A deterministic model to assess the impact of HAART in Sub-Saharan countries. An application to Botswana.

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Abstract

Recently news about the severe acute respiratory syndrome and avian flu viruses has caused significant panic in many countries. These viruses, for Europe still very much a theoretical danger obscure the much more immediate danger of the human immune deficiency virus/acquired immune deficiency syndrome, HIV/AIDS.
We develop a deterministic compartmental simulation model to assess the impact of highly active antiretroviral therapy (HAART) and other interventions in sub-Saharan countries. We calibrate this model using data from Botswana. We also include a cost-effectiveness analysis. To our knowledge our model is the first deterministic model to include all the important factors of the HIV/AIDS transmission and a dynamic calculation of the life expectancy.
The model shows that HAART alone, at the current implementation level, cannot significantly impact the number of HIV/AIDS infected individuals in the long term. The association of HAART with the treatment of other sexually transmitted diseases (STDs) shows the maximal cost-effectiveness under the current model settings.

Introduction

The human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) epidemic is today one of the world's major health care challenges. Despite increase in funding and progress in antiretroviral therapy, the epidemic continues to outpace the global response. The total number of infected people has exceeded 40 million people in 2005. (UNAIDS, 2005) Despite the fact that the steepest increase occurred in East/Central Asia and Eastern Europe, Sub-Saharan Africa remains the worst affected region with almost 26 million people living with HIV in 2005. An even more alarming situation is that women are increasingly infected: in 2004 17,5 million of women were estimated to be infected, from them 13,5 million are living in sub-Saharan countries. 76% of young people (15-24 years) living with HIV in Sub Saharan Africa are female. (UNAIDS, 2004) (Kotlin *et al*, 2004).

Recently, access to antiretroviral (ARV) drugs has been made possible in sub-Saharan countries through non governmental organizations (NGOs) and international organizations such as the world health organization (WHO) The WHO "3 by 5" initiative –Treat 3 million people living with HIV by 2005- is reflecting the efforts of the international community in this direction. (WHO, 2002), (WHO, 2001a)
The aim of the present work is to evaluate the impact of recently implemented interventions against HIV/AIDS in developing countries by means of a deterministic compartmental simulation model. We especially focus on assessing the impact of the highly active antiretroviral therapies (HAART) in the heterosexual population living in Botswana which is plagued by a high HIV/AIDS prevalence (WHO, 2004) and one of the most advanced sub-Saharan countries in the fight against this disease.

Although mathematical modeling has been largely used in the past to describe and understand the HIV infection transmission mechanisms (epidemiology models), the role of policy models in the final decision process remains unclear (Rauner *et al*, 2001), (Kahn *et al*, 1994), (Kahn *et al*,1998), (Stover, 2000). Causes of the reluctance from decision makers to use policy models that can be found in the literature include a lack of realism to describe the epidemiological situation (Koopman, 2004) and/or a lack of model standardization (WHO, 1989).

Objectives

Programs have been put in place in 2002 to massively implement antiretroviral therapy in developing countries, (Fleshman, 2005), (principally WHO 3 x 5 and the United States President's Emergency Plan for AIDS Relief (PEPFAR)) . Although such programs show compassion to people living with HIV, controversies about the 3 x 5 Initiative current performance has raised (Susman, 2004) Therefore, our first objective is to assess the global impact of HAART in fighting against HIV/AIDS.
The role of policy models in supporting decision remains unclear (Rauner et al, 2001,Stover, 2000). In a recent review (Viladent, unpublished), we identified that most of the HIV/AIDS policy models focus on one or two epidemiologically important factors only such as, behavioural changes (Brandeau et al, 1991), number of sex acts (Rehle et al, 1998), the migration process (Bernstein et al, 1998) , the role of STD and pair formation (Van der Ploeg, 1998) , the role of sexually transmitted diseases (STD's) and prostitution (Nagelkerke et al,

2002) , the core group influence on the epidemic spread (Bailey, 1993) . Therefore, we argue that the major reason for policy makers sulking models in their decision process is due to a lack of model realism and standardization. In an effort to overcome this objection we design a realistic model which incorporates all the critical points in HIV transmission.

Dynamic Hypotheses

Hypothesis 1: The infection rate increases with the number of infected individuals who become rapidly infectious (Figure 1). Infectious individuals can contaminate their partner(s) through sexual contacts.

