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The effect of interventions

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Abstract

In order to identify best strategies for HIV/AIDS control in two different countries, India and Botswana, we developed and used a dynamic compartmental simulation model. Several interventions were considered: a) a sex worker (CSW) focussed behavioural intervention; b) a Mwanza-style conventional STI (sexually transmitted infections) treatment programme; c) A mother-to-child transmission prevention programme; d) a highly active anti-retroviral therapy (HAART) treatment programme for the entire population; e) a HAART treatment programme for sex workers only. Both the Mwanza-style and CSW intervention hold promise for long term control, although their ranking is difficult to decide with certainty. Mother to child transmission programmes will do just that but will not dent the epidemic itself. HAART interventions may have short lived effects on transmission, but within decades drug resistance will be generalized and the epidemic will continue unabated. A more restrictive use, targeting only late stage patients, would delay the development of resistance somewhat.

INTRODUCTION

The HIV epidemic is still out of control in most of Sub-Sahara Africa (1). While in many countries in this area the epidemic seems to have stabilized, it has done so at unacceptably high levels. All countries in Sub-Sahara Africa have been seriously affected, although the spread of HIV in Africa has not been homogeneous, neither in time nor in extent. In South Africa, where HIV levels had been low until the early 1990s the epidemic has exploded in recent years and is reaching levels comparable to the worst hit parts of the rest of Africa (2) (3). In Botswana, over one in three adults aged 15-59 are HIV infected, which is triple the level less than 10 years ago. Yet, half of the African population lives in countries where (as yet) less than 5% of the adult population is infected. In other parts of the world, seroprevalence is lower, often below 1% of the adult population. However, levels have been growing steadily, especially in many Asian countries, with the exception of Thailand where the government responded effectively to a growing HIV problem. In Asia, HIV is especially threatening India. Although levels are still low compared to Africa, it is unclear what levels would be reached in the absence of control measures. In view of the apparent increase in prevalence observed in sentinel surveillance among antenatal care women, the epidemic is still in its early stages.

Control measures are urgently needed. Several interventions have been proposed. Randomized trials or reliable epidemiological studies have suggested that some of these interventions are highly effective in either preventing HIV transmission or in reducing mortality from HIV infection. These are:

1. Interventions focused on high-risk individuals, such as sex workers, to change sexual behaviour. It has been estimated that there are at least several million female sex workers in India. The number of clients is of course much higher. In India, in places where this

has been examined, it has been shown that most men with STIs probably acquired their infections from sex workers. As many Botswana men often work in South Africa for prolonged periods of time, sex worker contact is probably even far more widespread among them than among Indian men. It is also known that condom use during sex worker-client contacts in both countries is low. Focused interventions have proven to be very effective in curbing transmission in view of the central role their target groups play in spreading infection (4) (5) (6). It has long been recognized that sexual behaviour is very heterogeneous, most people have few partners, while a minority (the core group) have many and therefore account for a much of the transmission of HIV and STI in a population [7].

2. Improved treatment of bacterial sexually transmitted infections (STI). There are many epidemiological studies that support the hypothesis that STI are associated with an increased HIV susceptibility and infectivity. However, it is difficult to obtain reliable estimates of these cofactor effects from these observational studies as it is difficult to adequately control for confounding. Only two experimental studies have been carried out to date, one in Tanzania and one in Uganda. Another one in Masaka, Uganda, is in progress. Improved STI management has proven to be effective in a controlled community trial in Mwanza, Tanzania, with an approximate 40% reduction in HIV transmission (8) (9). However, this result has not been reproduced anywhere else, making it is difficult to predict the effects of such an intervention in India, say, where many factors, such as health care and the role of STIs in HIV transmission, may not be the same as in Mwanza. Especially the failure in Rakai, Uganda, to reduce HIV transmission through a different, mass-treatment, programme to control STIs has sparked debate about the circumstances under which a Mwanza style intervention could be successful (10) (11) (12) (13) (14) (15) (16) (17).

3. Prevention of mother-to-child transmission through peripartum antiretroviral treatment of mother and child, possibly followed by non-breastfeeding (18) (19) (20). Although near total avoidance of transmission is possible if breastfeeding can be avoided (21), regimes that include formula feeding for all may not be feasible or desirable in parts of the developing world, so that a 50% reduction overall in vertical transmission seems a reasonable goal.

4. Highly Active Anti-Retroviral Therapy (HAART). While the first three interventions are based on transmission control, i.e. prevention of new cases, HAART targets morbidity and mortality. HAART therapy has had a dramatic impact on the life expectancy of HIV infected individuals in Western countries [22] [23]. However, it is very novel and its long-term effects are still unclear. HAART may also affect transmission, either positively (e.g. it makes individuals less infective), or negatively as it may promote high-risk behaviour. It has also been argued that the longer life span of HIV patients under HAART may actually increase transmission (24). As yet, its effects on transmission are uncertain. Also in other respects, HAART has definite limitations (25).

The association of male circumcision with lower HIV prevalence found in many observational studies provides strong evidence that male circumcision is effective in reducing male susceptibility to HIV, but as yet, unfortunately, this has not been confirmed in a randomised clinical trial (26) (27) (28). We have not included the intervention of male circumcision in our study, due to the absence of experiment-based effect estimates.

The benefits of these interventions in early versus in full scale-scale epidemics are largely unknown. Here, in order to formulate strategies for interventions, we use mathematical modelling to explore the possible medium term (several decades) societal *benefits* of different interventions if implemented and sustained on a countrywide scale. We consider heterosexual

epidemics in both a low prevalence setting (of India) and a full epidemic (Botswana). We take a public health perspective and explore medium term HIV prevalence etc in response to interventions.

METHODS

We developed a simple dynamic compartmental model for the HIV-1 epidemics in two countries, with the objective of exploring the effects of interventions on these epidemics. One, a large Asian country ("India") with parameters chosen to resemble India as much as possible (29) and the other a small Africa country ("Botswana") with parameters chosen to resemble Botswana, with the important exception that the population was considered "closed". This may not be entirely correct for Botswana where traditionally many men migrate to South Africa to find work and while there may acquire HIV infection from, for example, CSWs (30).

The model assumes sex work driven heterosexual epidemics of HIV-1. That is that unsafe sex work is widespread in these countries and contributes substantially to the spread of the infection. In India, from current knowledge, approximately 80% of sexually transmitted infections are first generation infections derived from sex work, so this seems reasonable (31). Also, HIV infection in monogamous women is probably linked to their husbands having visited sex workers (32). For Botswana, less information appears to be available but sex work also appears to play an important role in maintaining the epidemic in most of sub-Sahara Africa.

For each of the two countries one scenario was modelled. For India, the model corresponded to a rapid spread scenario in which HIV-1 prevalence rapidly grows from its current level of approximately 1% of the sexually active Indian population to an equilibrium prevalence of

almost 5 % of the sexually active population over the next decades. For Botswana, where HIV prevalence levels are already among the highest in the world, no major growth of the epidemic was anticipated. Model parameters and starting values were set to reflect approximate equilibrium levels of about 30% of the sexually active adult population (see below for a definition). Apart from the population size and other starting values, the most important *intrinsic* differences we assumed to exist between Botswana and India were the rate by which men become a CSW client (in Botswana 4 times higher than in India), and the number of infections that are caused by infected individuals among non high- risk individuals of the opposite gender (in Botswana twice as high as in India).

2.1 The Model

We used compartmental models, i.e. individuals can be in one of several boxes (compartments) and move from one box to another e.g. by acquiring HIV. For example, for women we considered sex workers (CSWs) and other (low risk) women, each of which was split into one uninfected and three infected components, viz. i) infected with drug (HAART) sensitive strains of HIV and not under HAART treatment, ii) infected with drug sensitive strains and currently undergoing HAART treatment, and iii) those with drug resistant strains (either undergoing – ineffective –treatment or not). Movements between boxes (flows) are a function of the state of the epidemic. For modelling we used the microcomputer program **ModelMaker** (Cherwell UK). The structure of the model is shown in figure 1. A description of the model, model parameter assumptions and formal definitions are given in appendix I.

2.2 Interventions

We considered several possible interventions. A major uncertainty of the proposed interventions is the extent to which these can bring about the desired changes in condom use, transmission efficiency etc. The intervention effects used in modelling were either taken

from the results of intervention trials or longitudinal observational studies. However, the extent to which, for example, the results obtained in an experimental setting in one location can be replicated under routine conditions in another remains to be seen. All interventions are assumed to start in 2003.

2.2.1 . Sex worker intervention (or high-risk men intervention).

The objective of this intervention is to reduce the percentage of unprotected sex worker - client contacts [4 6]. Sex workers are both at high risk of becoming infected and subsequently spreading the infection. Many are (easily) accessible and amenable to an intervention that improves their health. Sex workers are targeted with the major message that they should use condoms using a peer educator strategy. Condoms are provided as part of the intervention. We assumed that the intervention reduces the percentage of unprotected contacts from 67% to 25%. This may seem to be a modest target for this type of interventions. For example, many programmes in India and Africa have shown increases in condom use to 80% among those reached. However, reaching this level among all sex workers all of the time may be hard to achieve and condoms may not be fully 100% protective. We therefore adopted a slightly more modest target. It was not assumed that this intervention also reduced the risk of transmission per sex worker-client contact through a reduction in STI prevalence, although this may well be the case. The predicted effects of this intervention may therefore be underestimated. We assumed the rate of "leakage" to the general population to be unaltered. The same objective of increasing condom use during CSW-client contacts could (in principle at least) be reached by targeting high risk CSW-client men. If we assumed that this intervention has the same objective and success as the sex worker intervention, then these interventions would be indistinguishable in terms of their predictions.

2.2.2. STI management

The objective of this intervention is to reduce the prevalence of these cofactors for HIV transmission and thereby decrease HIV transmission efficiency 8 9. Various strategies may be possible, for example a "Mwanza" type intervention, based on improved STI services using syndromic management and passive STI case finding (we called the intervention therefore "Mwanza-type"). In view of the debate surrounding this type of intervention, any figure about the effect such an intervention would have in India or Botswana is highly speculative. Here, we assumed that the HIV transmission parameters went down by 30% in response to the intervention. The 30% were based on the assumption (also speculative) that the effects of Mwanza (almost 40% reduction in transmission of HIV) could not be reproduced completely. No other effects of the intervention, e.g. on sexual behaviour, were assumed. Note that the way a 30% reduction in transmission is achieved is irrelevant for our predictions. An interventions that increases condom use in the general population to reduce unprotected sex to 70% of its baseline value would be equally effective (Assuming condom use would be "random" and not selectively used in high-risk contacts. In the latter case it would be more effective).

2.2.3. Maternal intervention

There are now a number of anti-retroviral regimens that have been shown to reduce mother-child transmission (MCT), or "vertical" transmission of HIV 18 19 20. The intervention consists of HIV screening, the administration of nevirapine (or other antiretrovirals (33)) to mother and child at the time of birth to prevent perinatal transmission, and providing alternatives to breast-feeding to prevent post-natal transmission. Access to pregnant women through antenatal care clinics is relatively easy provided ANC attendance is sufficiently high. In Botswana 90% of all pregnant women attend an antenatal clinic 30, but in India this figure may be as low as 60% [34]. There, access to most pregnant women would require much effort.

We nevertheless assumed that 100% of all women could be reached to show what could maximally be achieved. We assumed a reduction in MCT from 33% by 50% to 16.5% in HIV infected drug sensitive women as a result of feasible interventions. We assumed that the intervention would be useless in women who developed resistance to HAART. These resistant women would transmit to their children at the original rate of 33%.

2.2.4. HAART therapy

The fourth type of intervention considered is HAART (highly active anti-retroviral therapy) [22 23]. We assumed there to be a single standard combination regimen only, as this seems to be the most plausible and feasible method of implementation . Individuals with drug sensitive HIV are recruited into HAART programmes, with (annual) rates possibly depending on the type of individual (e.g. CSWs). Once under therapy these individuals are considered no longer infectious. Although this is probably not completely true, they tend to have low viral loads as long as they remain drug sensitive [35]. However, individuals under treatment develop drug resistant strains at an annual rate of 25% after which they become infectious again and will – if they spread infection – spread resistant strains. After developing resistance no benefits are accrued from further treatment. Thus, HAART increases the life expectancy of an individual infected with drug susceptible HIV by 4 years. We believe that this 25% rate of developing resistance is optimistic, although not altogether impossible. While a 10% rate appears to be achievable under trial conditions, an annual rate of 40% has been observed in clinical practice, seemingly driven mainly by non-adherence to very demanding therapeutic regimens [36]. Once drug resistance develops they are assumed no longer to enjoy any survival benefits from HAART. Unlike assumed in some other models, we did **not** assume that drug resistant strains could revert to drug sensitive when the selective pressure of treatment is removed [37], despite some in-vitro evidence that this may occur [38]. In practice, resistant strains are increasingly found in drug-naïve patients who acquired their infection through IV drug

use, sexually [39 40 41 42 43 44 45 46], but also vertically [47]. This suggests that such strains are both easily transmitted and able to retain their resistance. We therefore believed this assumption to be too optimistic: as long as any drug resistant strains survive they will be quickly selected for once therapy is resumed.

Depending on the type of intervention that is "on" individuals in HAART programmes can be assumed to have been thoroughly counselled (or not) so that they are "less infectious" (or not) than other HIV positive individuals. However, individuals with primary resistance (i.e. they have become infected with a resistant strain) are always considered as infectious as drug susceptible HIV positives who are not enrolled in HAART programmes. We have not assumed any general change in sexual behaviour as a result of the implementation of a HAART programme. Naturally, the availability of HAART might lead to spurious feelings of security and thereby increase risk taking. However, this is by no means certain. Reports give contradictory results [48 49].

