of STD [55, 56]. Models are also developed to assess the transmission patterns in specific risk groups such as the gay community [94,95] and the IDUs [73, 74, 78].

The Proceedings of the UN/WHO workshop on modeling the demographic impact of AIDS in Pattern II countries [43] clearly indicates the need for two types of models: “a standard model to produce simple extrapolations for use by decision makers and a second, complex model is needed for pinpointing appropriate interventions and gaining increased understanding of the epidemic process” (page 55). To our knowledge, such standard policy model does not yet exist. Our goal is to develop such a standard model, using the term “generic” for pattern II countries. In those countries, HIV prevalence is usually high among women and HIV is mainly transmitted through heterosexual contacts and from mother to child during parturition or breast feeding. In the next section, we provide recommendations for the global structure of such a model and discuss which factors should be included.

Toward a generic HIV policy model ? An illustration for pattern II countries

The generic model described below must not be viewed as a unique and fixed model but rather as a reference system that incorporates all the critically important elements at a point of time that can be easily upgraded with more elements at a later stage and adapted to the needs of specific countries.

Model structure

Following Barton et al. [96], we recommend a deterministic compartmental structure including all epidemiological factors previously discussed. The model structure must be designed in a way to reproduce the reality of HIV transmission dynamics and minimize the

use of exogenous variables. Moreover, the generic model must be easy to parameterize to reflect the local or regional conditions such as the initial HIV prevalence or population(s) size.

Populations

Population groups such as newborns, infants and adults should be included. The age classes should be the same as the age classes used by WHO [68]. The population groups must be divided into high risk or core groups such as female sex workers or women with multiple partners, non core groups such as the general rural and urban populations and bridge groups which are different according to the country or region (e.g. in developed countries, the bridge groups are represented by bisexual or individuals having sex with IDUs or having multiple partners [97], while the main bridge group in sub-Saharan Africa are represented by mobile workers [98]).

HIV transmission modes

As heterosexual contacts and mother to child contamination are the prominent modes of HIV propagation in pattern II countries, both transmission modes should be included in the generic model.

Infection matrices

Infection matrices reflect the type of sexual relationships among the various population groups (who infects whom). Although most of the deterministic models that were reviewed provide details concerning the populations included, the infection matrices are usually not detailed or simplistic and do not allow for taking into consideration heterogeneous mixing among the various population groups [92]. As an example, young girls in sub-Saharan countries are more at risk of being infected by older men who can be infected by female sex workers [99]. Therefore the generic model must incorporate elaborate infection matrices which reflect the pattern of sexual relationships and local cultural patterns.

Critical factors

There are a number of factors that must be incorporated in a generic model. These factors contribute to either modulate HIV transmission risk (e.g. the variability in infectiousness over time [34]), increase the risk (e.g. other STDs [100-102], resistance to ART [103]) or to decrease this risk (e.g. long-term condom use [104]).

Circumcision has been recently identified as an important factor for reducing HIV transmission risk from females to males both in cross-sectional and cohort studies [105-107]. The World Health Organization currently recommends including circumcision in a comprehensive HIV prevention package [108].

Cost effectiveness analysis (CEA)

Disability Adjusted Life Years (DALY) has been recommended to assess the burden of diseases in poor settings [109]. However, it has been observed that it is often unclear from papers how researchers have calculated DALY [110]. DALY are calculated as the sum of years of life lost (YLL) and years lived with the disease (YLD), the latter are weighted according to the stage of the disease. Interventions targeted to the general population influence life expectation in the long term. Fox-Rusby [110] emphasizes the need to calculate YLL dynamically when the interventions last more than one year and recommends including a dynamic life calculator in models developed to assess long term interventions.

The WHO recommends evaluating the economic impact of interventions by making a comparison with the economic situation without intervention. This method is described as the generalized cost effectiveness analysis (GCEA) [111].

Model use

The various interventions should be tested individually and in combination. In the latter case one should consider both simultaneous and sequential implementation of the interventions. The impact of the interventions should be assessed in the various stages of the epidemics, with various prevalence levels. As HAART are becoming more widely used in developing countries [112,113], a special emphasis must be placed on assessing the impact of HAART. While recent epidemiological studies have been performed on HAART in Africa [112, 114], a model enabling one to assess the long term effects of HAART under the current roll-out conditions in pattern II countries whether in isolation or in combination with other interventions is highly desirable.

Conclusion

The alarming situation of the HIV/AIDS epidemic in most developing countries in combination with a lack of resources and time pressure, has made rational decision making

processes more necessary than ever. Recent large-scale initiatives such as the UNAIDS 3 by 5 initiative, launched in 2003 with the objective to enrol 3 million AIDS patients in HAART treatment by 2005, have triggered controversial opinions without objective arguments to support them [77,78]. All these elements militate in favor of developing a generic HIV/AIDS policy model which can help to define the most efficient intervention(s) in a timely manner and limit arbitrary decision making. A generic HIV/AIDS policy model must include all the epidemiological factors of critical importance in terms of HIV transmission and be designed on a multidisciplinary basis. We have illustrated this by providing a list of key elements to be included in such a model for pattern II countries.

Potential conflict of interest: none

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