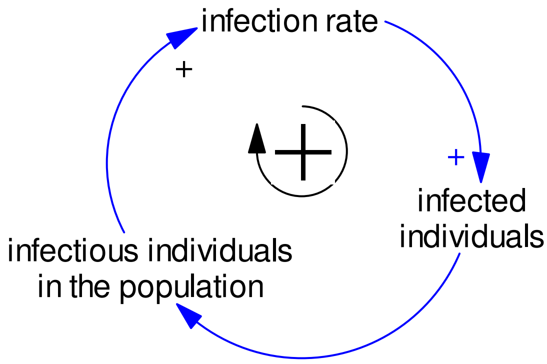


Figure 1

Hypothesis 2: A growing number of infected child bearers lead to an increasing number of infected children. The combination of the infected children who will all die before reaching puberty and the number of infected pregnant females who die before delivering their babies lead to a population decrease (Figure 2).

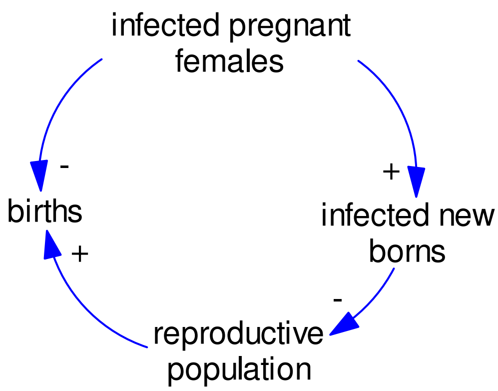


Figure 2

Hypothesis 3: Male mobile workers (truckers, miners) are infected by female sex workers (FSW) who, in turn infect the females in the general population, either urban or rural, through regular and/ or casual and/ or concurrent partnerships. Ultimately, due to the high prevalence among the rurban female groups, the mobile male workers get infected from the rurban females and bring the infection to the female sex workers who work in the vicinity of the mines and truck stops. Consequently, we posit that the mobile worker group and the female sex workers group are the major drivers of the epidemics in Botswana (Figure 3).

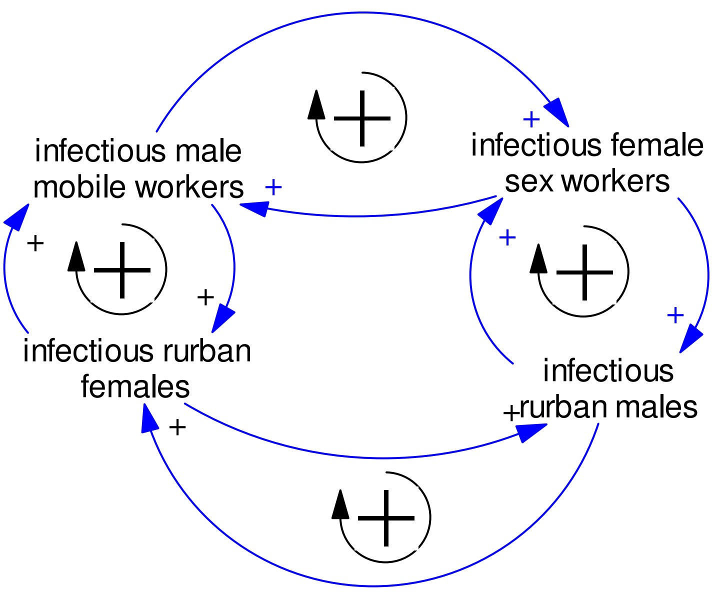


Figure 3

Hypothesis 4: HAART has a double effect:

1-It reduces the proportion of infectious individuals by reducing the viral loads in blood and body fluids. This first effect is beneficial as it reduces the infection rate
2-It leads to an increase of the number of infected due to the life prolonging effect of the drugs. Additionally, infected treated individuals
who were not participating to sexual transmission prior to HAART treatment may participate again to sexual transmission

due to the quality of life improvement effect of the drugs. These individuals may become potentially infectious in case of poor treatment observance and/or if their virus strain becomes resistant to the drugs. (Figure 4)