Two HAART programmes were considered. One for which all HIV infected individuals would be eligible and be recruited at an annual rate of 50%, and one for which only sex workers (CSWs) were eligible, similarly recruited at an annual rate of 50%. At this rate the average duration to entering a HAART program is 2 years, and about 76% percent will be reached and on therapy before developing AIDS. For each of the two interventions, two effect sizes were explored. One, "the effective counselling" one, in which drug resistant individuals spread 50% less HIV (by whatever means, e.g. increased condom use) than HIV infected individuals who have not been recruited into the programme, and one "the no counselling one" in which individuals are just as infectious as other HIV positive individuals.

3. RESULTS

Table 1a and 1b show the predicted total number of new (incident) HIV cases for each year under the different interventions in Botswana and India. These figures include vertical transmissions. As (especially in Botswana) the population size depends on the intervention (e.g. the population in Botswana is predicted to decline in the absence of intervention), these figures should be interpreted with great care. As all HIV infections, even with HAART therapy, are assumed to be ultimately fatal, these figures approximately equal AIDS deaths several years later. The difference being a small percentage of individuals who will die (e.g. due to accidents or malaria) *with* HIV but not *from* HIV.

Figure 2 shows adult HIV prevalences under the different scenarios in India and Botswana. In India the CSW intervention would be most effective, followed by the Mwanza style intervention. In Botswana the CSW intervention would lead to a more modest reduction in HIV prevalence, while here the Mwanza style intervention would be superior. HAART therapy, whatever the mode of delivering it, is faring worst and the effect of the intervention appears to wane over time due to increased drug resistance.

Figure 3 shows the effect of HAART interventions on the prevalence of HAART resistance among adult HIV positive individuals in both countries. In India, resistance increases very rapidly, independent of which type of HAART programme is considered. In Botswana, the increases is slower if HAART is restricted to CSWs, because more new infections occur outside CSW settings than in India. Counselling improves the rate of development of resistance a bit, but not much. In general, it appears, the more widespread the use of HAART the greater the rate of developing resistance.

In Figure 4 the fraction of births that are HIV infected in India and Botswana are shown. Although, MCT intervention has the highest impact on vertical transmission

initially, even in this respect this intervention is ultimately always surpassed by an intervention that controls sexual transmission.

In figure 5 (adult annual incidence rate) the ratio of the annual number of new cases (Table 1) and the *adult* population is shown. As the numerator includes vertical transmissions the term "adult incidence "is a misnomer. However, as the sexually active population approximately coincides with the economically active population, this ratio is a good measure of the total burden of new cases that has to be borne by each economically active member of the population. Although, the incidence rate shows changes in epidemiology earlier than the prevalence rate, the conclusions that can be drawn from this figure are similar to those that follow from the prevalence rate.

To explore how sensitive our findings are with respect to the assumed rate of developing resistance (25% annually), we reran all the HAART interventions with a 10% and 5% annual rate of developing resistance. The results are shown in Figure 6 (labels refer to particular interventions, e.g. ALL5+counsel refers to HAART made available to all HIV positives, the annual rate of developing resistance is 5%, and HIV positive drug resistant patients are 50% less infectious as a result of counselling). Similarly, the rates of developing resistance are shown in Figure 7. Clearly, while the adverse effects (resistance increases and will ultimately make the interventions void) occur more slowly than with a 25% annual rate, essentially the same happens.

4. DISCUSSION

Using a mathematical model we explored the effects, in terms of adult HIV prevalence, drug resistance and fraction of new-borns that are HIV infected, of several different intervention projects. As HIV can affects population size, we did not consider number of deaths averted as

an outcome (since the smaller the population the fewer deaths occur anyway). Note that each of these interventions was assumed to cover all of India or Botswana. Interventions were also assumed to remain effective until the end of the intervention period (2033). Vertical transmission projects were assumed to have no effect on adult prevalence whatsoever.
We adopted a public health perspective throughout, and considered societal benefits. Our public health focus imposes two limitations. First, for people currently living with HIV/AIDS, and their physicians, this perspective may be unsatisfactory, as it does not address their needs. Second, it ignores costs. Costs may vary considerably between interventions. For example, currently HAART costs thousand of dollars per patient per year. However, we deliberately avoided the issue of costs and cost-effectiveness for several reasons: costs may change with time (e.g. drug costs are already falling fast); the benefits of interventions accrue long after expenses have been incurred; scaling-up interventions may change cost-structure due to economies and diseconomies of scale; and costing interventions for several decades is well nigh impossible anyway.

Not surprisingly, the mother-to-child transmission intervention does what it is supposed to do, viz. it reduces vertical transmission. Unfortunately, unlike other interventions, they do nothing to prevent continued heterosexual spread. While it is desirable to prevent children becoming infected, the best way to do that is to reduce the prevalence in their mothers. This has the added advantage of children having live mothers.

Both the CSW intervention and the Mwanza style intervention, have a permanent effect on adult prevalence of HIV and thereby – indirectly – on vertical transmission. However, this is only true under the assumption that the Mwanza style intervention can indeed achieve a 30% reduction in transmission parameters. Again, this intervention has only demonstrated

effectiveness in Mwanza, Tanzania. It is unknown whether it could have similar positive effects in either India or Botswana, where, for example, available health care differs from that in Tanzania. Our results showing that CSW focused interventions have a high impact on the epidemic are consistent with the core group concept of the epidemiology of HIV/STI. Perhaps more surprising is the finding that the CSW intervention and the Mwanza style intervention do not have the same ranking of effectiveness in India and Botswana. In India, the sex worker intervention appears to be more effective than the Mwanza type intervention, whereas in Botswana the reverse seems to hold true. This needs some explanation. In India, the modelled moderate effect of the CSW intervention apparently drives the HIV epidemic to extinction, that is the intervention reduces the basic reproductive number (R_0, the number of secondary cases directly infected by a single typical case when the population is totally susceptible [50]. With $R_0 < 1$ the epidemic will fade out) below unity and thereby drives the epidemic to extinction, whereas the Mwanza style intervention apparently does not. In Botswana, where much higher levels of sex work and other risky contacts (as parameterized by a higher "leak" parameter, cf Appendix I) were assumed, neither of the two interventions would suffice to push R_0 below unity. Given this failure to eradicate (potentially) the infection, the Mwanza style intervention, with an assumed reduction of 30% of *all* types of HIV transmission, appears to do more to protect the "general population" than does the CSW intervention. Even higher assumed levels of effectiveness (e.g. 100% condom use) of the CSW intervention in Botswana, unfortunately, would not be successful in completely driving the epidemic to extinction although prevalence would go down to low levels (results not shown).

The different HAART style interventions all have dramatic short run effects. However, under the assumption that only a single HAART regimen would be available, no long term positive

effects can be expected. With a very high recruitment rate (50%) annually, and a low rate of developing resistance (25% annually), within a couple of years most HIV positives would be on HAART and would not yet have developed resistance. As these patients were assumed to be not infectious, a high recruitment rate would initially reduce HIV transmission considerably. In the long run these effects on transmission inevitably wane due to widespread drug resistance. Assuming an even lower rate of developing resistance (5% or 10% annually) would slow down these adverse effects and would provide a longer window of opportunity to develop more permanent interventions or to develop new drugs to replace the old ones.

Another adverse effect of widespread administration of HAART therapy, and its consequent development of resistance to antiretrovirals, is that once drug resistance has spread, prevention of mother-to-child transmission also becomes difficult. The greater the success in recruiting patients into these programmes the more rapid the development and spread of resistant strains. It is doubtful however, whether our assumed high (50% annually) recruitment rates are possible at all. Very frequent HIV screening of the population would be a prerequisite. In addition, we have ignored in our model the “bathtub” effect. It is believed that HIV infected individuals are most infectious shortly after infection (due to high viraemia) and later when they develop AIDS, with a period of reduced infectiousness in between, although this is not certain [51]. It would seem very difficult to identify individuals shortly after infection before they seroconverted, so that a high recruitment rate may be less effective in terms of infections avoided than is assumed in our model.

Thus, HAART programmes only contribute significantly to a reduction in transmission if one of the following two conditions are met, viz.

drug resistance can be prevented or new drugs can continuously replace old ones, and

individuals enrolled in the programme can be prevented (e.g. though counselling) from spreading their infection (while they are drug sensitive, this may not be a problem as they are probably not very infectious; while drug resistant, adoption of safer habits is key).

There are no indications that either of these conditions can easily be met in either India or Botswana.

Thus, interventions including this therapy – if successful in recruiting a substantial proportion of the HIV positive population – will ultimately fail completely due to generalized drug resistance, unless transmission of resistant strains could be prevented. Currently there are no proven counseling techniques that could achieve this [52], and even if there were, then a VCT (voluntary counseling and testing) programme *without* HAART therapy would be equally effective in controlling HIV spread. Although our predictions about the (long-term) failure of HAART therapy may sound gloomy and unduly pessimistic, we believe they are not unrealistic. Experience with antibiotics has shown that resistance can develop and spread rapidly [53]. Multi-drug resistance tuberculosis is becoming a widespread problem in many parts of the world, even though treatment for TB (standard DOTS, for example) is simple (compared to HAART therapy), short and curative and could therefore avoid the problem of development of resistance altogether [54]. Of course, a failure to recruit a sizeable percentage of HIV positives into HAART programmes would prolong the life span of these drugs.

Our approach of compartmental modelling is one of "macromodelling". It is based on the expectation that the model "system" behaves sufficiently similar to the real world to justify predictions. It ignores many real world details. For example, placing all individuals in a small number of compartments can never adequately reflect the great heterogeneity and complexity of sexual behaviour. Unfortunately, details of this in India and Botswana, but even in better researched societies in the West, are unknown, thereby vitiating the use of more refined

methods of modelling, such as microsimulation [55]. Our knowledge of baseline parameters, such as transmission probabilities, is also imprecise. Estimates from other countries were assumed to apply to India and Botswana, despite the obvious differences in populations. Consequently, our projections of the effects of interventions are subject to substantial uncertainty. Nevertheless, as the relative effects of interventions are unlikely to be very sensitive to the exact choice of baseline parameter values, conclusions about prioritization are probably sufficiently robust. All conclusions however *do* hinge crucially on the effect size we assumed for the interventions. Thus, our results should be interpreted as conditional statements in the sense that *if* intervention X would result in Y *then* HIV prevalence would be reduced by Z.

Whether these assumed effect sizes are in fact realistic is uncertain. For the CSW and Mwanza style intervention empirical data, much of it from Africa, supports our choices. For HAART interventions, which are very new, no long-term empirical data are available at all. The effects that we put into the model were what we believed these effects could reasonably be and could be defended in terms of available data. Others may hold different beliefs, with as much (or rather little) empirical foundation as ours. Comparatively certain are the possible effects of interventions targeting maternal-to-child transmission. It stands out that available interventions targeting maternal-to-child HIV transmission can be at least 50% effective.

In our simulations we have only explored and shown the effects of *single* interventions. This was done to demonstrate what the relative potentials of each of these interventions are. However, in practice, interventions need not be implemented exclusively. Several interventions can be implemented simultaneously, or introduced at different points in time. In fact, this has been the – highly successful –approach in Thailand where information and

education were combined with a tightly supervised CSW programme, STI treatment, and an MCT component. We have to keep in mind that the effect of combining interventions on the incidence of HIV infection is highly non-linear, as can be explored using our model. Such interventions may, for example, have strongly positive synergistic effects, with each intervention strongly increasing the effect on transmission parameters of the other. This would suggest that under these circumstances combining interventions would bring us nearer to our ultimate goal of eliminating the infection from the population and to do so in the least expensive manner. As a "rule", it appears that any additional intervention that changes the course of the epidemic from a rising or endemic prevalence (albeit slower and lower than in the total absence of control measures) into a declining one (possibly leading to R_0 decreasing below 1 and thus ultimate elimination), has a disproportionate impact on the incidence of infection. By contrast, computer simulations (results not shown) exploring the effects of additional control measure *beyond* what is needed to achieve a reasonably fast decline (for example a 50% decline per decade) in incidence rate, suggest that such additional intervention will prevent comparatively few infections and must therefore be relative cost *in*effective (whatever the cost structure of the interventions might be). This seems plausible and acceptable for nascent epidemics where one may be content with low prevalence in combination with ultimate elimination. In high-prevalence situations where HIV threatens to disrupt society, one may not be content with the idea that the problem is on its way out, and there may be a legitimate political need to do this as fast as possible, using all possible means. Nevertheless, as interventions take time to become fully operational (admittedly ignored in our simulations), even under such circumstances more may be achieved by making sure that the existing interventions remain operational, e.g. by extending and improving the coverage of the first intervention. As soon as concrete planning starts, such operational aspects may be explored in greater detail.

5. RECOMMENDATIONS

From our modelling results several points emerge. We shall try to translate these into recommendations for policy making.

Avoid bad interventions. From a public health perspective, interventions that according to the model are ultimately likely to fail, such as large scale provision of a single regimen HAART to the general population (except for the control of MCT) should not be given priority unless the creation and transmission of resistant strains can be avoided.

