System Dynamic Simulation of Treatment Policies to Address Colliding Epidemics of Tuberculosis, Drug Resistant Tuberculosis, and injecting drug users driven HIV in Russia

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Abstract: The explosive increase in the number of people infected with tuberculosis, multi drug resistant tuberculosis (MDRTB), and injecting drug users (IDU) HIV/AIDS has become a serious public health challenge in Russia. The World Health Organization is recommending policies including simultaneous use of highly active antiretroviral therapy (HAART) to treat HIV/AIDS and second line drugs to treat MDRTB.

We developed a System Dynamics simulation model to represent the dynamic transmission of tuberculosis, MDRTB, and HIV. The model simulated scenarios regarding MDRTB cure rate and HAART coverage, that is the HIV/AIDS population covered by HAART.

The results over a 20 year period indicate that reduction in tuberculosis and HIV associated tuberculosis deaths would be negligible for HAART coverage up to 50%. The reduction is only significant for HAART coverage of 70% and above. Similarly, high MDRTB cure rate reduces significantly deaths from tuberculosis and MDRTB and this reduction is more important as the HAART coverage is increased.

Key words: Health Service, HIV, Tuberculosis, HAART, System Dynamics, Russia.

Introduction

The Russian Federation has experienced marked increases in both the prevalence of human immunodeficiency virus (HIV) and the incidence of tuberculosis infections. These diseases pose major threats in their own right but the interaction between them creates especially serious challenges for public health policy because of the consequences of HIV's immunosuppressant effect on persons with tuberculosis such that HIV has become a key driver of tuberculosis infection and subsequent mortality in many parts of the world (Currie et al, 2003). Indeed, each year, 200,000 deaths from tuberculosis in sub-Saharan Africa are attributable to co-infection with HIV (Williams and Dye, 2003). Where tuberculosis is multi-drug resistant (MDRTB) the challenges are even greater (Coker, 2004)

This combination of HIV and tuberculosis can only have dramatic consequences given that the spread of each disease is exacerbated and amplified by the other one (Currie et al, 2003). Therefore, there is a need for an integrated policy to address them simultaneously. Strategies designed to control HIV and tuberculosis need to take account of the complex interplay between these two diseases (Coetzee et al, 2004). In the context of the Russian Federation, where there are worrying signs of colliding epidemics of tuberculosis and HIV (Drobniewski et al, 2004), the WHO is recommending policies which include simultaneous use of highly active antiretroviral therapy (HAART) to treat HIV/AIDS and second line drugs to treat MDRTB (WHO, 2007).

Although it is relatively easy to predict the effect of these treatments at the individual level, it is more challenging to predict their impact at the population level. HAART treatment enables individuals infected with HIV to live longer, but because infection is not eradicated, this individual may infect others causing an increase in the number of HIV infections in the population (HIV incidence). Such an individual may also remain at greater risk of tuberculosis infection and, therefore, can also contribute to the spread of tuberculosis in the population. The same can be said about MDRTB, where duration of infectiousness may be prolonged. An individual co-infected with both HIV and MDRTB may remain infectious for both diseases unless MDRTB treatment is effective.

From a public health perspective, this means that the impact of decisions regarding the level of HAART coverage (that is the fraction of individuals with HIV/AIDS treated with HAART) and/or the MDRTB cure rate (that is the fraction of individuals with MDRTB successfully treated with second line drugs) on the transmission dynamics of HIV and tuberculosis at the population level and their consequences in terms of the number of infections, incidence,

prevalence, and the number of deaths cannot be easily predicted. It is unclear at what level of HAART coverage and MDRTB cure rates a significant reduction in the number of infections and deaths can be achieved.

There have been numerous studies applying dynamical models to TB and HIV. As an example, studies explored the transmission of HIV and impact of HAART (Griffiths et al, 2006; Dangerfield et al, 2001; Dangerfield and Roberts, 1999), allocation of resources for HIV treatment in developing countries (Lasry et all, 2007), strategies to prevent mother child transmission of HIV (Rauner et al, 2005), and the impact of age distribution and incubation period on TB transmission patterns (Vynnycky and Fine, 2000). However, no research explored the effects of the interaction between TB and HIV/AIDS on the transmission dynamics of these diseases and its consequences.