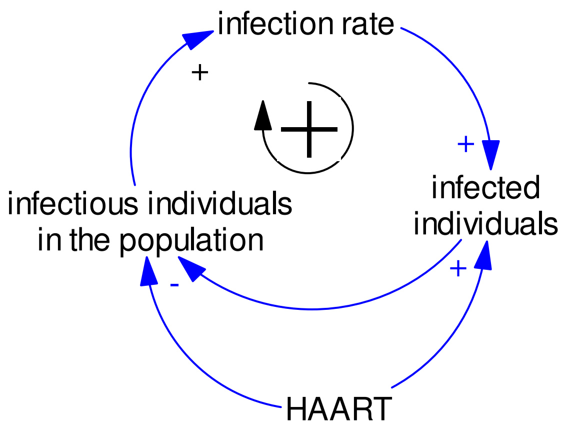


Figure 4

Note than antiretroviral therapy can also be given to HIV positive child bearers prior to delivery in order to reduce the risk of transmission to the new born (Prevention of Mother To Child Transmission-PMTCT-) (Figure 5). Infected young children can also be treated but do not reach puberty.

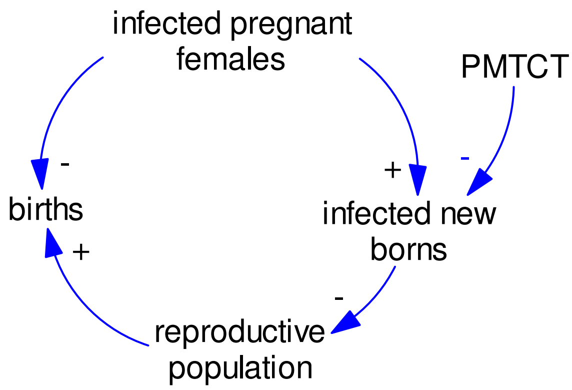


Figure 5

Model description

We designed a two-sex model, based on the above mentioned hypotheses, including a highly infected core group (the female sex workers), a bridge group (the male mobile workers) and a

non core group consisting of the males and females in the general population. We do not differentiate between rural and urban populations regarding modes and levels of HIV infections.
The male and female groups in the general population are divided into 7 age groups, 0-1, 2-5, 6-14, 15-24, 25-49, 50-79, 80+ (not represented in figure 6). Additional groups are included: the female sex workers (FSW) and the mobile male workers (MMW), each of theses two is divided into two age classes: 15-24 and 25-49. We include four disease stages for infected people.
The contaminations between the various groups take place as represented in figure 3. Other STD's are included as an aggravating factor in HIV transmission.
We assume the transmission through blood transfusion and men having sex with men negligible.

Disease stages
Infected individuals can exit their disease stage due to death from HIV or non HIV associated causes or to enter the following stage. We included 4 stages in according to WHO HIV/AIDS classification.
The lengths of stay in each stage without treatment are as follows:
Stage 1: 36 months
Stage 2: 36 months
Stage 3: 24 months
Stage 4: 8 months

The duration of the infectiousness is driven by the sojourn time in each HIV/AIDS stage. We assumed that only stage 1 and stage 2 individuals participate to the spread of infection. Stage 3 and 4 individuals are supposed to be so ill and stigmatized that we assumed they do not have sexual intercourses therefore they are not participating to infection transmission any longer.

Although the infectivity level has been described to be higher during the early days after the infection, we assume no significant difference in infectivity level between stage 1 and 2.

Sexual relationship patterns and infection risk
We assume the women between 15 and 24 have sexual intercourses with men of all ages *(Glynn et al, 2001, Gregson et al, 2002)* while women aged between 25 and 49 are assumed to only have sexual relationships with men of their age class.
We assume female sex workers between 15 and 49 have sexual relationships with both rurban and mobile men workers aged between15 to 49.

Casual, regular and concurrent sexual partnerships have been included in the infection matrices. Few publications report the number and type of sexual relationships, we based our assumptions for rurban men and women on findings from Gregson et al (Gregson et al, 2002). The number of casual intercourses is assumed to be high as it has been described that some women, although not regular sex workers, seek for casual intercourses in return for commodities in Botswana (Mac Donald, 1996).