Avoid over-reliance on modelling in choosing the right intervention. Choosing between interventions that are promising is more difficult, especially where it comes to combining (effective) interventions. While mathematical modelling may give clues and insights, in reality (where much is uncertain), one is faced with the complex task of finding out which strategy would be "just enough", i.e. enough to push R_0 below unity. As the state of the epidemic, the value of transmission parameters, and the effect of interventions on transmission parameters, are imprecisely known, and perhaps subject to change, this cannot be done with absolute certainty. Even predictions of the impact of HIV in the absence of major interventions have been highly variable [56]. In the face of this uncertainty, other aspects (costs, feasibility, and confidence in reproducibility of results) may become important here. Uncertainty analysis may be of use to resolve some issues, but should best be carried out by considering the effects of interventions as predicted by a range of models, rather than a range of parameter values. This is because certain model *structures* may generally overestimate or

underestimate the effects of specific interventions. Several HIV transmission models have been developed and may be (or have been) adapted to include antiretroviral therapy and resistance [57]. If different models agree on the best intervention strategy then this greatly reduces the uncertainty in decision making.

How much intervention. As a general strategy in deciding "how much" intervention is needed, we should try to achieve a reversion in the trend in incidence (from an increase to a decrease) with the best (most cost-effective) means available. For India a sex worker programme with moderate success (increasing condom use from 33% to 75%) may achieve this objective. For Botswana more would seem to be needed, as in our simulations this intervention would only stabilize the prevalence. A combination of a CSW intervention with a "Mwanza type" intervention would need approximately 50 years to drive prevalence below 1% (results not shown) and would ultimately eradicate the infection. Putting all available intervention strategies in place at great expense, where a single one would have led (ultimately) to elimination of HIV infection from the (general) population, may be a waste of resources.

Dynamic decision making, model updates, research and surveillance. In view of the above uncertainty, it may be recommendable to adopt a dynamic approach to intervention. Under circumstances (as in India) where modelling suggests that a single intervention (in the case of India, the sex worker intervention) is enough to control the epidemic, it may seems wise to first implement this, make sure it functions properly, and closely monitor what effect this has on the epidemic in the general population. In addition, a well-defined (operational) research agenda should be part of the intervention. For examples, problems due to inadequate implementation should be identified quickly. If such an intervention has the desired effect,

then this should be measurable and results can also be used to validate and update the model. For this, adequate surveillance is key. Standard sentinel surveillance is important but needs improvements to pick up a response to the intervention(s). If the intervention is effective, then the incidence rate should change faster than the prevalence rate. It would seem that changes in HIV incidence would be slow to be picked up by standard prevalence surveys or sentinel surveillance. However, this is not necessarily true if surveys and surveillance would make effective use of the time lag between p24 positively (or PCR positivity) and HIV seroconversion by Elisa, or – more simply - the time lag between two different Elisa tests (a fast sensitive one and a slow one) [58 59]. In addition, an effective sex worker intervention would lead to changes in several epidemiological indicators that *can* be observed at an early stage. First, it would lead to a reduction in STI incidence *per se*. Second, widespread condom use by sex workers would lead to a reduction in the percentage of male STI patients reporting (unprotected) sex with a sex worker as the probable source of their infection. If the effect of a single intervention (provided it functions properly) would not achieve adequate changes in these measures, then increased control efforts may be called for. Thus, improved surveillance appears to be an essential element of a careful cost-conscious but effective approach to HIV control. When modelling casts doubt on the adequacy of a single intervention, as in Botswana, it may seem better, if feasible, to try a more comprehensive package of intervention.

Appendix I. Formal description of the model. Parameters are as for the Botswana and India base model. Time represents years (1998-2033). Interventions, when turned "on", all start in year 5 (2003). Where for compartments and parameters two values are given, the first is for Botswana, the second for India.

AI.1. The population

We considered a model for the sexually active population only. Sexually active in the restrictive sense that they may still occasionally change partners. Men and women who either become sexually inactive or will never acquire new partners any more during their lifetime, and whose partners also will not change partners, are considered to have moved out of this population. Such women are also considered to have become infertile. Thus, approximately, the population under consideration is those aged 15-59, some 50% of the total population. The annual rate by which (uninfected) men and women move out of this population is *muneg*. The annual rate by which HIV infected individuals (before developing AIDS) move out of the population (through death) is parameterized by *mupos*. In addition they develop AIDS at an annual rate *aidsrate* from where they die at an annual rate *muaids*. The number of children born is *brate* times the number of women. However, these children are kept outside of the population and are only used to explore vertical (mother-to-child) transmission. In order to avoid creating a separate compartment of children "waiting" to move into the sexually active population, we simply modelled the influx of men and women to be proportional to the population size, with annual rates *malegr* and *femgr* respectively. We ignored the effects of vertical transmission on influx.

AI.2 Compartments

We considered eight interacting compartments for each sex. For women we considered sex workers (CSWs) and other (low risk) women, each of which was split into one uninfected and three infected components, viz. i) infected with drug (HAART) sensitive strains of HIV and not under HAART treatment, ii) infected with drug sensitive strains and currently undergoing HAART treatment, and iii) those with drug resistant strains (either undergoing – ineffective – treatment or not). For men we distinguished sex worker clients and other men, each category broken down into separate compartments by HIV infection and drug sensitivity status as above. In addition, we considered uninfected and infected births, but these compartments did not interact with any other compartment.

AI.3. Flows between risk categories

Men can move from the non-client to the client state and from the client state to the non-client state, with annual rates *cust1* and *uncust1* respectively. The number of annual contact of a client with a sex worker was parameterized as *cr1*. Similarly women can move from non-sex worker state to sex worker state, and from sex worker state to non-sex worker state with annual rates *cust3**exp(annual_sex worker_sexcontact/1000-1) and *cust4.* Thus, the flow of women from non-sex worker state was made dependent upon the demand for sex work. This demand is supposed to be "autonomous" and defined by the *cr1* parameter. With 1000 contacts per sex worker annually, the rate would be exactly *cust3*, if current sex workers have more than 1000 contacts then that increases the flow into sex work. For example, with 1500 contacts annually the rate would be 1.65*cust3.*

AI.4. Sexual transmission

Three different male-female partnerships were considered. First, sex worker-client relationships. The risk of transmission during a single unprotected sex worker-client contact is determined by the parameters *fmrisk* and *mfrisk* for the risk of transmission from female-to-male and from male-to-female, respectively. The number of sex contacts between sex workers and clients is determined by the demand for it and the number of available sex workers. Second, spousal relationships. "Spousal" partnerships between low risk (non-client) men and low risk (non CSW) women were considered to be more risky than given by those transmission parameters above by a factor *stabfactor*, as these partnerships usually involve several or many sexual encounters. However, per sexual act these partnerships are implicitly assumed to be safer than individual sex worker contacts. These latter partnerships are formed by men at an annual rate of *marrate.* The rate by which women form such partnerships is determined by the rate by which men form such partnerships. This simply ensures that the number of partnerships formed by men equals that formed by women, and it does not aim to be reflective of any realistic pattern of partnership formation. Transmission can occur when one of the two partners is HIV positive and enters into such a relationship. Third, in addition to these new "spousal" partnerships formed at (presumably) a low rate between low risk men and low risk women, all other sexual relationships between men and women. We modelled the effect of transmission occurring as a result of such relationships and subsequent HIV transmission to existing "spousal" partnerships and other contacts by allowing HIV positive individuals to "leak" infection to low-risk individuals of the opposite sex. Most individuals are married or have other "spouse-like" sex partners among the low risk population. If these people become HIV infected from other partners (via sex work or other routes) they have a high risk of "leaking" the infection to their spouses or other partners. We modelled these infections by including a *leak* parameter.

AI.5. Condom use

The fraction of sex worker-client contacts unprotected by condoms was parameterized by *unprot1*. By manipulating this parameter, the effects of interventions could be studied. Condom use among other partnerships was ignored. Condom use was assumed to be random in the sense that each CSW-client contact had the same probability of being (un)protected by a condom.

AI.6. Vertical transmission

HIV infected women were considered as fertile as uninfected women. The fraction of their births infected with HIV was parameterized as *vtrate.*

AI.7. Differences between India and Botswana

The major differences in sexual behaviour assumed to exist between India and Botswana were a higher rate among non CSW-client men of becoming client in Botswana than in India (1 out 10 annually instead of 1 out of 40) reflecting the importance of migrant labour practices and a much higher "leak" parameter (0.2 in Botswana and 0.1 in India) reflecting a freer sexual morality in Botswana than in India. No intrinsic differences in transmission probabilities were assumed.

AI.8 Formal description of the model

COMPARTMENTS

AIDS
```
dAIDS/dt = +hivcsw+aidscli+aidsmen+aidsffem-
hivdying+hivcswr+aidscli2+aidsmen2+aidsfem2
Initial Value = 0.0
```

CLI_AR_R
```
dCLI_AR_R/dt = +RD_CLI-aidscli2+infect1r-F4-mupos*CLI_AR_R+F5
Initial Value = 0.0
```

CLI_AR_S
```
dCLI_AR_S/dt = +CLIdet-RD_CLI-F3-mupos*CLI_AR_S+F8
Initial Value = 0.0
```

clients_inf
```
dclients_inf/dt = +infection1-mupos*clients_inf+custom2-uncustom2-aidscli-CLIdet
Initial Value = 20000      1000000
```

clients_uninf
```
dclients_uninf/dt = -infection1-clients_uninf*muneg+custom1-uncustom1-infect1r
Initial Value = 80000 40000000
```

CSW_AR_R
```
dCSW_AR_R/dt = +RD_CSW-hivcswr+infect2r-F2-mupos*CSW_AR_R+F6
Initial Value = 0.0
```

CSW_AR_S
```
dCSW_AR_S/dt = +CSWdet-RD_CSW-F1-mupos*CSW_AR_S+F7
Initial Value = 0.0
```

CSW_inf
```
dCSW_inf/dt = +infection2+custom5-custom6-mupos*csw_inf-hivcsw-CSWdet
Initial Value = 4000       1000000
```

CSW_uninf
```
dCSW_uninf/dt = -csw_uninf*muneg-infection2+custom3-custom4-infect2r
Initial Value = 2000 2000000
```

FEM_AR_R
```
dFEM_AR_R/dt = +RD_FEM-aidsfem2+infect4r+F2-mupos*FEM_AR_R-F6
Initial Value = 0.0
```

FEM_AR_S
```
dFEM_AR_S/dt = +FEMdet-RD_FEM+F1-mupos*FEM_AR_S-F7
Initial Value = 0.0
```

Fem_inf
```
dFem_inf/dt = -custom5+custom6+infection4-mupos*fem_inf-aidsffem-FEMdet
Initial Value = 100000     500000
```

Fem_uninf
```
dFem_uninf/dt = +population*femgr-fem_uninf*muneg-custom3+custom4-infection4-
infect4r
Initial Value = 300000     200000000
```

hivdeaths
```
dhivdeaths/dt = +hivdying
Initial Value = 0.0
```

males_inf
dmales_inf/dt = -males_inf*mupos-custom2+uncustom2+infection3-aidsmen-MENdet
Initial Value = 100000 500000

males_uninf
dmales_uninf/dt = +population*malegr-muneg*males_uninf-custom1+uncustom1-infection3-infect3r
Initial Value = 300000 200000000

MEN_AR_R
dMEN_AR_R/dt = +RD_MEN-aidsmen2+infect3r+F4-mupos*MEN_AR_R-F5
Initial Value = 0.0

MEN_AR_S
dMEN_AR_S/dt = -RD_MEN+MENdet+F3-mupos*MEN_AR_S-F8
Initial Value = 0.0

FLOWS

aidscli
Flow from clients_inf to AIDS
aidscli = aidsrate* clients_inf

aidscli2
Flow from CLI_AR_R to AIDS
aidscli2 = aidsrate * CLI_AR_R

aidsfem2
Flow from FEM_AR_R to AIDS
aidsfem2 = aidsrate * FEM_AR_R

aidsffem
Flow from Fem_inf to AIDS
aidsffem = aidsrate * Fem_inf

aidsmen
Flow from males_inf to AIDS
aidsmen = aidsrate * males_inf

aidsmen2
Flow from MEN_AR_R to AIDS
aidsmen2 = aidsrate * MEN_AR_R

CLIdet
Flow from clients_inf to CLI_AR_S
CLIdet = AR_CLI_RATE * clients_inf

CSWdet
Flow from CSW_inf to CSW_AR_S
CSWdet = AR_CSW_RATE * CSW_inf

custom1
Flow from males_uninf to clients_uninf
custom1 = cust1* males_uninf

custom2
Flow from males_inf to clients_inf
custom2 = cust1* males_inf

custom3
Flow from Fem_uninf to CSW_uninf
custom3 = cust3* Fem_uninf*exp(csw_sexcontacts/1000-1)

custom4
Flow from CSW_uninf to Fem_uninf
custom4 = cust4* CSW_uninf

custom5
Flow from Fem_inf to CSW_inf
custom5 = cust3* Fem_inf*exp(csw_sexcontacts/1000-1)

custom6
Flow from CSW_inf to Fem_inf
custom6 = cust4* CSW_inf

F1
Flow from CSW_AR_S to FEM_AR_S
F1 = cust4 * CSW_AR_S

F2
Flow from CSW_AR_R to FEM_AR_R
F2 = cust4 * CSW_AR_R

F3
Flow from CLI_AR_S to MEN_AR_S
F3 = uncust1 * CLI_AR_S

F4
Flow from CLI_AR_R to MEN_AR_R
F4 = uncust1 * CLI_AR_R

F5
Flow from MEN_AR_R to CLI_AR_R
F5 = cust1* MEN_AR_R

F6
Flow from FEM_AR_R to CSW_AR_R
F6 = cust3*exp(csw_sexcontacts/1000-1) * FEM_AR_R

