Research

Theme Paper

Modelling HIV/AIDS epidemics in Botswana and India: impact of interventions to prevent transmission*

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Objective To describe a dynamic compartmental simulation model for Botswana and India, developed to identify the best strategies for preventing spread of HIV/AIDS.
Methods The following interventions were considered: a behavioural intervention focused on female sex workers; a conventional programme for the treatment of sexually transmitted infections; a programme for the prevention of mother-to-child transmission; an antiretroviral treatment programme for the entire population, based on a single regimen; and an antiretroviral treatment programme for sex workers only, also based on a single regimen.
Findings The interventions directed at sex workers as well as those dealing with sexually transmitted infections showed promise for long-term prevention of human immunodeficiency virus (HIV) infection, although their relative ranking was uncertain. In India, a sex worker intervention would drive the epidemic to extinction. In Botswana none of the interventions alone would achieve this, although the prevalence of HIV would be reduced by almost 50%. Mother-to-child transmission programmes could reduce HIV transmission to infants, but would have no impact on the epidemic itself. In the long run, interventions targeting sexual transmission would be even more effective in reducing the number of HIV-infected children than mother-to-child transmission programmes. Antiretroviral therapy would prevent transmission in the short term, but eventually its effects would wane because of the development of drug resistance.
Conclusion Depending on the country and how the antiretroviral therapy was targeted, 25–100% of HIV cases would be drug-resistant after 30 years of use.

Keywords HIV infections/epidemiology/prevention and control/drug therapy; Disease outbreaks/prevention and control; Disease transmission//prevention and control/prevention and control; Computer simulation; Models, Theoretical; Botswana; India (*source: MeSH, NLM*).
Mots clés HIV, Infection/épidémiologie/prévention et contrôle/chimiothérapie; Epidémie/prévention et contrôle; Transmission maladie/prévention et contrôle; Simulation ordinateur; Modèle théorique; Botswana; Inde (*source: MeSH, INSERM*).
Palabras clave Infecciones por VIH/epidemiología/prevención y control/quimioterapia; Brotes de enfermedades/prevención y control; Transmisión de enfermedad/prevención y control; Simulación por computador; Modelos teóricos; Botswana; India (*fuente: DeCS, BIREME*).

Bulletin of the World Health Organization 2002;80:89-96.

Voir page 94 le résumé en français. En la página 94 figura un resumen en español.

Introduction

The human immunodeficiency virus (HIV) epidemic is still out of control in most of sub-Saharan Africa (*1–3*); in Botswana, for example, one in three adults is infected. In Asia, HIV seroprevalences in many countries have been growing steadily, Thailand being a notable exception. HIV is threatening India, in particular, although the epidemic is still in its early stages there (*4*).

Measures to control the epidemic are urgently needed. Randomized trials and epidemiological studies suggest that certain interventions are effective in preventing HIV transmission or mortality, particularly those listed below.

1. Interventions focusing on high-risk individuals, such as female sex workers, in order to increase their use of condoms and encourage the adoption of other safer sex practices (*5*).
2. Treatment of bacterial sexually transmitted infections (STIs) in order to reduce the prevalence of these cofactors for HIV transmission (*6–8*).
3. Prevention of mother-to-child transmission through peripartum antiretroviral treatment of mother and child, possibly followed by the avoidance of breastfeeding (*9–11*).
4. Highly active antiretroviral therapy (HAART), an intervention that targets morbidity and mortality but may also affect

* Based on: Nagelkerke NJD, Jha P, de Vlas SJ, Korenromp EL, Moses S, Blanchard JF et al. *Modelling HIV/AIDS epidemics in Botswana and India: the effects of interventions.* (CMH Working Paper Series, Paper No. WG5: 4. Available at: URL: http://www.cmhealth.org/docs/wg5_paper4.pdf).

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Ref. No. **01-1557**

transmission — either positively by making individuals less infective or negatively by leading to higher-risk behaviour or increasing the lifespan of infected individuals (*12*).