Infectivity risk

In order to calculate the infection risk for each group we considered on one hand high risk individuals: FSW or mobile men workers and high risk contacts (unprotected sexual intercourses with casual and/or concurrent partners) and on the other hand, low risk individuals: rurban men and women and low risk contacts (protected sexual intercourses). We also consider as mentioned by Kaplan (Kaplan, 1990) that assuming a constant HIV infectivity per partner is reasonable, while assuming a constant infectivity per sex act is not. The first contacts largely influence the overall infectivity risk. Therefore to quantify the infectivity risk per partnership, β_p , we use the double binomial equation from Rottingen and Garnett: (Rottingen et al, 2002)

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

where

f , is the fraction of individuals in the high-risk group, and

$\beta_a^{\,h}$ and $\beta_a^{\,l}$, the transmission probabilities in the high-risk and low-risk groups, respectively and

n, the number of acts per partnership

Other important factors in HIV transmission

Other sexually transmitted diseases

The presence of other STDs, especially the diseases which cause genital ulceration such as herpes and syphilis, have been reported to significantly contribute to HIV propagation *(Lurie et al, 2003, Flemming et al, 1999, Wasserheit, 1992)*

Condom use
Based on the study from Mc Donald *(Mac Donald, 1996)* and assuming that female condoms are not used, we place males in control of the male condom use. We assume a very low level of condom use in Botswana , however we assume an increase in condom usage from the late 90'. President Mogae took office in 1998 and initiate policies to tackle the epidemics. As we assume the campaigns mainly targeted to youngest people, we assume a different condom use among the two age classes (10% by male 15-24 and 2% by male 25-49). We include a contamination risk (10%) despite a condom use. This risk depends of the condom quality and the way of using it.
We assume no condom use in regular relationships.
We assume no impact of condom use on birth rates.

Life Expectancy
We include a dynamic determination of the life expectancy. We built-in the dynamic life expectancy tables according to the WHO life expectancy determination method (WHO, 2001b) Therefore, the life expectancy is dependant of the level of HIV/AIDS prevalence and of the interventions against it.

The model is developed on Vensim © software (Ventana Systems,inc.
Harvard, MA, USA)

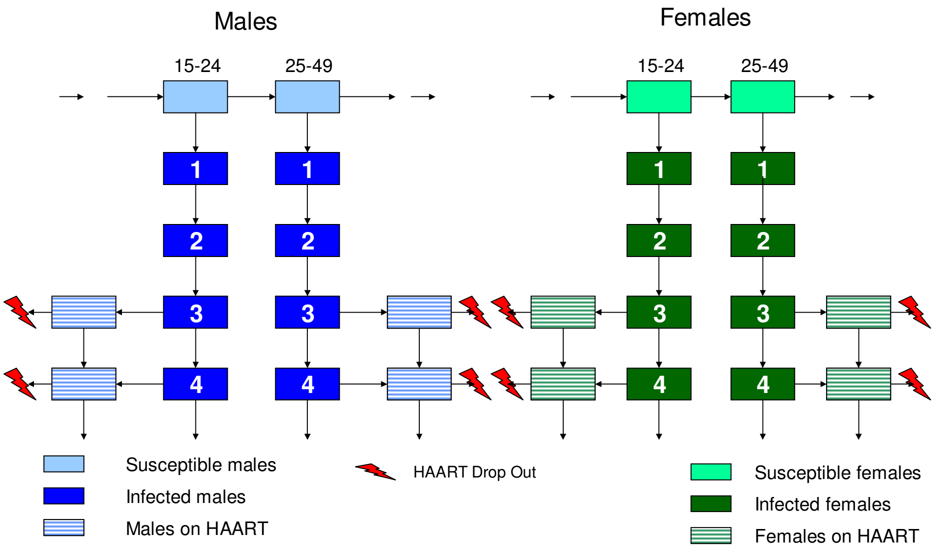


Figure 6 Schematic representation of the stock and flow model

ARV therapy

We set a switch to simulate the initiation of HAART in Botswana in 2002, as the first HAART implementation was initiated during that year in Botswana.

We assume the pace of new HAART treatments at 18,500 /year as it is indicated in the literature). The total number of treated individual reached 37,000 end of 2003 (Fleshman, 2005).