F7
Flow from FEM_AR_S to CSW_AR_S
F7 = cust3*exp(csw_sexcontacts/1000-1) * FEM_AR_S

F8
Flow from MEN_AR_S to CLI_AR_S
F8 = cust1 * MEN_AR_S

FEMdet
Flow from Fem_inf to FEM_AR_S
FEMdet = AR_FEM_RATE * Fem_inf

hivcsw
Flow from CSW_inf to AIDS
hivcsw = aidsrate * CSW_inf

hivcswr
Flow from CSW_AR_R to AIDS
hivcswr = aidsrate * CSW_AR_R

hivdying
hivdying = muaids* AIDS

infect1r
Flow from clients_uninf to CLI_AR_R
infect1r = (counselcsw*res_csw1+(1-
res_csw1))*(csw_ar_r/csw)*clients_uninf*cr1*fmrisk*mw*unprot

infect2r
Flow from CSW_uninf to CSW_AR_R
infect2r = (counsel*res_cli1+ (1-res_cli1))*unprot*csw_contacts*mfrisk*mw*
CSW_uninf*(CLI_AR_R)/(clients)

infect3r
Flow from males_uninf to MEN_AR_R
infect3r = ((counselcsw*csw_ar_r*res_csw1+counsel*fem_ar_r*res_fem1)*leak*mw*(1-
male_prevalence)+stabfactor*counsel*fmrisk*mw*marrate*fem_ar_r *
res_fem1*males_uninf/(fem_inf+fem_uninf+fem_ar_r+fem_ar_s)) +((csw_ar_r*(1-
res_csw1)+fem_ar_r*(1-res_fem1))*leak*mw*(1-
male_prevalence)+stabfactor*fmrisk*mw*marrate*fem_ar_r *(1-res_fem1)*
males_uninf/(fem_inf+fem_uninf+fem_ar_r+fem_ar_s))

infect4r
Flow from Fem_uninf to FEM_AR_R
infect4r = counsel*((cli_ar_r*res_cli1+men_ar_r*res_men1)*leak*mw*(1-
female_prevalence)+marrate2 *
Fem_uninf*mfrisk*mw*stabfactor*res_men1*men_ar_r/(males_inf+males_uninf+men_ar_r+me
n_ar_s)) +((cli_ar_r*(1-res_cli1)+men_ar_r*(1-res_men1))*leak*mw*(1-
female_prevalence)+marrate2 * Fem_uninf*mfrisk*mw*stabfactor*(1-
res_men1)*men_ar_r/(males_inf+males_uninf+men_ar_r+men_ar_s))

infection1
Flow from clients_uninf to clients_inf
infection1 = clients_uninf*cr1*fmrisk*mw*unprot*(csw_inf)/(csw)

infection2
Flow from CSW_uninf to CSW_inf
infection2 = unprot*csw_contacts*mfrisk*mw*CSW_uninf*(clients_inf)/(clients)

infection3
Flow from males_uninf to males_inf
infection3 = females*(fem_prev_sus)*leak*mw*(1-
male_prevalence)+stabfactor*fmrisk*mw*marrate*fem_inf *
males_uninf/(fem_inf+fem_uninf+fem_ar_s+fem_ar_r)

infection4
Flow from Fem_uninf to Fem_inf
infection4 = males*male_prev_sus*leak*mw*(1-female_prevalence)+marrate2*
Fem_uninf*mfrisk*mw*stabfactor*(males_inf)/(males_inf+males_uninf+men_ar_s+men_ar_r
)

MENdet
Flow from males_inf to MEN_AR_S
MENdet = AR_MEN_RATE * males_inf

RD_CLI
Flow from CLI_AR_S to CLI_AR_R
RD_CLI = RDR * CLI_AR_S

RD_CSW
Flow from CSW_AR_S to CSW_AR_R
RD_CSW = RDR * CSW_AR_S

RD_FEM
Flow from FEM_AR_S to FEM_AR_R
RD_FEM = RDR * FEM_AR_S

RD_MEN
Flow from MEN_AR_S to MEN_AR_R
RD_MEN = RDR * MEN_AR_S

uncustom1
Flow from clients_uninf to males_uninf
uncustom1 = uncust1* clients_uninf

uncustom2
Flow from clients_inf to males_inf
uncustom2 = uncust1 * clients_inf

VARIABLES

aids_dead
aids_dead = round(hivdying+inf_births)

clients
clients = clients_inf+clients_uninf+cli_ar_s+cli_ar_r

CSW
CSW = CSW_inf+CSW_uninf+CSW_AR_S+CSW_AR_R

csw_contacts
csw_contacts =
cr1*(clients_inf+clients_uninf+cli_ar_s+cli_ar_r)/(csw_inf+csw_uninf+csw_ar_r+csw_a
r_r)

CSW_sexcontacts
CSW_sexcontacts = cr1*clients/csw

fem_prev_res
fem_prev_res = (csw_ar_r+fem_ar_r)/females

fem_prev_sus
fem_prev_sus = (csw_inf+fem_inf)/females

female_prevalence
female_prevalence = (csw_inf+fem_inf+csw_ar_s+csw_ar_r+fem_ar_s+fem_ar_r)/females

females
females = csw_inf+csw_uninf+fem_inf+fem_uninf+csw_ar_s+csw_ar_r+fem_ar_r+fem_ar_s

incidence
incidence =
round(infection1+infection2+infection3+infection4+infect1r+infect2r+infect3r+infect
4r+Inf_Births)

Inf_Births
Inf_Births = round(brate*vtrate*((csw_inf+fem_inf)*(azt_rate*azt_fac+(1-
azt_rate))+(csw_ar_s+fem_ar_s)*azt_fac+csw_ar_r+fem_ar_r))

male_prev_res
male_prev_res = (cli_ar_r+men_ar_r)/males

male_prev_sus
male_prev_sus = (clients_inf+males_inf)/males

male_prevalence
male_prevalence = (clients_inf+males_inf+cli_ar_s+cli_ar_r+men_ar_s+men_ar_r)/males

males
males =
clients_inf+clients_uninf+males_inf+males_uninf+cli_ar_s+cli_ar_r+men_ar_s+men_ar_r

marrate2
marrate2 =
marrate*(males_inf+males_uninf+men_ar_s+men_ar_r)/(fem_inf+fem_uninf+fem_ar_s+fem_a
r_r)

population
population = round(males+females)

preval_res
preval_res = (males*male_prev_res+females*fem_prev_res)/(males+females)

prevalence
prevalence = (males*male_prevalence+females*female_prevalence)/(males+females)

res_cli
res_cli = (0.01+RD_CLI)/(RD_CLI+infect1r+0.01)

res_csw
res_csw = (0.01+RD_CSW)/(RD_CSW+infect2r+0.01)

res_fem
res_fem = (0.01+RD_FEM)/(RD_FEM+infect4r+0.01)

res_men
res_men = (0.01+RD_MEN)/(RD_MEN+infect3r+0.01)

uninf_births
uninf_births = round(brate*females-inf_births)

DEFINED VALUES (parameters that can be changed by interventions)

AR_CLI_RATE
AR_CLI_RATE = 0

AR_CSW_RATE
AR_CSW_RATE = 0

AR_FEM_RATE
AR_FEM_RATE = 0

AR_MEN_RATE
AR_MEN_RATE = 0

azt_rate
azt_rate = 0

mw
mw = 1

unprot
unprot = unprot1

INDEPENDENT EVENTS (interventions)

mwanza_inter
Non-periodic triggers at:
startyear5
Actions:
mw = mwanza1;

HAART_pop
Non-periodic triggers at:
startyear4
Actions:
AR_CLI_RATE = AR_CLI_RATE1;
AR_FEM_RATE=AR_FEM_RATE1;
AR_MEN_RATE = AR_MEN_RATE1;

HAART_CSW
Non-periodic triggers at:
startyear3
Actions:
AR_CSW_RATE = AR_CSW_RATE1;

CSW_inter
Non-periodic triggers at:
startyear2
Actions:
unprot = unprot2;

MCT_inter
Non-periodic triggers at:
startyear1
Actions:
azt_rate = azt_rate1;

DELAYS

res_cli1
Delay = 1.5
Initial Value = 1
Maximum Delay = 2

res_csw1
Delay = 1.5
Initial Value = 1
Maximum Delay = 2

res_fem1
Delay = 1.5
Initial Value = 1
Maximum Delay = 2

res_men1
Delay = 1.5
Initial Value = 1
Maximum Delay = 2

PARAMETERS

t	35	
aidsrate	0.154	
AR_CLI_RATE1	0.5	
AR_CSW_RATE1	0.5	
AR_FEM_RATE1	0.5	
AR_MEN_RATE1	0.5	
azt_fac	0.5	
azt_rate1	1	
brate	0.15	
counsel	1	
counselcsw	1	
cr1	40	
cust1	0.1	0.025
cust3	0.005	
cust4	0.25	
femgr	0.03	
fmrisk	0.005	
leak	0.2	0.1
malegr	0.03	
marrate	0.1	
mfrisk	0.01	
muaids	1	
muneg	0.03	
mupos	0.03	
mwanza1	0.7	
RDR	0.25	
stabfactor	5	
startyear1	35	
startyear2	35	
startyear3	35	
startyear4	35	
startyear5	35	

```
uncust1             0.1
unprot1             0.67
unprot2             0.25
vtrate              0.33
```

Table 1a. Incident HIV cases in India

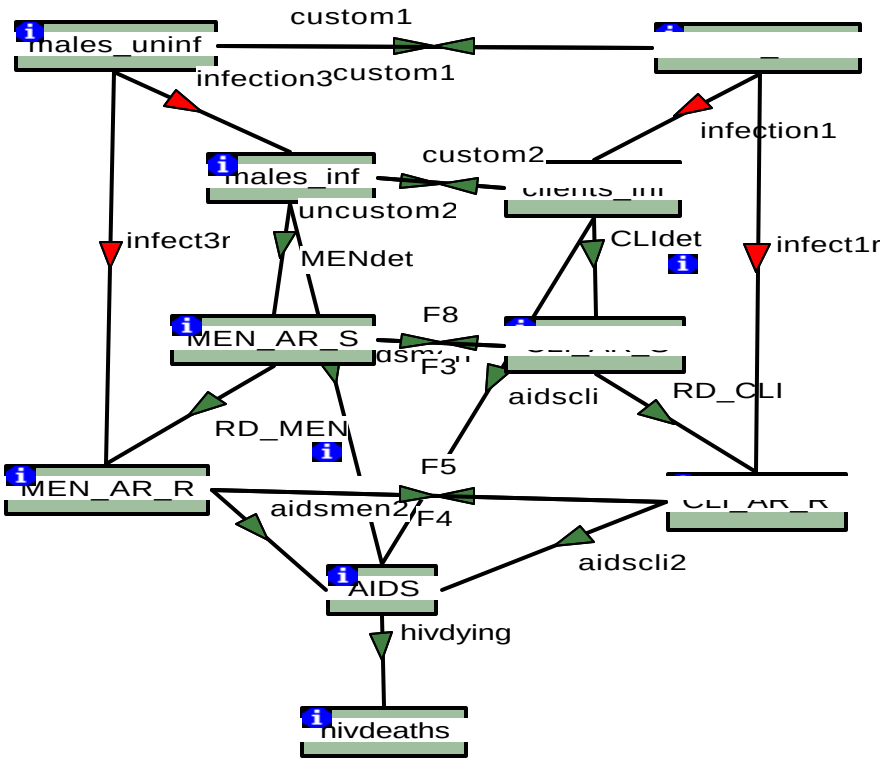
year	No intervention	CSW intervention	Mwanza intervention	HAARTall +counselling	HAART all	HAART CSW + counselling	HAART CSW	MCT intervention
1998	2341287	2341287	2341287	2341287	2341287	2341287	2341287	2341287
1999	2653131	2653131	2653114	2653114	2653114	2653114	2653114	2653131
2000	3181869	3181869	3181849	3181849	3181849	3181849	3181849	3181869
2001	3760519	3760519	3760501	3760501	3760501	3760501	3760501	3760519
2002	4292349	4292349	4292334	4292334	4292334	4292334	4292334	4292349
2003	4738583	4738583	4738571	4738571	4738571	4738571	4738571	4738583
2004	5101156	2583948	3388928	3466478	3583140	4305099	4364412	4976860
2005	5399884	2489140	3419354	2783051	3162494	4142250	4307739	5256760
2006	5655665	2402240	3458317	2473938	3151398	4082891	4361638	5493940
2007	5884038	2319303	3501081	2422936	3373683	4103619	4472878	5704164
2008	6095044	2238581	3546106	2554292	3717628	4165730	4613852	5897636
2009	6294889	2159472	3593005	2817390	4111568	4257601	4769987	6080666
2010	6487445	2081893	3641804	3167398	4512122	4369245	4934315	6257178
2011	6675214	2005963	3692654	3565858	4895558	4495092	5103715	6429683
2012	6859901	1931856	3745743	3982788	5251069	4632114	5276824	6599864
2013	7042734	1859727	3801252	4397217	5575757	4778809	5453025	6768899
2014	7224645	1789702	3859346	4796361	5871113	4934494	5632006	6937659
2015	7406367	1721861	3920173	5173709	6140732	5098852	5813585	7106811
2016	7588510	1656253	3983863	5527120	6388926	5271674	5997642	7276890
2017	7771587	1592896	4050532	5857218	6619973	5452735	6184096	7448340
2018	7956041	1531781	4120282	6166172	6837748	5641747	6372902	7621537
2019	8142268	1472885	4193206	6456854	7045595	5838356	6564045	7796808
2020	8330615	1416171	4269389	6732295	7246315	6042159	6757539	7974445
2021	8521402	1361591	4348907	6995393	7442214	6252721	6953428	8154711
2022	8714920	1309089	4431832	7248765	7635170	6469602	7151780	8337847
2023	8911439	1258605	4518234	7494695	7826711	6692370	7352685	8524078
2024	9111208	1210076	4608179	7735145	8018074	6920621	7556259	8713615
2025	9314466	1163438	4701732	7971779	8210267	7153984	7762628	8906658
2026	9521439	1118625	4798957	8206002	8404113	7392137	7971938	9103402
2027	9732340	1075570	4899921	8439002	8600293	7634807	8184348	9304031
2028	9947376	1034210	5004688	8671785	8799374	7881773	8400022	9508725
2029	10166749	994479	5113327	8905207	9001831	8132864	8619140	9717664
2030	10390651	956313	5225907	9140006	9208076	8387964	8841880	9931018
2031	10619274	919653	5342499	9376816	9418460	8647003	9068433	10148958
2032	10852803	884437	5463179	9616198	9633296	8909953	9298989	10371653
2033	11091421	850610	5588023	9858642	9852862	9176831	9533742	10599269