The benefits of these interventions both in epidemics that are at an early stage or are full-scale are largely unknown. This paper reports the results obtained using mathematical models to explore the medium-term impacts of these interventions if they are sustained on a countrywide scale in a low-prevalence setting and in a mature HIV epidemic, with heterosexual spread.

Methods

We developed a dynamic compartmental model for the HIV-1 epidemics in Botswana and India. Parameters were chosen to resemble the epidemic situations in India (*13*) and Botswana, except that the populations were considered to be closed. However, this does not entirely reflect reality, especially in Botswana, where many men migrate to South Africa for work and acquire HIV infection there (*3, 15*).

The model assumed unsafe sex work to be important in driving the epidemics. Female sex workers and their clients were assigned separate compartments to reflect this assumption, which is supported by the finding in India that approximately 80% of cases of STIs presenting at sexually transmitted disease clinics are first-generation infections derived from sex work (*16*). Furthermore, early female HIV infections occurred predominantly among female sex workers, while monogamous women who were infected probably became so after their husbands had visited such workers (*4, 18*). Less information is available for Botswana but, as elsewhere in sub-Saharan Africa, unsafe sex work probably plays a very important role in the transmission of HIV (*19–24*).

Modelling carried out by UNAIDS has suggested that in India by 2010 a total of 25 million people will be living with HIV/AIDS under a worst-case scenario, with the corresponding number being 5 million under a best-case scenario, i.e. an adult seroprevalence of approximately 1–5%. Our model corresponds to a scenario in which prevalence grows from its current level of approximately 1% of the sexually active population to an equilibrium level of almost 5%. For Botswana, where HIV prevalence levels are already high, no major growth of the epidemic is anticipated. Model parameters and initial values were set to reflect an equilibrium HIV/AIDS prevalence of about 30% of the sexually active adult population. The most important intrinsic differences assumed between Botswana and India were as follows: the rate at which men became clients of female sex workers, which was taken to be four times higher in Botswana than in India; and in the number of infections caused by infected individuals among low-risk individuals of the opposite sex, which was twice as high in Botswana as in India, reflecting the higher frequency of non-commercial extramarital sex in sub-Saharan Africa (*25*).

The model

In the model, individuals moved between sex-specific compartments. For example, for women there were two groupings, female sex workers and low-risk, each of which was split into one uninfected component and three infected components, as follows: infected with HAART-sensitive strains, but not receiving HAART; infected with drug-sensitive strains and undergoing HAART; and infected with resistant strains, irrespective of treatment. We used the *ModelMaker* computer program (Cherwell, Old Beaconsfield, England) to construct the model. Fig. 1 shows the model structure, whose formal description can be examined in the full version of the present paper (*26*).

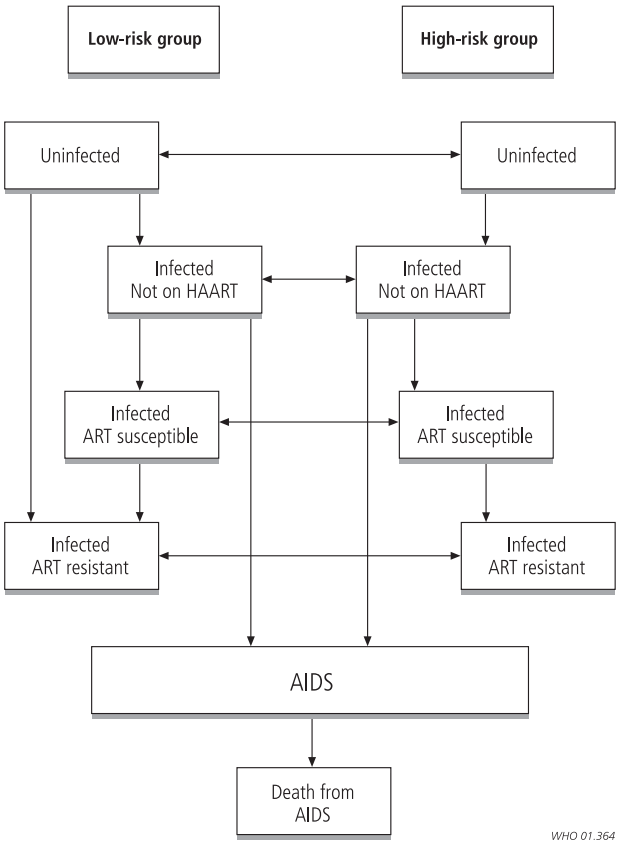
Interventions

It was assumed that the four interventions modelled would begin in 2003 and continue until 2033.