The simulation model developed in this research explored TB, MDRTB and HIV/AIDS co-infection and the impact of combining different interventions at various coverage levels and was part of a four-year research project funded by the UK Department for International Development (2002-2005). The project explored how contextual and health systems factors influenced the design and implementation of internationally approved Tuberculosis control programmes in the Russian Federation. This novel project involved a multidisciplinary group of British and Russian researchers, which included health system experts, epidemiologists, microbiologists, tuberculosis- and HIV-specialists, sociologists, operations research specialists and health economists, and focused on the analysis of the drivers of tuberculosis infection and transmission in Samara Region, and policy interventions to address these—including the introduction of the World Health Organization approved treatment regimens for tuberculosis (Directly Observed Therapy Short Course: also known as DOTS), changes to health regulations, financing and delivery of health services to effectively respond to current and emerging public health challenges.

Samara Region is particularly interesting setting for the research as the region has colliding epidemics of tuberculosis, MDRTB and HIV. Samara Oblast has a population of 3.3million with an average income level similar to the Russian average and the notification of new tuberculosis cases in the last decade in Samara mirrored that in Russia as a whole (Coker et al, 2003) The Region which also had high levels of MDRTB (Balabanova et al, 2006) has a well established tuberculosis control network of specialized outpatient and inpatient tuberculosis services and a good surveillance system for tuberculosis and regularly collects data on notifications, prevalence, financing, provider payments and health service utilization, enabling detailed analysis of patient data and funds flows for tuberculosis services (Floyd et

al, 2006). At the time of the study, the region was also experiencing an explosive epidemic of HIV with most new infections registered in the injecting drug user (IDUs) population (Atun et al, 2005a).

Dynamic Complexity of Tuberculosis and HIV/AIDS transmissions

The transmission dynamics of tuberculosis and HIV at the population level (macro level) cannot be disassociated from the behaviour of these diseases at the individual level (micro level). However, while the behaviour of these two diseases at the individual level has been the subject of much biomedical research for many years and is, therefore, relatively well understood, the behaviour of these interacting diseases at the population level is more difficult to understand. The reason is that this behaviour is driven by complex interactions between variables related to the epidemiology of the diseases within single individuals, behaviour of these and other individuals, health service structures and processes, and the policies put in place to deal with these diseases (Atun et al, 2005b). For example, an aggressive policy to detect individuals with the drug sensitive tuberculosis (DSTB) disease can have counter-productive results if the treatment capacity and resources are not adequate to treat the detected individuals. This will potentially lead to a high rate of DSTB deaths (and potentially more infections with MDRTB if individuals receive interruptions to their treatment). Similarly, an effective treatment system for tuberculosis will not have the desired effect on the spread of tuberculosis if individuals with the disease remain undetected in the population and infect others. If individuals do not receive appropriate treatment for DSTB, they can develop MDRTB and infect others. This can have far reaching consequences in terms of the size of the population with MDRTB and the resources required for their detection and treatment. The long delay between HIV infection and AIDS means many persons with HIV infection may remain unaware of their HIV status and continue their high risk behaviour, until they succumb to an opportunistic infection, such as TB as their immune function deteriorates.

System Dynamics (SD) modelling (Sterman, 2000) enable us to make explicit our understanding of the complex interplay between diseases and the environment within which they sit and support policy design and decision-making by providing the policy makers simulation tools to determine effectiveness of policy options (Homer and Hirsch, 2006; Dangerfield, 1999) and understand possible outcomes (in this case to control TB and HIV) given different policy combinations. SD is an appropriate modelling approach for our task as it focuses on patient states rather than modelling patients at the individual level. In SD, the population can be divided into large homogenous groups, in which all the patients are in the

same disease state, rather than modelling the flow of each individual patient within the population (Brailsford et al, 2004). SD employs qualitative and quantitative modelling tools to explicitly represent the structure of complex systems and simulate their behaviour enabling, therefore, a better and easier understanding of the link between a system's structure and its behaviour. Furthermore, SD enables the modelling of "soft" behavioural variables, which, as important as they are, they are not captured by other traditional mathematical models.