Table 1b. Incident HIV cases in Botswana

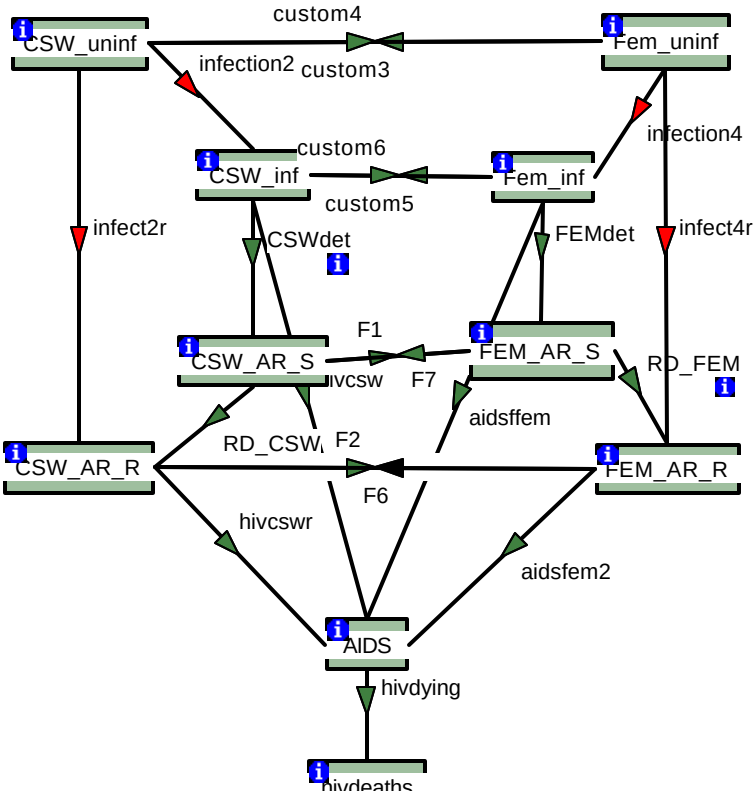
year	No intervention	CSW intervention	Mwanza intervention	HAARTall +counselling	HAART all	HAART CSW + counselling	HAART CSW	MCT intervention
1998	48304	48304	48304	48304	48304	48304	48304	48304
1999	50852	50852	50852	50852	50852	50852	50852	50852
2000	52336	52336	52336	52336	52336	52336	52336	52336
2001	53243	53243	53243	53243	53243	53243	53243	53243
2002	53795	53795	53795	53795	53795	53795	53795	53795
2003	54066	54066	54066	54066	54066	54066	54066	54066
2004	54101	45430	38682	36204	37392	50325	50577	51365
2005	53938	44954	37887	27542	31324	48478	49140	51175
2006	53608	44447	37122	23968	30654	47447	48491	50821
2007	53135	43924	36392	23398	32642	46771	48092	50331
2008	52539	43392	35700	24675	35735	46221	47738	49724
2009	51842	42853	35048	27092	39051	45714	47353	49022
2010	51058	42314	34434	30137	42123	45211	46917	48239
2011	50200	41774	33858	33403	44737	44693	46431	47389
2012	49284	41236	33319	36595	46828	44157	45896	46487
2013	48317	40701	32816	39518	48407	43604	45320	45541
2014	47313	40171	32346	42072	49523	43034	44709	44562
2015	46278	39645	31908	44224	50237	42450	44069	43556
2016	45221	39125	31500	45985	50612	41855	43402	42533
2017	44150	38610	31121	47384	50706	41253	42715	41500
2018	43068	38101	30769	48458	50570	40642	42009	40459
2019	41984	37597	30443	49245	50245	40026	41289	39418
2020	40898	37100	30140	49784	49769	39407	40557	38379
2021	39819	36610	29861	50104	49169	38785	39816	37348
2022	38746	36125	29603	50237	48473	38160	39069	36325
2023	37686	35647	29364	50205	47700	37535	38316	35316
2024	36639	35176	29146	50032	46865	36912	37562	34321
2025	35608	34711	28947	49738	45982	36289	36808	33342
2026	34594	34253	28764	49338	45065	35667	36054	32382
2027	33599	33801	28597	48847	44120	35049	35303	31440
2028	32625	33357	28446	48279	43158	34434	34555	30519
2029	31671	32918	28311	47644	42184	33821	33814	29619
2030	30740	32487	28190	46954	41203	33214	33078	28741
2031	29831	32061	28081	46216	40222	32612	32349	27884
2032	28944	31642	27986	45439	39243	32014	31628	27049
2033	28081	31230	27902	44630	38270	31422	30916	26237

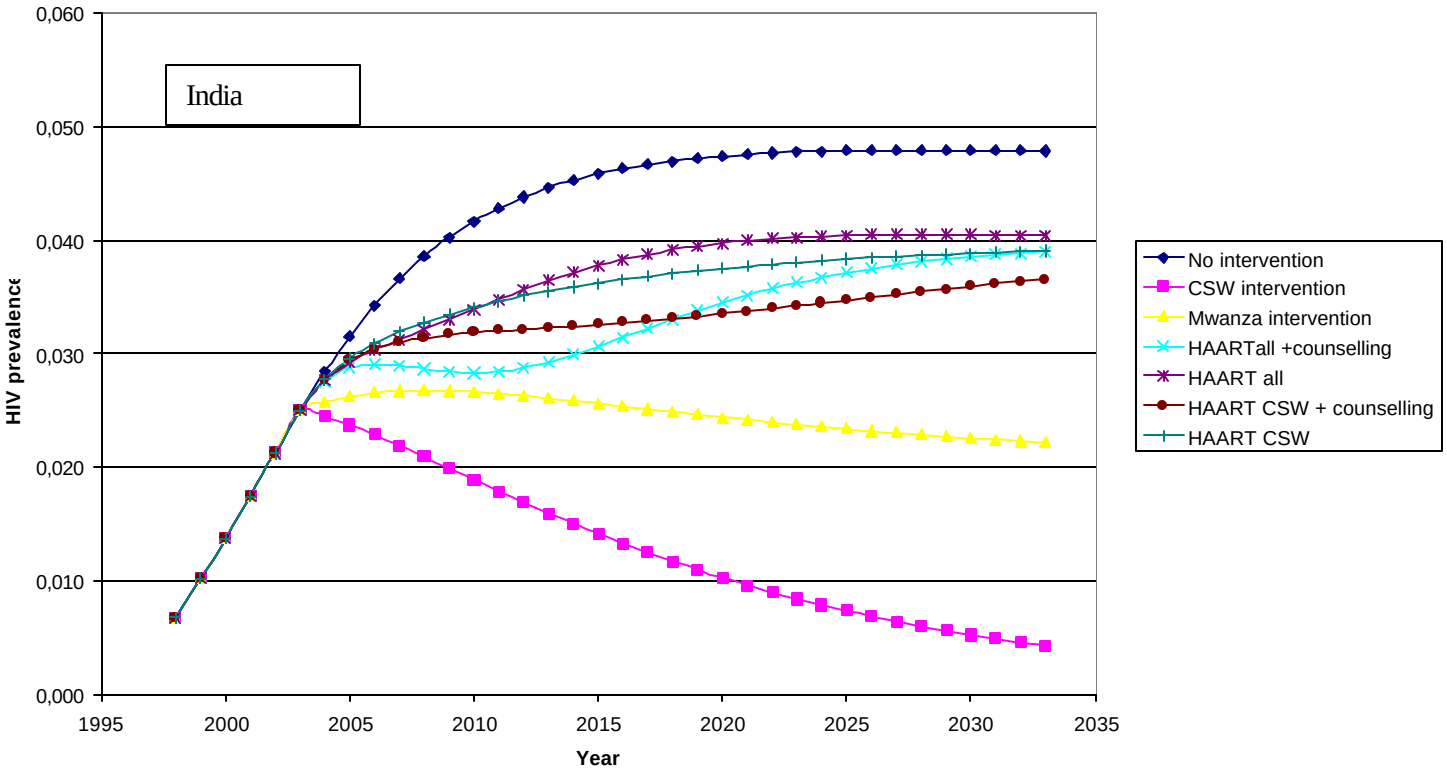
Figure 1. Schematic representation of ModelMaker HIV model. Rectangular boxes represent model compartments. Arrows represent flows (transitions between stats, e.g. seroconversions).

MEN



WOMEN




India
HIV prevalence
0,060
0,050
0,040
0,030
0,020
0,010
0,000
1995
2000
2005
2010
2015
2020
2025
2030
2035
Year
No intervention
CSW intervention
Mwanza intervention
HAARTall +counselling
HAART all
HAART CSW + counselling
HAART CSW

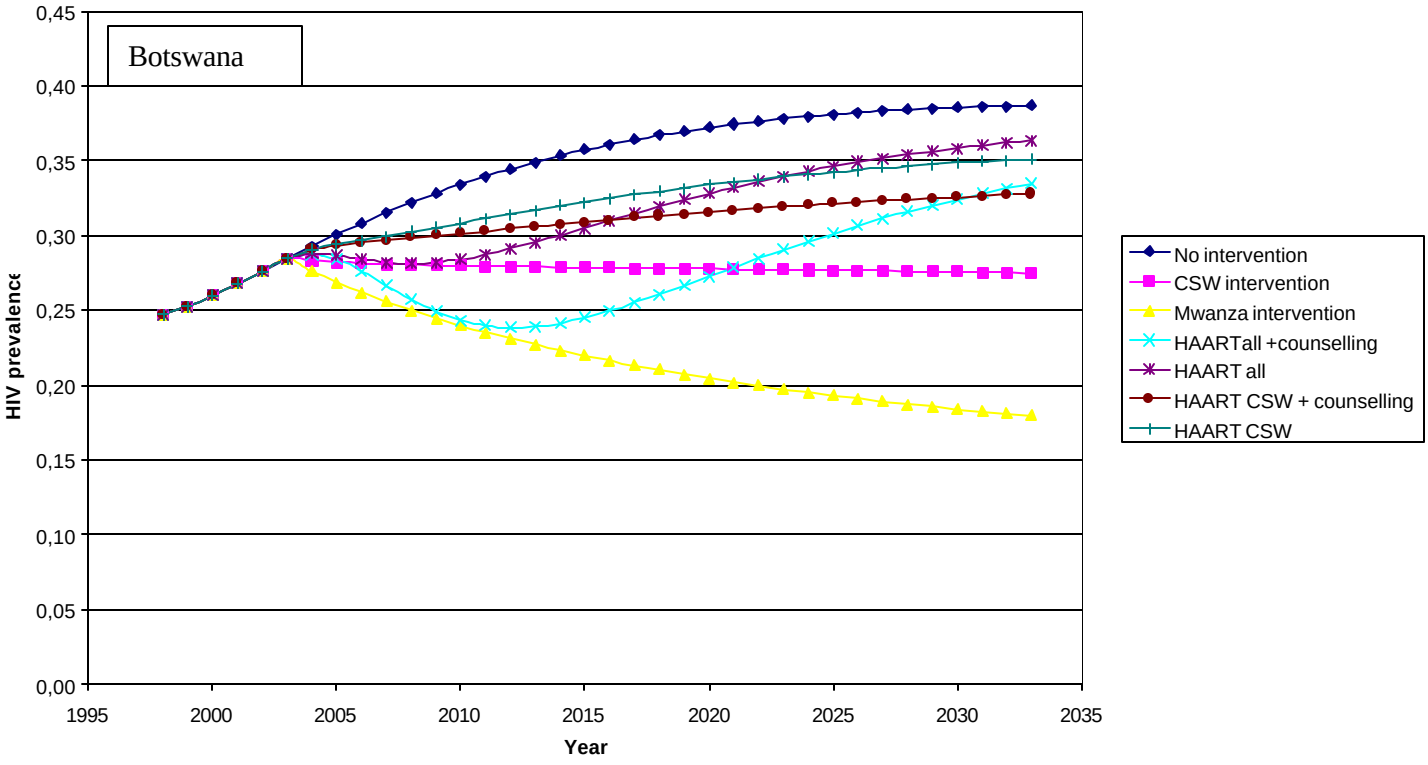
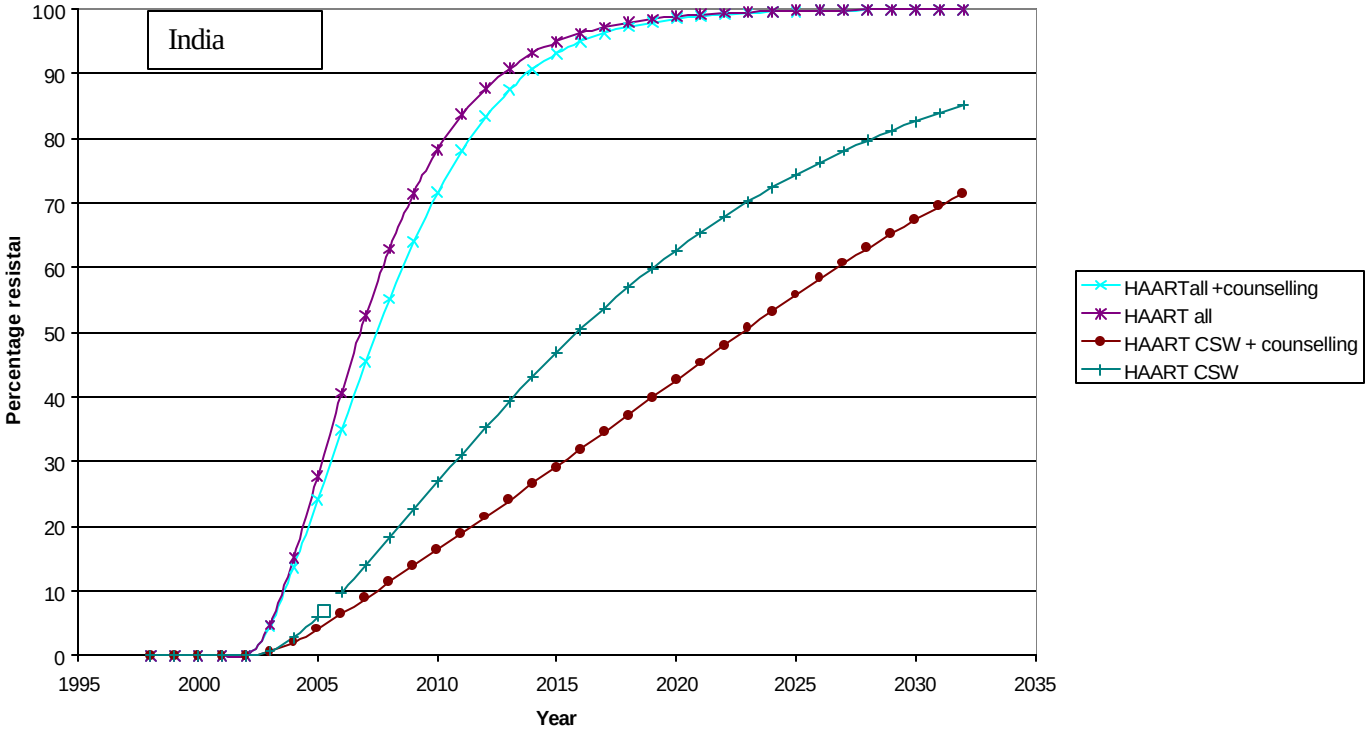