Female sex worker interventions

The objective of these interventions is to increase the use of condoms in contacts between female sex workers and their clients. In India there are probably several million such workers, with a far greater number of clients. Since many men from Botswana often find temporary work in South Africa, their contact with female sex workers is probably even more widespread than that of Indians. In both countries the use of condoms during sex worker–client contacts is generally low. Focused interventions have proved very effective in increasing condom use in this context. This reduces HIV transmission not only among sex workers and their clients but also in the general population, because of the core role of these groups in spreading infection (*27–29*). Many peer-mediated female sex worker intervention programmes in India and Africa have

Fig. 1. **Schematic representation of *ModelMaker* HIV model.** Rectangular boxes represent model compartments. Arrows represent flows (transitions between states, e.g. seroconversions). Each sex is represented by a series of compartments as shown below. High-risk groups are female sex workers and their male clients; low-risk groups are all other members of the population (HAART = highly active anti-retroviral therapy; ART = anti-retroviral therapy)



reported increases in condom use of 80% or more among those reached (*30–33*). We conservatively assumed that this intervention reduced the proportion of unprotected contacts from 67% to 25%. We were also conservative in not assuming an additional reduction in the risk of transmission per female sex worker–client contact through a reduction in STI prevalence.

STI management

Epidemiological studies support the hypothesis that STIs are associated with increased HIV susceptibility and infectiousness. However, confounding makes it difficult to estimate these cofactor effects reliably from observational studies (*34*). Improved STI management has proved effective in a controlled community trial in Mwanza, United Republic of Tanzania, with a reduction in HIV transmission of approximately 40% (*6*). In Rakai, Uganda, however, failure to reduce HIV transmission through an STI mass-treatment programme sparked debate about such interventions (*35–41*).

Nevertheless, we assumed that STI management would cause a 30% reduction in HIV transmission parameters. Arguably, this was a considerable simplification of reality and required averaging over partnerships with and without STI. The average effect of the intervention possibly also varied between risk categories, e.g. female sex workers and other women, depending on largely unknown factors such as the extent of its uptake. The intervention was assumed to have no effects on sexual behaviour. It is worth noting that the way in which the 30% reduction was achieved made no difference to our predictions. An increase in the use of condoms among the general population could be equally effective.

Maternal interventions

A number of regimens can reduce mother-to-child, i.e. vertical, transmission of HIV. The intervention in the model consists of HIV screening during antenatal care, administering nevirapine or other antiretrovirals (*42*) to mother and child, and providing alternatives to breastfeeding. It is possible to prevent almost all transmission when breastfeeding is avoided (*43*). We assumed a modest 50% reduction in mother-to-child transmission, from 33% to 16.5%, in order to reflect that regimens including formula feeding might not be available in parts of the developing world. We also assumed that there would be no effect in women with HAART resistance and that 100% of women would be reached. In Botswana, 90% of all pregnant women have been reported to attend antenatal clinics (*14*). In India the corresponding proportion might be as low as 60% (*44*), and reaching all women would require much effort.

HAART

HAART has had a dramatic impact on the mortality of HIV patients in developed countries (*45, 46*) but its long-term effects are unclear (*47*).