Model Development Process

The research team obtained ethical approval from the local research ethics committee, and permission from the regional Ministry of Health to access epidemiological, health services and health financing data. A multidisciplinary design team, comprising local and international researchers (clinicians, health system and public health specialists and microbiologists) with knowledge and experience of modelling TB and HIV was established. The members of the design team worked closely with policy makers and were hence aware of the local, national and international issues relevant to policy makers. Through an iterative process of discussions and triangulation, drawing on the expertise of the group, policy documents, surveillance reports, and published literature, model components and details were developed, parameters identified and the model populated. Local practitioners, experts and policy makers were also involved in discussions in model development, to test assumptions, check model validity and in scenario planning.

During the model development stage, the British research team made several visits to Samara Region to interview key informants and to visit provider units where TB services were delivered. The structure of TB and HIV transmission dynamics were determined drawing on the published literature and the knowledge of team members, complemented by interviews with clinicians and public health specialists in Samara. The literature review and discussions among the research team members led to an initial, high-level, simplified map of the disease epidemiology. Following this, around 20 interviews were conducted in Samara with a broad set of stakeholders comprising clinicians, nurses, managers from healthcare provider facilities, and policymakers from the Ministry of Health. The causal loop diagram (CLD) was presented to interviewees and iteratively refined following their comments. It was 'frozen' once all the interviewees and the research team agreed on its structure.

Model Building

Tuberculosis model

The tuberculosis model includes two sub-models: the DSTB sub-model and the MDRTB sub-model. The general structure of these two sub-models is identical except for the process of 'secondary' acquisition of MDRTB, which constitute the link between the two sub-models (See figure 1). The population in the model is assumed to be homogenous, with respect to the risk of acquiring and transmitting tuberculosis. This is because the model is restricted to the adult population, which in the region, are subject to relatively the same socio-economic conditions.

The DSTB sub-model

The DSTB sub-model is simulated through a stock and flow structure where stocks represent the sub-population in each state of DSTB and flows represent the time related movement of individuals between the DSTB states. The spread of the disease is initiated through the infection of TB 'susceptible' individuals (individual free of TB) as a result of their contact with 'infectious' individuals. The rate of infection depends on the size of the susceptible population, the average number of contacts per unit time between susceptible and infectious individuals, the probability that an individual is infectious, and the probability of infection of a susceptible individual.

$$I_t = S_t \times C \times IN_t \times F \qquad (1)$$

Where

I_t: Infection rate DSTB

S_t: Susceptible population DSTB

C: Average number of contacts per unit time between susceptible and infectious individuals

IN_t: Probability that an individual is DSTB infectious

F: Probability of DSTB infection of a susceptible individual

A fraction of the individuals infected with DSTB (known as DSTB latently infected) progress to a disease state. Some individuals progress to disease within 3-5 years (fast breakdown) whereas it may take up to 20 years (slow breakdown) for other infected individuals to make this transition. Untreated individuals in the disease state may die, self-cure, or remain in the persistent (chronic) state of the disease.

Some individuals in the disease state are detected through routine medical checks or self-referral to specialised tuberculosis health services. Once detected, these individuals enter a treatment phase from which they are cured, die, or remain in the persistent state disease. Those in the persistent state of the disease may go through several rounds of treatment from which they may die, be cured, or remain in the persistent state of the disease.

The MDRTB sub-model

In addition to the outcomes associated with individuals entering the DSTB treatment phase (death, cure, DSTB persistent), some individuals develop resistance to one of more of the drugs used in the DSTB treatment phase (known as first line drugs). Drug resistance generally develops as a result of inappropriate treatment, a process known as 'secondary' acquisition of MDRTB (MDRTB is resistant to the first line treatment drugs Isoniazid and Rifampicin with or without resistance to other drugs).