Botswana
HIV prevalence
0,45
0,40
0,35
0,30
0,25
0,20
0,15
0,10
0,05
0,00
1995
2000
2005
2010
2015
2020
2025
2030
2035
Year
No intervention
CSW intervention
Mwanza intervention
HAARTall +counselling
HAART all
HAART CSW + counselling
HAART CSW

Figure 3. The development of drug resistance in response to HAART treatment



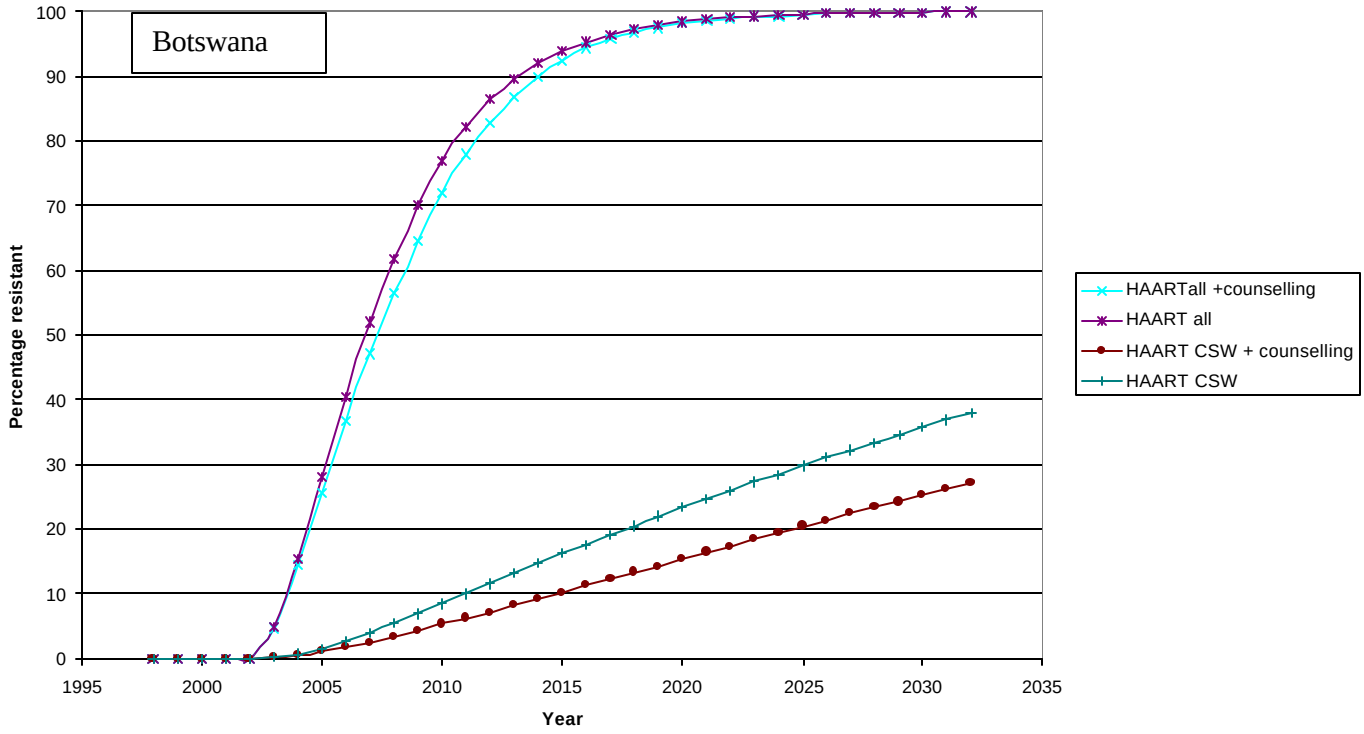
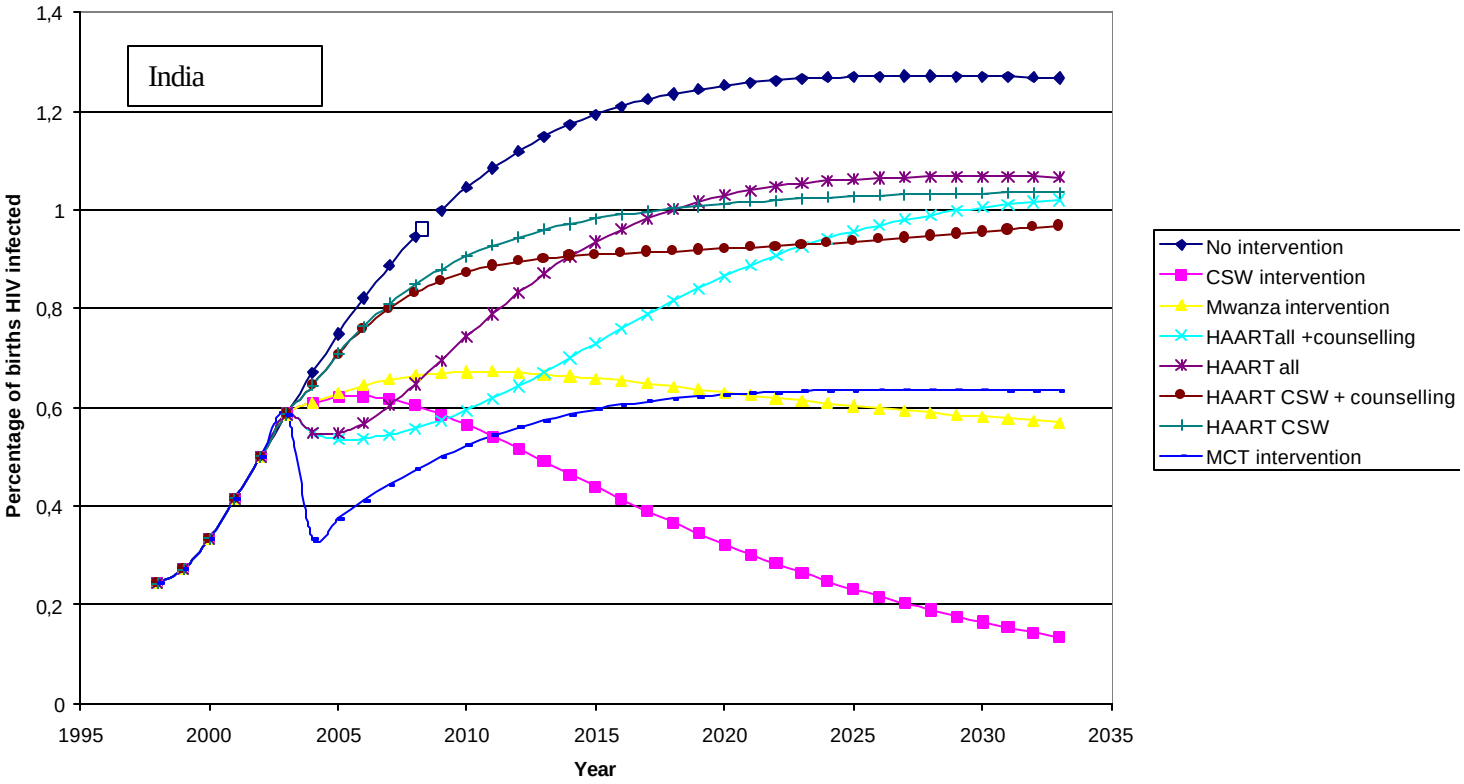