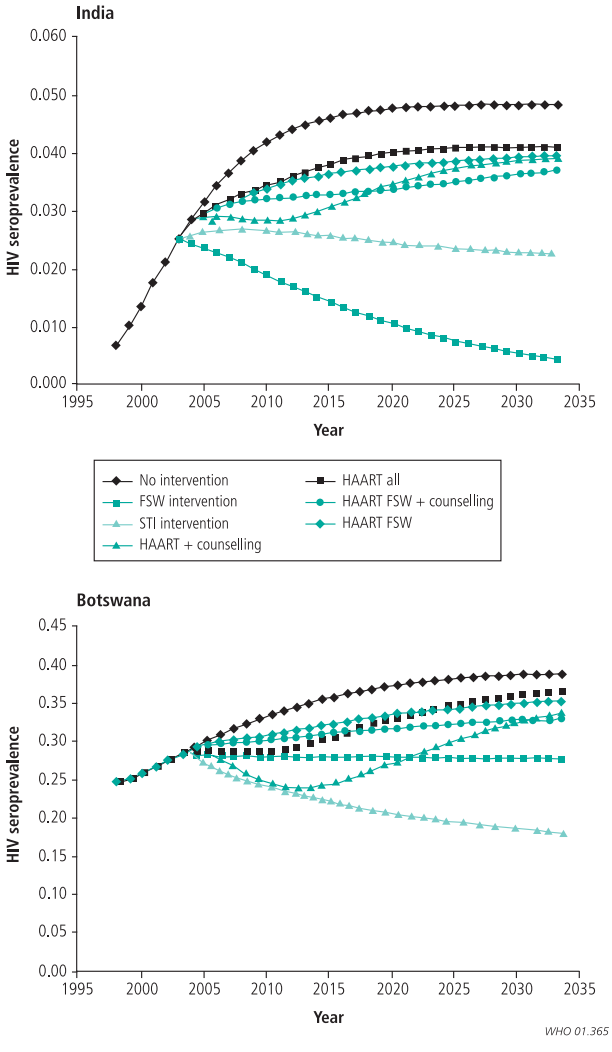
We assumed a single standard combination regimen, the most plausible method of implementation. Under therapy HIV-infected individuals are assumed to be uninfectious because of low viral loads (*48*). However, individuals under treatment engender drug-resistant strains at an annual rate of 25%, after which they become infectious again and spread resistant strains. After resistance has developed there are no benefits from treatment. HAART increases the life expectancy of an individual with drug-susceptible HIV by 4 years. We did not assume changes in sexual behaviour as a result of the availability of HAART since findings on this issue are contradictory (*6, 50*).

Two HAART programmes were considered: one in which all infected individuals were recruited at an annual rate of 50%; and one in which only female sex workers were eligible and were also recruited at an annual rate of 50%. These rates are probably higher than would be achieved in practice, and would result in an average interval of 2 years between infection and receipt of HAART. For each of the two interventions, two scenarios were explored: a "no counselling" scenario in which individuals were as infectious as other HIV-positive individuals; and an "effective counselling" scenario in which drug-resistant individuals spread 50% less HIV than HIV-infected individuals not receiving HAART. However, individuals with primary resistance (i.e. originally infected with resistant strains) were always considered to be as infectious as drug-susceptible HIV positives not receiving HAART.

Results

Fig. 2 shows the projected adult HIV seroprevalence over time in both countries, following intervention. In India the female sex worker intervention was the most effective, with a fivefold

Fig. 2. **Effect of interventions on adult seroprevalence of human immunodeficiency virus (HIV) infection in India and Botswana** (FSW = female sex worker; HAART = highly active anti-retroviral therapy)



decline in HIV seroprevalence after 30 years relative to the level in the absence of intervention. The STI intervention was the next most effective, with a two- to threefold decline in seroprevalence. After an initially positive impact, all the HAART interventions resulted in a levelling off of seroprevalence at about 20–30% below baseline levels. In Botswana the STI intervention fared best, followed by the female sex worker intervention. The performance of the HAART interventions was similar to that in India.

Fig. 3 shows the effect of HAART interventions on the prevalence of drug resistance among adult HIV-positive individuals. In India, resistance increased rapidly, independently of the type of HAART programme. In Botswana, the increase in resistance was slower if HAART was restricted to female sex workers because more infections occurred outside this group than in India. The rate of development of resistance improved somewhat as a result of counselling. In general, the rate of development of resistance increased with HAART usage.