The starting regimen for adult men and non pregnant women is zidovudine + lamivudine + efavirenz . The regimen for pregnant women and children below 5 is zidovudine + lamivudine+nevirapine. The government provides ARV therapy free of charge in the public sector *(WHO, 2005)*

Based on recent studies (*William et al, 2005), (Severe et al, 2005) w*e made the following assumptions:

- Patients did not receive ARV therapy prior to receive HAART
- HAART treatment is equally distributed between men and women
- Each group of individuals has access to HAART except female sex workers
- Only stage 3 and 4 patients received HAART
- 2% of pregnant women in average receive an efficient PMCT and give birth to non-infected children from 1999 onwards. We assume the same rate treatment rate for infected new-born than for adults
- Drop out rate : 5%
- Negligible virus resistance against HAART

Prevention of mother-to-child-transmission (PMTCT) and HAART treatment for new borns

We assume that an average of 2% of pregnant women in stage 1 and 2 receive efficient PMCT and give birth to non-infected children from 1999 onwards. We also assume that infected new-born are treated with HAART at the same rate than adults.

Survival time with HAART

	Survival time (months) **Adults**	Survival time (months) **New born/Infants**
Stage 1	NA	15
Stage 2	NA	10
Stage 3	60	5
Stage 4	20	2

Table 1: Survival time (months) under HAART treatment

Drop-out rate

Due to the compliance system that Botswana put in place (counseling and "buddy" fellows *(Rollnick, 2002)*, we assume that only 5% (monthly rate: 0.004) of the patients under HAART drop out each year either voluntarily or because of virologic failure (virus resistance to therapy).

Cost Effectiveness Analysis (CEA)

We performed a generalized CEA (GCEA) according to the WHO recommendations (WHO, 2003) which means comparing the outcome of interventions versus no intervention. For each scenario we generated the life expectancy at the age of 1, the number of Disability-Adjusted Life Years (DALY) averted and the cost per DALY averted. We use the DALY formulas, without discounting and age weights, as provided by WHO (WHO, 2001b)

DALY = YLL + YLD where YLL is the number of years of life lost due to the disease and YLD, the number of years lived with the disease (WHO, 2001b) .

YLL= N*L where N is the number of deaths and L is the standard life expectancy at age of death in years

YLLs are generated thanks to the dynamic life expectancy determination included in the model.

YLD = I*DW*L where I is the number of incident cases, DW = disability weight and L is the average duration of the case until death in the case of AIDS. We used a DW of 0.6. The determination of the total cost for each intervention follows the WHO recommendation, except for cost discounting in the current model settings.(WHO, 2003).

Model settings

Initial time: 0 = year 1990
Final setting: 360 = year 2020
Time step =1 month
Initial population size: 1,220,000 (source CIA)

Model calibration
In order to calibrate the model we first fit the model to literature data. A 0/1 switch is placed in order to run the model with two conditions:
1-as if the HIV/AIDS epidemic never existed, in order to check the population growth
2-with the HIV/AIDS epidemic, assuming a 2.7 % HIV prevalence in 1990 in Botswana (Brocklehurst, private communication)

Scenarios testing

These scenarios describe the current HAART treatment or the implementation of other interventions to supplement the current HAART treatment. To render the outcome comparable, all the policies are initiated in 2002. Scenario outputs are compared to no action taken (no HAART therapy)

Scenario 1 : Current HAART treatment: 18,000 new treatment per year

Scenario 2: HAART treatments: 36,000 new treatment per year, all other conditions remaining

Scenario 3: Sexually Transmitted Diseases (STDs) reduction
Progressive reduction of STDs among the general population from 30% to 5%, other conditions similar to scenario 1.

Scenario 4: ABC Program ("Abstain, Be Faithful or Condomize")
This program leads to a progressive reduction of casual sexual relationships among the general population and progressive increased condom usage follow a media campaign which takes place for 2 consecutive years. We assume government provides condoms free to the public at a quantity of 1,000,000 per year during 4 years from the beginning of the media campaign.