Figure 4. Mother-to-child transmission



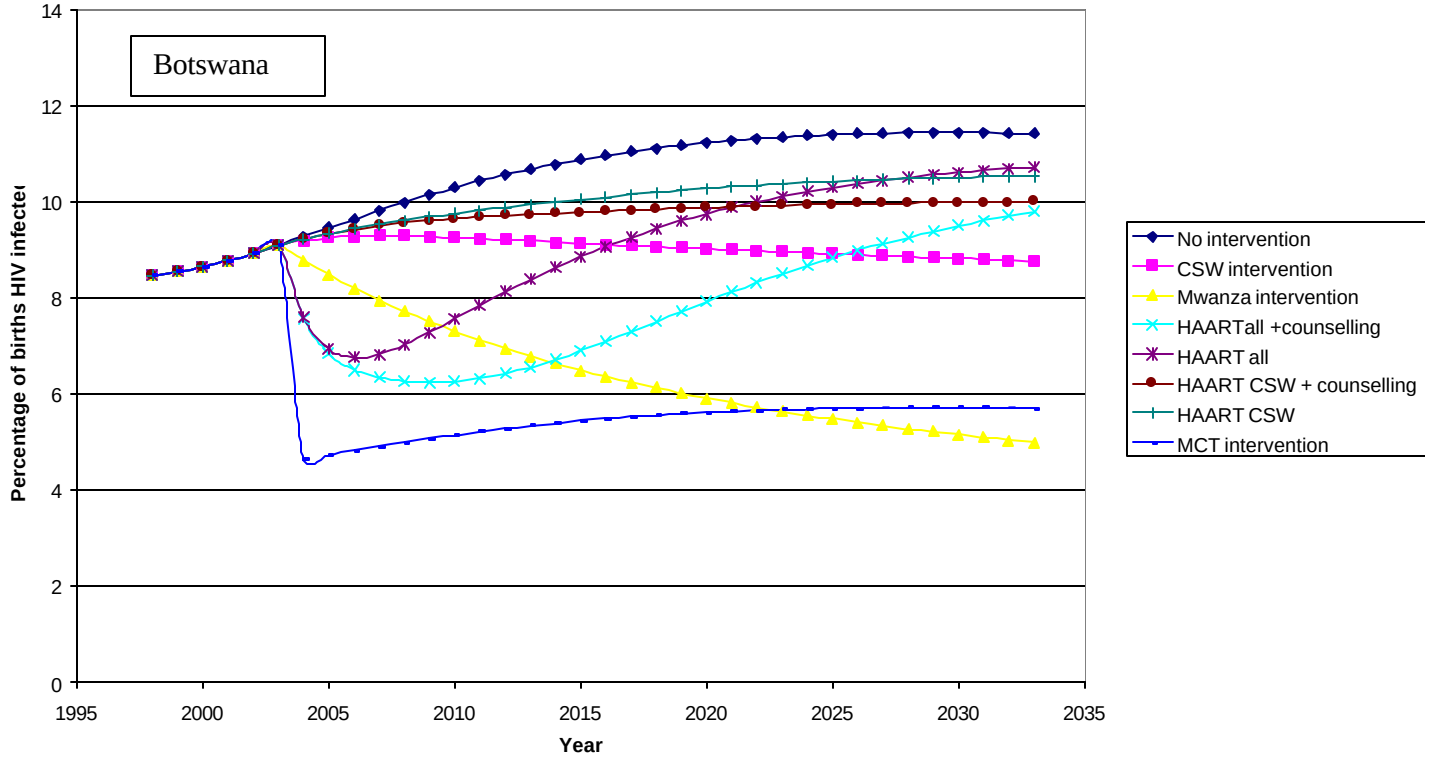
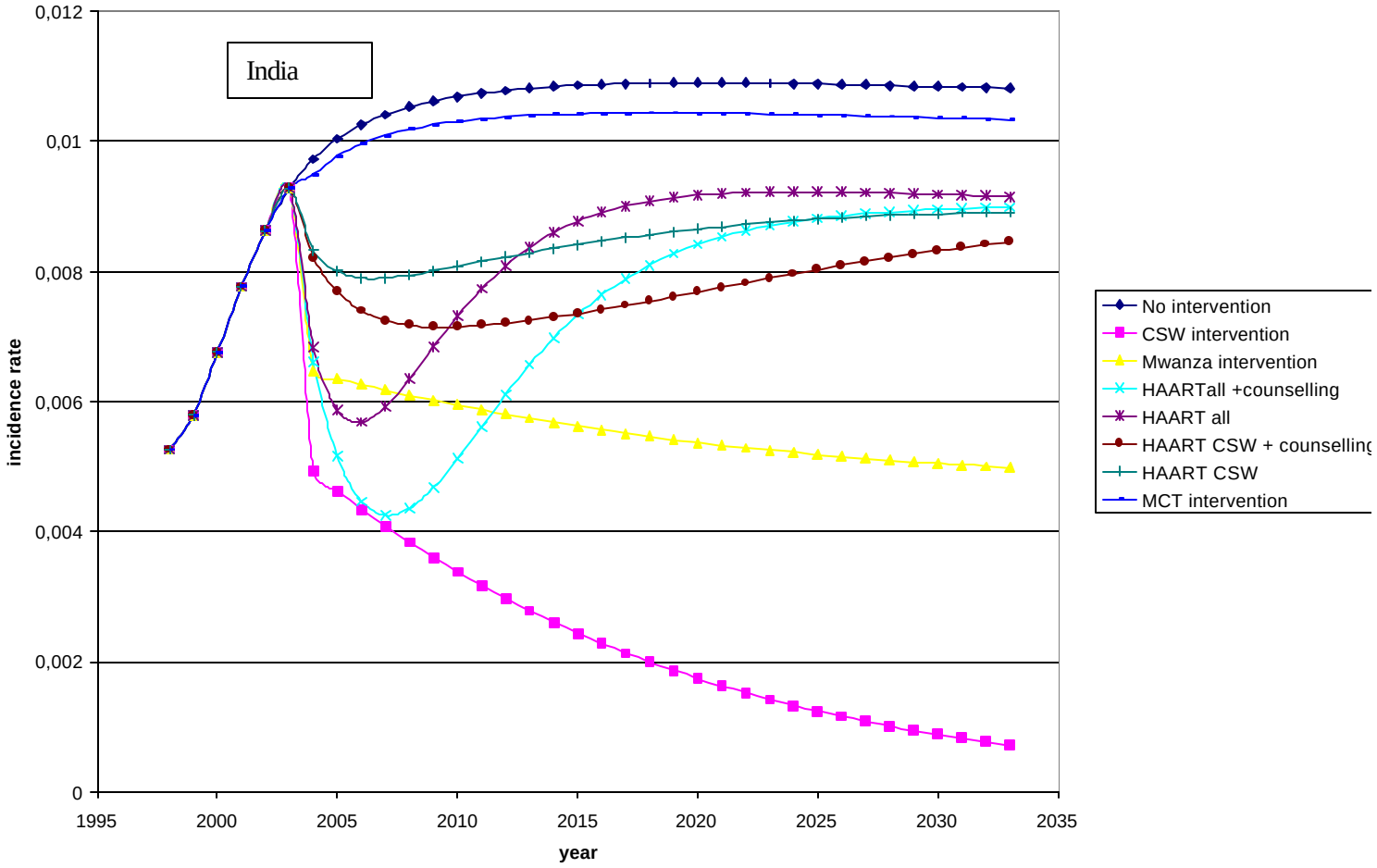


Figure5. HIV incidence rate among adults



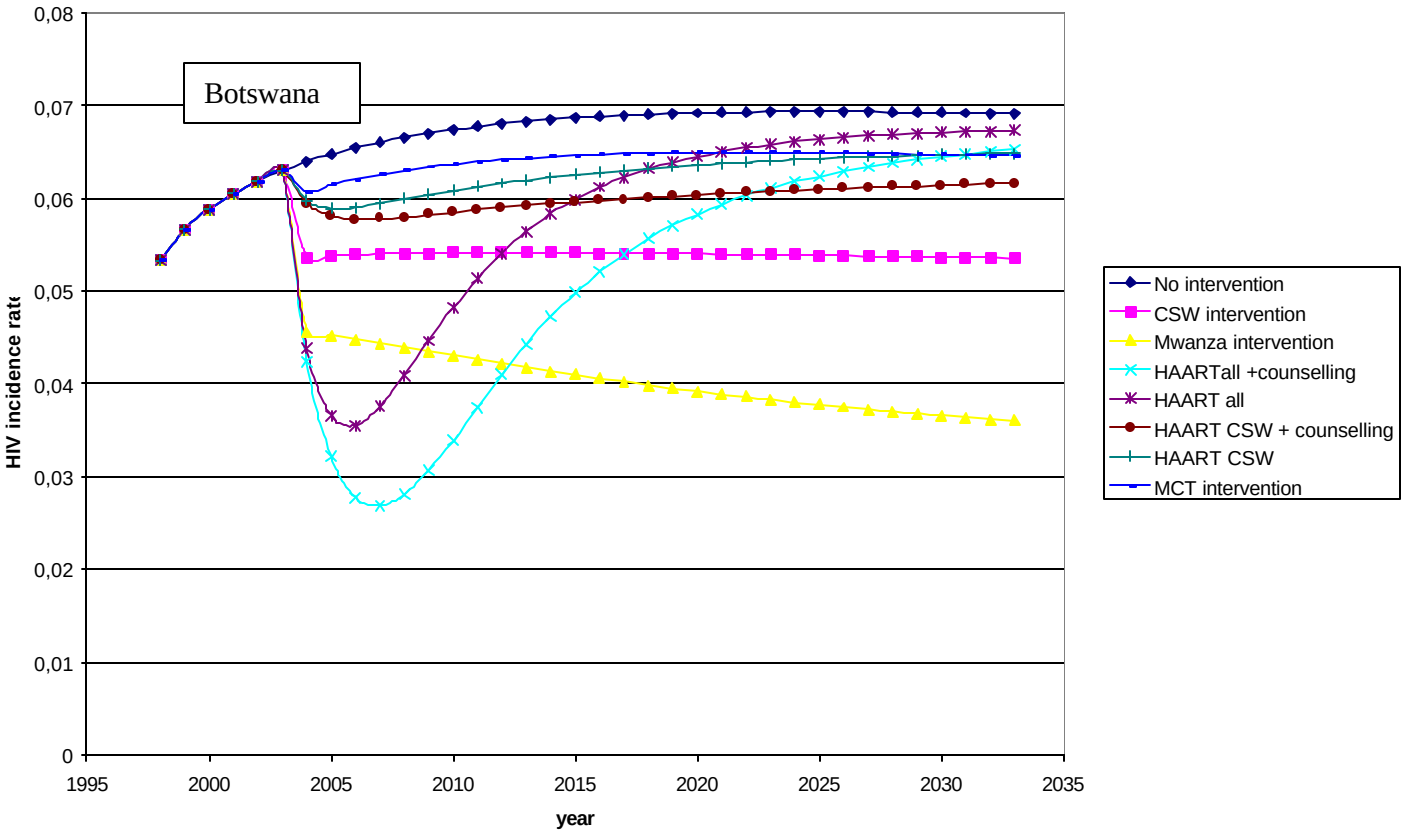
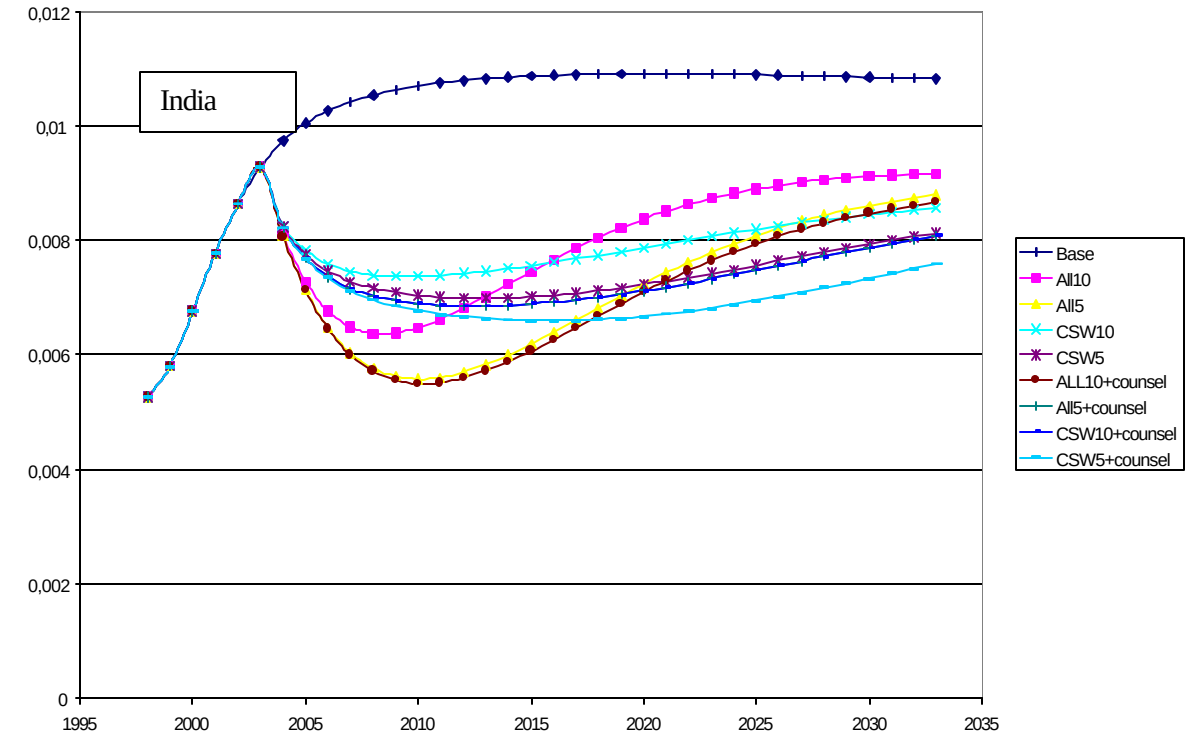


Figure 6. Sensitivity analysis of rate of developing resistance to HAART on incidence rate (adult+child infections)/adult population. All HAART intervention rerun with 5% and 10% annual rate of developing resistance