Fig. 4 shows the proportions of HIV-infected neonates for the various interventions. In India, although the intervention aimed at preventing mother-to-child transmission had the greatest impact initially, the female sex worker intervention ultimately surpassed it and the STI treatment intervention was ultimately as effective. In Botswana, the STI treatment and the intervention aimed at preventing mother-to-child transmission were about equally effective, and both performed better than the female sex worker intervention. Of course, the latter intervention would have little impact on overall HIV transmission.

In order to explore the sensitivity of our findings with respect to the assumptions on the development of drug resistance under HAART, we re-ran the model using annual rates of developing resistance of 10% and 5%. We also developed a version of the model in which HAART was restricted to the treatment of only late-stage disease. Although resistance developed more slowly than shown here, essentially the same patterns of HIV seroprevalence ensued over time (*25*).

Discussion

We did not include male circumcision in our models. Although the frequently found association between male circumcision and lower HIV prevalence suggests that it reduces male susceptibility to HIV, it needs to be confirmed in a clinical trial (*51–53*).

Fig. 3. **Development of drug resistance in response to highly active antiretroviral therapy (HAART) in India and Botswana** (FSW = female sex worker)

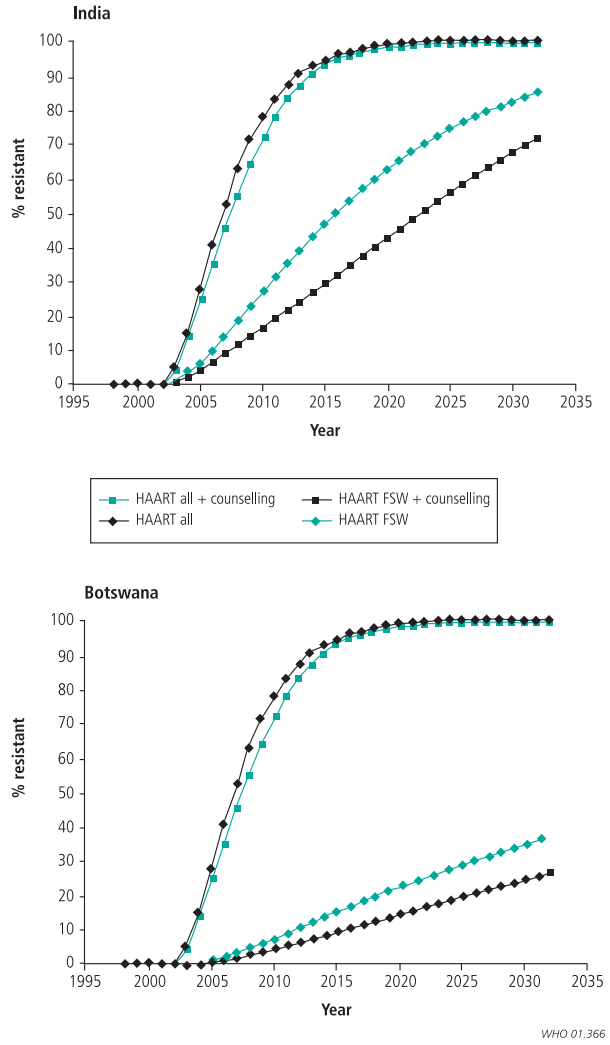
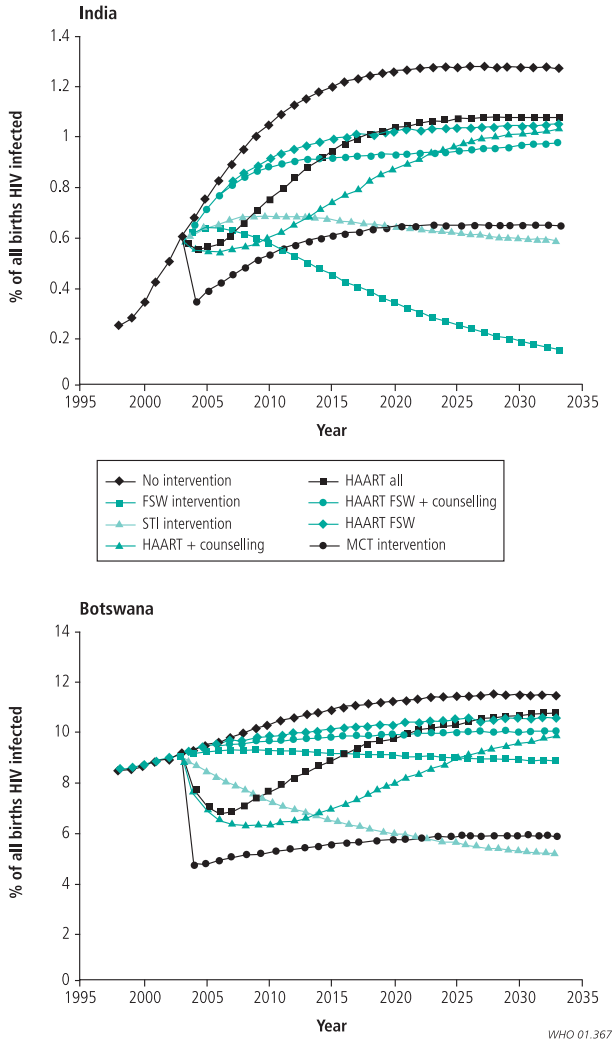