Scenario 5 : HAART provided to female sex workers
The HAART treatment is provided at the same rate than for the general population

Preliminary results

a-Number of infected individuals and infection risk

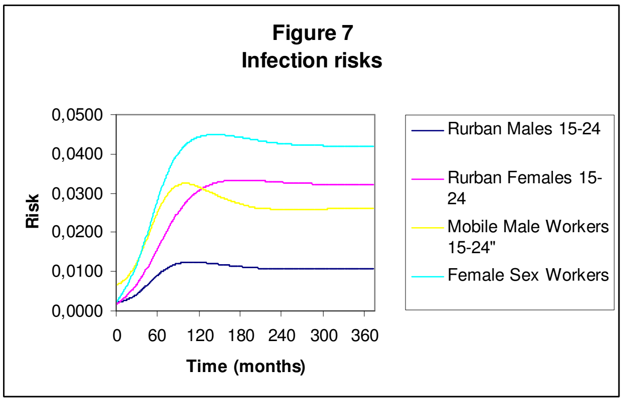


Figure 7
Infection risks

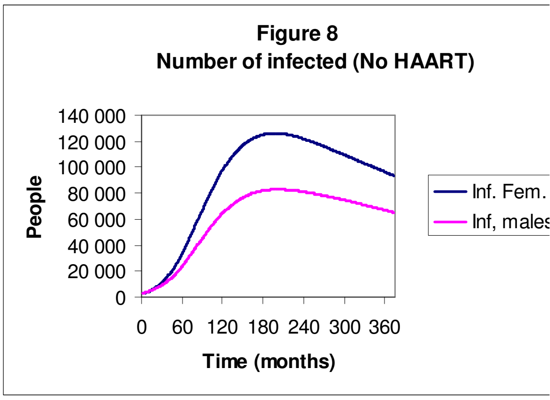


Figure 8
Number of infected (No HAART)