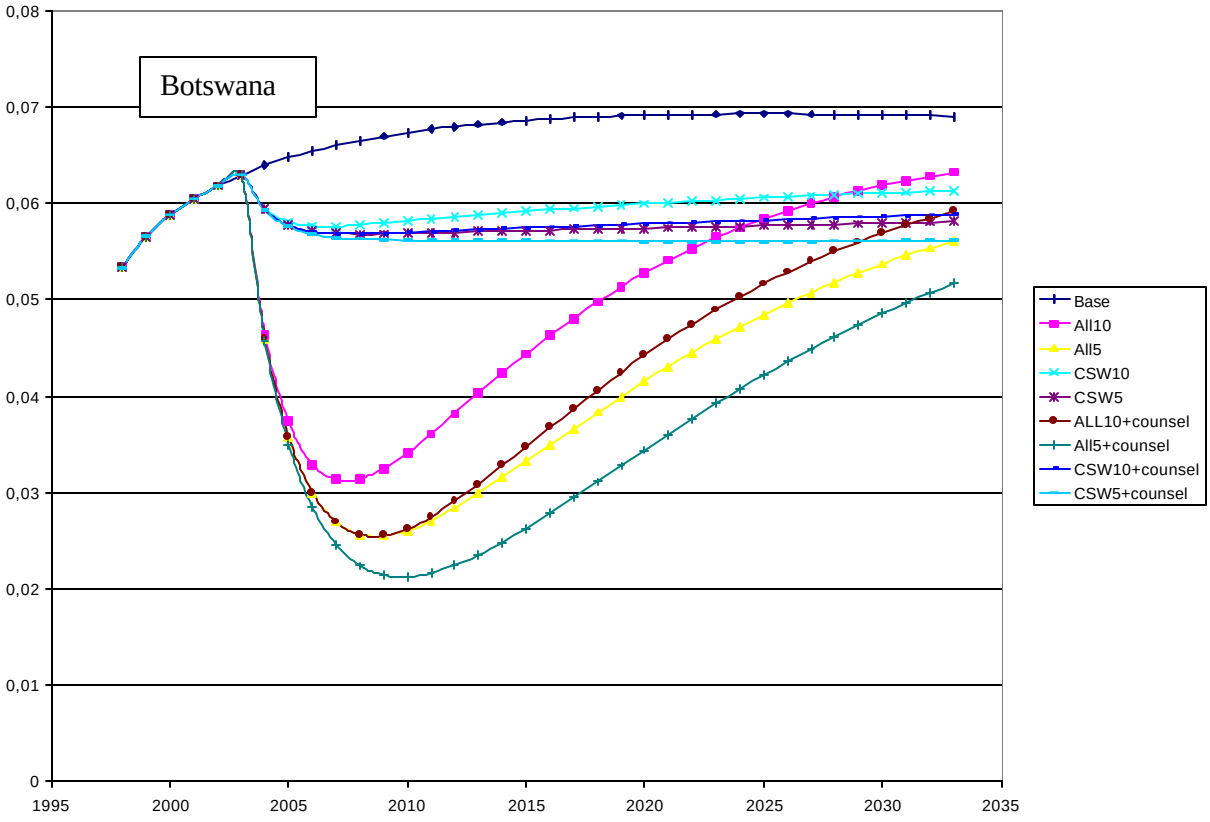
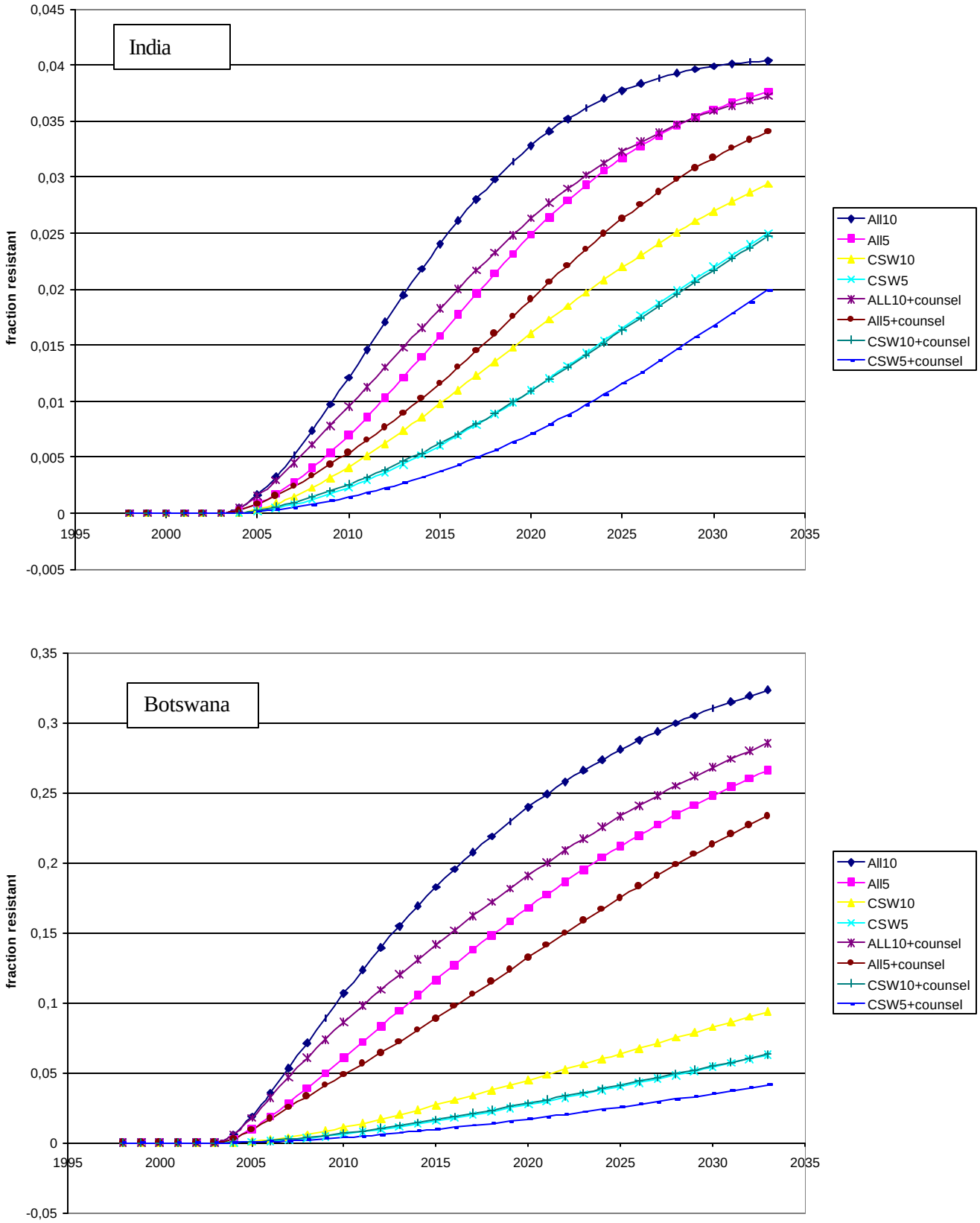


Figure 7. Sensitivity analysis of the development of the prevalence of resistance to different assumptions (5% and 10% annually) of the rate of developing resistance to HAART.

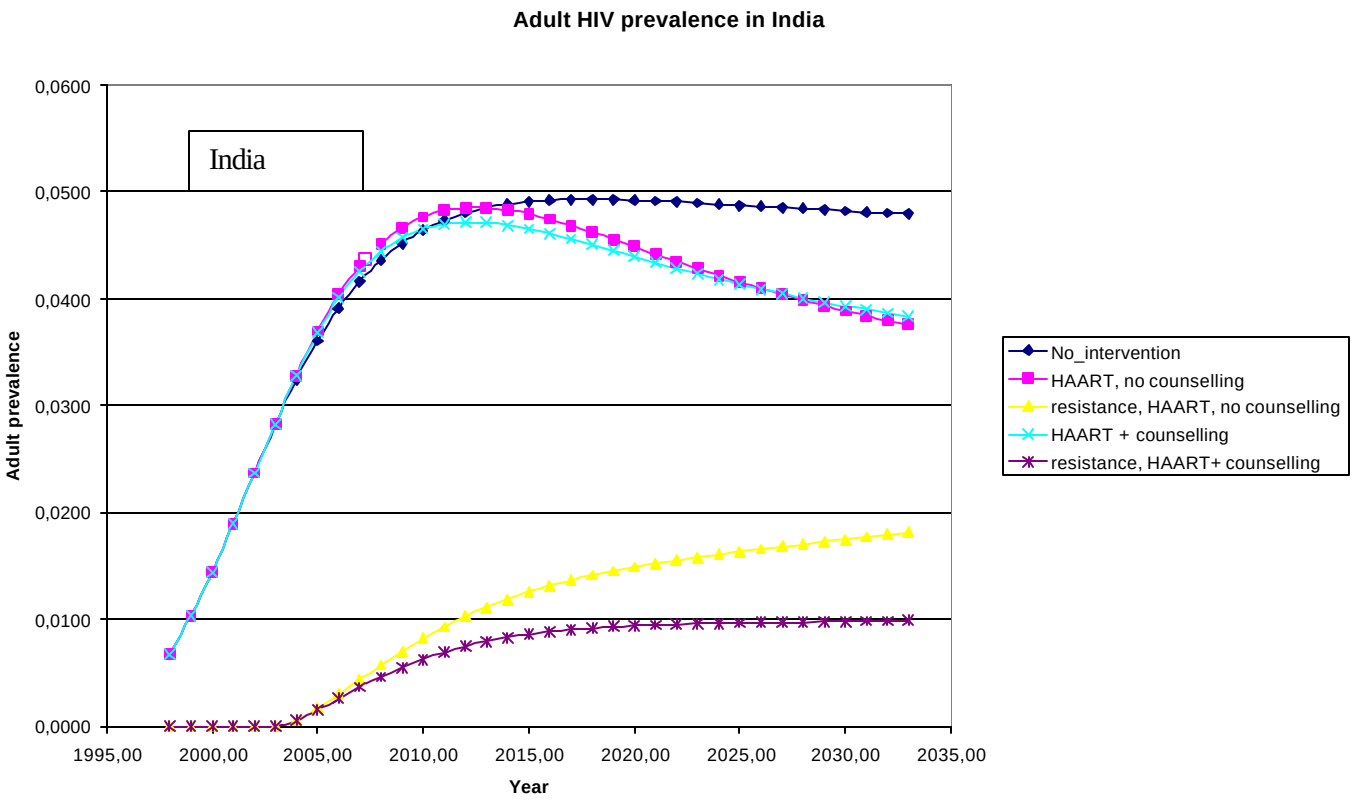


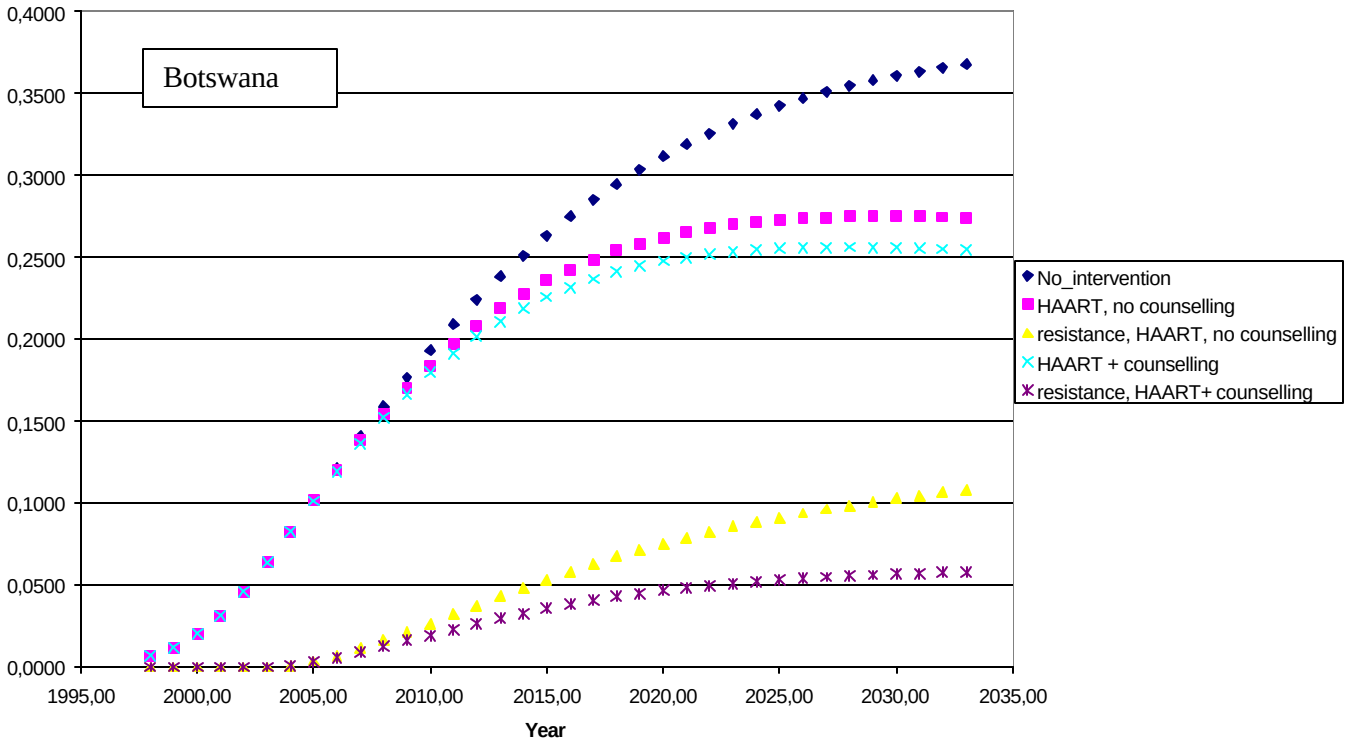
Appendix II. Late stage HAART only.

In the main section of the paper we assumed that all HIV positive individuals were eligible for HAART therapy. However, a more modest scheme might be to treat only those with already low CD4 (e.g. <350 or < 500) counts, or already symptomatic. In order to address the potential impact of such a scheme, we changed our model to have two different stages of pre-AIDS HIV disease. The early stage and the late stage, where the latter comprises (on average) the last 2 years of pre-AIDS HIV infection.

We only considered HAART for all schemes, as these are the ones under debate (HAART for CSW only schemes appear not to have taken on widely). We again looked at an average duration to developing resistance of 4 years. The assumed rate of recruitment was 1/year. Thus, 2 out of 3 HIV positives are ultimately recruited into the HAART regime before developing AIDS.

The general conclusion appears to be that, because of more restrictive use, resistance develops slower. Also, we assumed that because they are recruited into HAART with low CD4 counts, the survival of patients once resistance develops is also much shorter, so that they presumably have less opportunity to spread resistant strains. By 2035 in the absence of the “counseling” effect, only approximately 50% of all HIV positives are HAART resistant and in Botswana this is even a little less. Also, because resistance takes longer to develop, the reduction in prevalence persists for longer than in regimes that target all HIV positives. However, a crucial assumption is that infectiousness is constant. If late stage patients are more infectious because of high viral loads, this scenario may be too optimistic.


Adult HIV prevalence in India
India
0,0600
0,0500
0,0400
0,0300
0,0200
0,0100
0,0000
Adult prevalence
1995,00
2000,00
2005,00
2010,00
2015,00
2020,00
2025,00
2030,00
2035,00
Year
No_intervention
HAART, no counselling
resistance, HAART, no counselling
HAART + counselling
resistance, HAART+ counselling


Adult HIV prevalence in Botswana
Botswana
0,4000
0,3500
0,3000
0,2500
0,2000
0,1500
0,1000
0,0500
0,0000
1995,00
2000,00
2005,00
2010,00
2015,00
2020,00
2025,00
2030,00
2035,00
Year
No_intervention
HAART, no counselling
resistance, HAART, no counselling
HAART + counselling
resistance, HAART+ counselling

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