Fig. 4. **Mother-to-child transmission of human immunodeficiency virus (HIV) in India and Botswana** (FSW = female sex worker)



Female sex worker and STI interventions

Both the female sex worker and STI interventions had lasting effects on adult prevalence of HIV and thereby on vertical transmission. Our finding that female sex worker interventions had a high impact on the epidemic was consistent with the core group concept of HIV/STI epidemiology. Surprisingly, however, these interventions did not have the same effectiveness ranking in India and Botswana: in India, the female sex worker intervention had the greatest impact, whereas STI management was the most effective intervention in Botswana. In India the modelled effect of the female sex worker intervention apparently drove the epidemic to extinction by reducing the basic reproductive number, R_0, below unity, whereas the STI intervention did not have this effect (*54*). In Botswana, where higher levels of transmission were assumed, neither of the two interventions alone would push R_0 below unity. In view of this failure to eliminate transmission, the STI intervention, which was assumed to reduce all types of HIV transmission by an average of 30%, provided the best protection for the general population.

HAART

The various HAART-related interventions all had dramatic short-term effects on HIV prevalence, and had even greater short-term effects on incidence (*26*). With a very high recruitment rate and a low rate of developing resistance (50% and 25% per annum respectively), most HIV-positive individuals would be on HAART within a few years and still be drug-sensitive. Since these individuals were assumed not to be infectious, a high recruitment rate would initially reduce transmission. In the long run, however, these effects waned due to widespread drug resistance. Once resistance spreads, prevention of mother-to-child transmission also becomes difficult. The greater the success in recruiting patients, the more rapid is the spread of resistant strains. It is doubtful, however, whether our assumed high recruitment rates are feasible since frequent HIV screening of the population would be necessary.

In our model we ignored the "bathtub" effect, whereby HIV-infected individuals are most infectious shortly after infection and again when they become severely immunosuppressed and develop AIDS, with an intervening period of reduced infectiousness (*55*). Individuals are rarely identified very early after they become infected, so a high recruitment rate for HAART may be less effective in reducing transmission than is suggested by our model.

Although the development of drug resistance can be delayed (*56*), it cannot be completely avoided (*57*). Generalized drug resistance can be expected to occur unless the development and availability of new drug regimens keeps pace with the development of drug resistance. Although our predictions about the development of widespread resistance to HAART may seem pessimistic, we believe they are not unrealistic. Experience with antibiotics has shown that resistance can develop and spread rapidly and may outpace the development of new drugs (*58*). Tuberculosis treatment is short and curative, making the problem of development of resistance potentially avoidable (*59*). Nevertheless, resistance to a range of drugs is becoming a problem in the treatment of tuberculosis in many parts of the world.