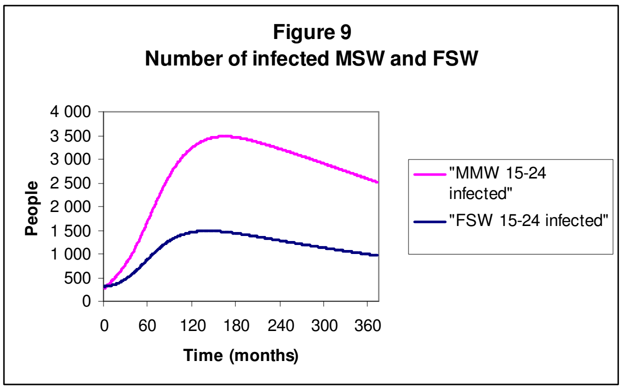


Figure 9
Number of infected MSW and FSW

b-Scenario outputs

1-Epidemiological impacts

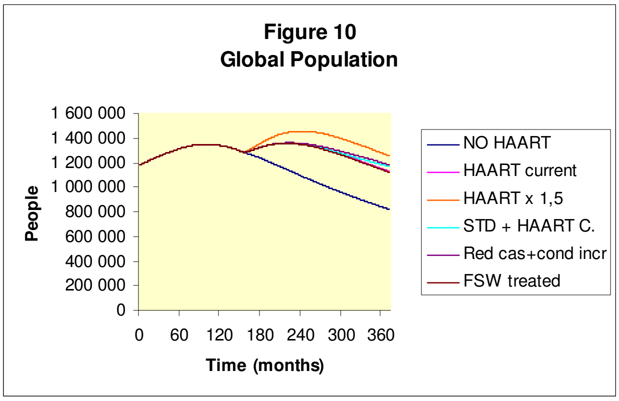


Figure 10
Global Population

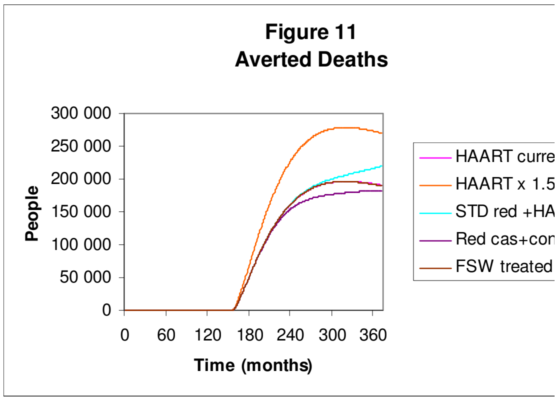


Figure 11
Averted Deaths

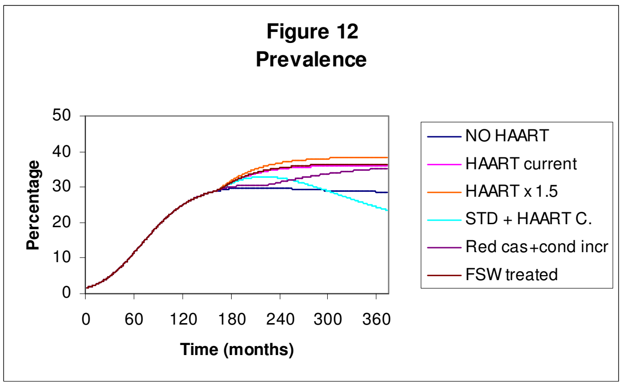


Figure 12
Prevalence

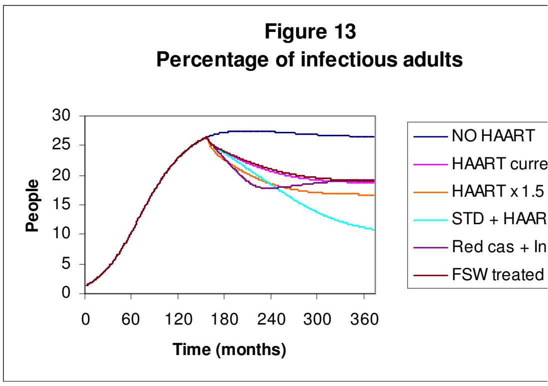
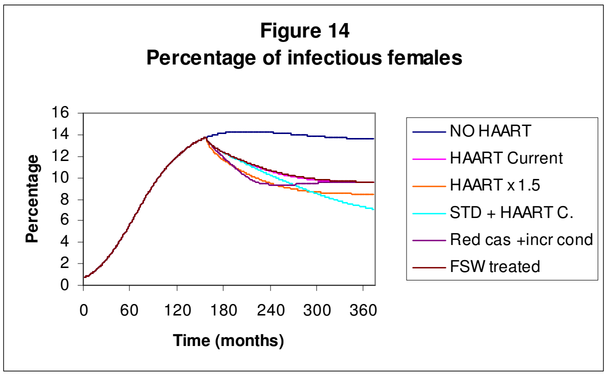
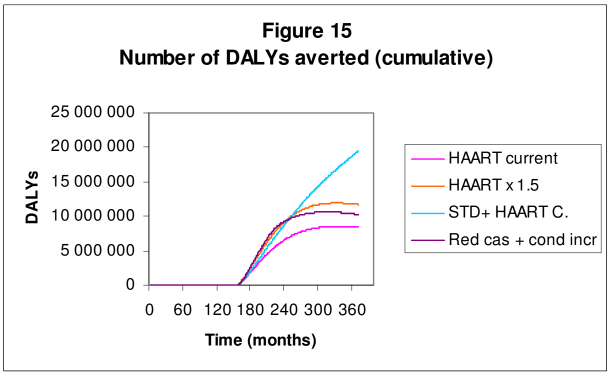
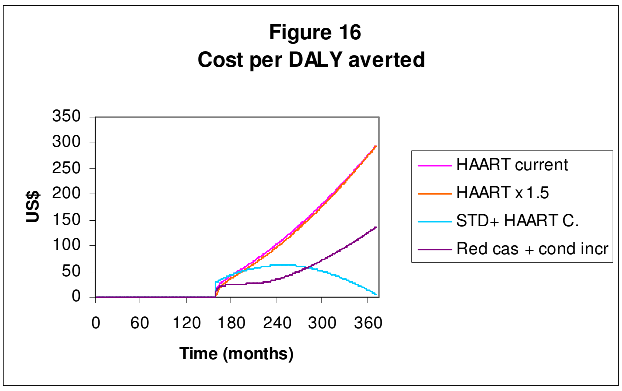


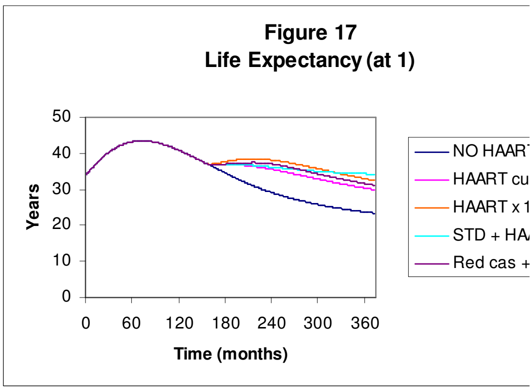
Figure 13
Percentage of infectious adults



2-Socio-economical impacts







Legend :

HAART current = Scenario 1
HAART x 1,5 = Scenario 2
STD + HAART C. = Scenario 3
Red cas + cond incr. = Scenario 4
FSW treated = Scenario 5

Discussion and conclusion

In a previous review we described all the significant factors driving the HIV/AIDS epidemics. These factors are the bridge groups (such as migrant workers), core and non-core groups (Hadeler, 1995), (Piot, 1987), (Kreiss et al, 1986), rate of partner change (May et al, 1987), concurrent sexual partnership (Ghani et al, 2000), variability of infectivity during the course of infection (Leynaert et al, 1998), and the amplifying effect of other STDs (Wasserheit, 1992), (Van der Ploeg et al, 1998). In an attempt to design a standard model, we include all these factors in our model. The model outputs allow to verify all the hypotheses. The infection risks among the various groups, without HAART treatment, initially increases with the number of infected individuals in the corresponding groups (Hypothesis 1) (Figures 7,8 and 9). Figure 7 shows the high level of infection risk within the female sex workers group and the initially high (during the first decade of the epidemic) risk among the mobile sex worker group. This confirms the hypothesis 3. Figure 7 also shows high risks among the rurban female group in the second and third decades. The infection risks reach a plateau around the 16th year while the number of infected decreases (Figure 8 and 9), this is due to the fact that, with no interventions, the global population decreases (Hypothesis 2) (Figure 10 , NO HAART curve), thus the number of infected, while the infection risk remains elevated.
Hypothesis
Concerning the socio-economic part, to our knowledge our model is the first deterministic model which incorporates a dynamic life expectancy determination allowing a dynamic analysis of the cost-effectiveness. This method takes into consideration Fox-Rushby's recommendations for DALYs calculation when interventions last more than one year (Fox-Rushby, 2001). We also provide details on our method to calculate the DALYs in order to avoid the lack of transparency in DALYs calculation which has been described to appear in several publications (Fox-Rushby, 2001).

The scenario outputs show the impact of various interventions on various epidemiological (Figures 10 to14) and on socio-economical parameters (Figures 15 to 17).

With the current model setting it appears that HAART alone, even when the rate of treatment is increased, cannot tackle the HIV/epidemics nor is cost effective. In fact, HAART allows the infected individuals to live longer and for some to resume risky sexual behaviours and infect more people thus maintaining a high number of infectious individuals in the population (this verifies the hypothesis 4)(Figure 13). The combination of HAART treatment and the treatment of the other sexually transmitted diseases shows the best results in term of clinical results (Figure 12, 13, 14) (although not showing the best efficiency to prevent deaths from HIV, Figure 11) and cost effectiveness (Figure 15 & 16) and allows a population stabilization in the 50 years horizon (results not shown here). Therefore, it seems from our preliminary results, that the treatment of other sexually transmitted diseases in the general population contribute to a reduction of HIV infection risk, however, due the high prevalence of HIV/AIDS in Botswana, it seems that sexually transmitted disease treatment alone is not sufficient (results not shown here). Therefore it seems that the treatment of other sexually transmitted diseases cannot be considered as the universal solution to stop the HIV epidemics. This contradicts previous findings (Oster, 2005). ABC programmes (Abstain, Be faithful or Condomize) have also been promoted as a remedy against HIV/AIDS epidemic (Green, 2003). Indeed an ABC campaign shows in our model a certain efficiency and a cost-effectiveness in the short term but because we assume only a transitory positive effect of the media campaign and free of charge condoms on risky behaviours, the beneficial effect of the campaign on the population parameters disappears after few years. Multiple ABC campaigns conducted with few years of interval may be cost-effective but this scenario was not tested here. Prostitution is a criminal offence in Botswana, so we do not expect that HAART treatment will be provided to female sex workers, however we include such scenario in our model. The result is that the treatment of the female sex workers does not seem to bring any improvement versus the current treatment in the general population, therefore we did not perform a CE analysis for this scenario.

We believe our model allows the testing of several combination of various interventions. The strategy consisting of mixing several combinations seems to be the only appropriate way to tackle HIV/epidemics in high prevalence setting.

We shortly envision a full model validation and a generalization to test the intervention impact in isolation or in combination in countries with lower HIV/AIDS prevalence.

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