Modelling methods

Our approach, involving compartmental modelling, is based on the expectation that the model system behaves sufficiently like the real world. However, it ignores much of the complexity of sexual behaviour. Few details are known about sexual networking in India and Botswana, or even in developed countries, where more research has been conducted. The use of more refined modelling methods, such as microsimulation, would therefore be inappropriate (*60–62*). Our knowledge of baseline parameters, such as transmission probabilities, is also imprecise. Consequently, our projections of the effects of interventions are subject to substantial uncertainty. Nevertheless, it is probable that the conclusions about prioritization are sufficiently robust if the assumed effect sizes of interventions are realistic. Whether this is the case is not always clear. For the female sex worker and STI interventions, empirical data, much of it from Africa, support our choices. Nevertheless, since there are few empirical data on STI interventions in India or Botswana, assumptions about their impact are speculative. Assumptions about the possible effects of interventions targeting mother-to-child transmission are more certain, with a proven efficacy of at least 50%. For HAART interventions, no long-term empirical data are available. We believe that our assumed 25% annual rate of developing resistance is realistic. While a 10% rate appears to be achievable under trial conditions, an annual rate of 40% has been observed in clinical practice, driven mainly by non-adherence to demanding regimens (*63*). In contrast to what has been done in some other models, we did not assume that drug-resistant strains would revert to being drug-sensitive when the selective pressure of treatment was removed (*64, 65*). Because resistant strains are increasingly found in drug-naive patients (*66–74*), such strains must be both transmissible and able to retain their resistance. Besides, in the absence of frequent sensitivity testing, as is likely to be the case in many developing countries, drug treatment and its selective pressure can often be expected to continue long after the development of resistance.

In our simulations we have explored and shown the effects of only single interventions. In practice, however, interventions need not be implemented individually. Several interventions can be implemented simultaneously or consecutively. In fact, this has been the approach in Thailand, where general education was combined with a focused female sex worker programme, STI treatment, and a mother-to-child transmission component. The effect of combining interventions on the incidence of HIV infection is non-linear but can be explored using our model. Such interventions may, for example, have strongly positive synergistic effects, in which case the combination of interventions would make elimination possible. As a rule it appears that any additional intervention that changes the course of the epidemic from a rising or endemic prevalence into one with R_0 less than 1 has a disproportionate impact on the incidence of infection. For India, a female sex worker programme may achieve this objective, but for Botswana more may be needed. Computer simulations, not reported here, exploring the effects of additional control measures beyond this point indicate that they would have a relatively small impact but that they would lead to a quicker decline in the incidence of infection.

While mathematical modelling may provide important insights, the task of identifying which strategy would be

sufficient to drive R_0 below unity is complex. This cannot be done with certainty because the state of the epidemic, the value of transmission parameters, and the effect of interventions are not precisely known and are in a state of flux. Even predictions of the course of HIV transmission in the absence of interventions have been highly variable (*75*). Uncertainty analysis is best performed by considering the effects of interventions predicted by a range of models rather than a range of parameter values. This is because certain model structures may overestimate or underestimate the effects of specific interventions. Several HIV transmission models have been developed and could be adapted to include considerations relating to HAART and drug resistance (*76*).

Conclusions

Because of the above uncertainties, we recommend a dynamic approach to interventions. In practice, HIV/AIDS prevention and control programmes should address a broad range of issues, but when modelling suggests that a given intervention may be sufficient to control an epidemic, as may be the case with sex worker interventions in India, it would seem wise to give the highest priority to this intervention and to monitor its impact. When modelling casts doubt on the adequacy of a single intervention, as in Botswana, it would seem advisable to direct resources to a more comprehensive package of interventions. Research and surveillance are essential for identifying implementation problems, monitoring impact, and validating and updating models. Standard sentinel surveillance may need refinements so that a response to interventions can be rapidly detected. Because effective interventions change incidence more rapidly than prevalence, surveillance could utilize the time lag between different enzyme-linked immunosorbent assays (ELISAs) to obtain improved estimates of incidence (*77, 78*). It is also important to monitor process outputs. For example, effective female sex worker interventions should lead to a reduction in STI incidence and in the percentage of male STI patients reporting unprotected sex with such workers as their probable source of infection. If interventions do not achieve adequate changes in these measures, increased programme efforts may be required. The dynamic nature of HIV intervention programmes requires that they be continuously evaluated to ensure that the results predicted by modelling exercises are reflected by what is occurring in practice. ■

Conflicts of interest: none declared.

Résumé

Modélisation de l'épidémie de VIH au Botswana et en Inde : impact des interventions destinées à empêcher la transmission

Objectif Décrire un modèle compartimental dynamique de simulation pour le Botswana et l'Inde, élaboré dans le but d'identifier les meilleures stratégies de prévention de la propagation du virus de l'immunodéficience humaine (VIH).

Méthodes Les interventions suivantes ont été examinées : une intervention comportementale axée sur les prostituées ; un programme classique de traitement des infections sexuellement transmissibles ; un programme de prévention de la transmission mère-enfant ; un programme de traitement antirétroviral destiné à l'ensemble de la population et reposant sur un schéma thérapeutique unique ; un programme de traitement antirétroviral axé uniquement sur les prostituées et reposant également sur un schéma thérapeutique unique.

Résultats L'intervention axée sur les prostituées et celle axée sur les infections sexuellement transmissibles sont intéressantes du point de vue de la prévention à long terme de l'infection à VIH, mais on ne sait pas exactement laquelle serait la plus efficace. En Inde, une intervention axée sur les prostituées pourrait conduire à l'extinction de l'épidémie. Au Botswana, aucune intervention n'y parviendrait à elle seule, mais la prévalence du VIH pourrait baisser de près de 50 %. Les programmes axés sur la transmission mère-enfant pourraient réduire la transmission du VIH aux nourrissons, mais n'auraient aucun impact sur l'épidémie elle-même. A long terme, les interventions axées sur la transmission sexuelle pourraient même être plus efficaces pour réduire le nombre d'enfants infectés par le VIH que les programmes mère-enfant. Le traitement antirétroviral empêcherait la transmission dans un premier temps, mais ses effets iraient en diminuant du fait de l'apparition d'une pharmacorésistance.

Conclusion Selon le pays et la façon dont le traitement serait ciblé, la proportion de cas résistants serait de 25 à 100 % au bout de 30 ans d'utilisation des antirétroviraux.

Resumen

Modelización de la epidemia de VIH en Botswana y la India: efecto de las intervenciones de prevención de la transmisión

Objetivo Describir un modelo dinámico de simulación por compartimentos para Botswana y la India, desarrollado con objeto de identificar las mejores estrategias para prevenir la propagación del virus de la inmunodeficiencia humana (VIH).

Métodos Se consideraron las siguientes intervenciones: una intervención conductual centrada en las profesionales del sexo, un programa convencional de tratamiento de las infecciones de transmisión sexual; un programa de prevención de la transmisión maternoinfantil; un programa de tratamiento antirretrovírico para la totalidad de la población, basado en un solo régimen; y un programa de tratamiento antirretrovírico destinado únicamente a las profesionales del sexo y basado también en un solo régimen.

Resultados Tanto las intervenciones centradas en las profesionales del sexo como las centradas en las infecciones de transmisión sexual tuvieron resultados prometedores para prevenir la infección por el VIH a largo plazo, pero resultaba difícil determinar su importancia relativa. En la India, una intervención centrada en las profesionales del sexo conduciría a la extinción de la epidemia. En Botswana, ninguna de las intervenciones tendría por sí sola ese resultado, pero la prevalencia de infección por el VIH se vería reducida casi en un 50%. Los programas contra la transmisión maternoinfantil permitirían

reducir la transmisión del VIH a los lactantes, pero no tendrían ningún efecto en la epidemia en sí. A largo plazo, las intervenciones focalizadas en la transmisión sexual serían incluso más eficaces que los programas de prevención de la transmisión maternoinfantil en lo que respecta a reducir el número de niños infectados por el VIH. El tratamiento antirretrovírico prevendría la transmisión a corto plazo, pero a la larga sus efectos tenderían a desaparecer como consecuencia del surgimiento de farmacorresistencia.

Conclusión En función del país y del perfil de destinatarios de la terapia antirretrovírica, el 25%-100% de los casos de infección por el VIH serían resistentes a los medicamentos al cabo de 30 años de tratamiento.

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