MDRTB secondary acquisition constitutes the link between the DSTB and MDRTB sub-models. Individuals who develop MDRTB through this process will pass on this strain of tuberculosis to susceptible tuberculosis individuals, a process known as 'primary' MDRTB acquisition. Once individuals get infected with MDRTB, they progress to the disease, detection, and treatment stages similar to DSTB infected individuals. The MDRTB treatment involves different drugs (known as second line drugs) and is lengthier that DSTB treatment period. Its outcomes are cure, death, or persistence with MDRTB disease. As for DSTB, some individuals go through several cycles of MDRTB treatment before they are cured.

HIV/AIDS Model

Although there are many routes of HIV infection, the model assumes that HIV acquisition occurs mainly through needle exchange in the injecting drug use (IDU) population as this is the route by which most HIV infections in Russia, and in particular in the region of Samara, is acquired (Rhodes et al, 2002). Given that IDUs tend to exhibit similar patterns of risky behaviour and belong to the same age group, it is assumed, in the model, that individuals have the same characteristics with regard to HIV infection and transmission.

The HIV/AIDS transmission model includes three stages: 'HIV sero-negative', 'HIV sero-positive' and 'AIDS' (May and Anderson, 1988). To capture the effect of HIV on tuberculosis transmission dynamics the "tuberculosis transmission model" developed in the first stage of modelling is replicated three times to represent the three stages of HIV/AIDS (through the

ARRAY function on ITHINK software). As a result, an individual in the combined tuberculosis and HIV/AIDS model is represented by a tuberculosis state and an HIV/AIDS state.

The combined tuberculosis and HIV/AIDS model allows movement of individuals both within a single tuberculosis model (that is within the same HIV/AIDS state) and between the three replicated tuberculosis models representing the three HIV/AIDS stages. For example, an individual in the state of 'DSTB latently infected' and 'HIV negative' who develop 'DSTB disease', while still in the "HIV negative" state, moves from the state of 'DSTB latently infected' to the state of 'DSTB disease' within the same tuberculosis model representing the 'HIV negative' state. However, if this individual becomes infected with HIV, s/he moves from the 'DSTB latently Infected' state in the tuberculosis model representing the 'HIV negative' state to the 'DSTB latently infected' state in the tuberculosis model representing the 'HIV positive' state.

Progression through HIV/AIDS occurs in two steps. First, individuals who get infected with HIV move from the state of "HIV negative" to the state of "HIV positive". This transition is possible for individuals in any state within the tuberculosis model. The rate at which individuals get infected with HIV depends on the size of the negative population (in each tuberculosis state), the average number of drug injections per unit time, the density of IDUs within the population, the fraction of IDUs sharing needles, the probability that an injection is HIV positive (which reflects the HIV prevalence in IDUs), and the probability of HIV transmission.

$$FHIV_t = NGV_t \times DIF \times PSH \times IDUS \times PRV \times TRS \qquad (2)$$

Where

$FHIV_t$: Rate of HIV positive infection

NGV_t: HIV negative population size

DIF: Average number of drug injections per unit time

PSH: Density of IDUs within the population

IDUS: Fraction of IDUs sharing needles

PRV: Probability that an injection is HIV positive.

TRS: Probability of HIV transmission

(Equation 2 is valid for all tuberculosis states).

Individuals in the “HIV positive” stage do not progress immediately to AIDS. They remain in the state of “HIV positive” for a long period of time before their immune function deteriorates such that they develop AIDS. In this second step, they move from the “HIV positive” state to the “AIDS” state (this transition is possible for all states within the tuberculosis model)

If an individual with AIDS is not treated with HAART, they will die within two years (Walensky et al, 2006). However, individuals treated with HAART may live for a longer period after reaching the AIDS disease state (Walensky et al, 2006) (See Figure 2 for the tuberculosis state ‘DSTB latently infected’). Furthermore, if an individual co-infected with AIDS and tuberculosis is treated with HAART, their tuberculosis disease progression is similar to an individual without HIV/AIDS.

A fraction of individuals in the AIDS state are offered HAART treatment immediately after getting to this state. This fraction is known as “HAART coverage”. Therefore, the AIDS population is divided into two groups: (i) Individuals with HAART treatment and (ii) Individuals without HAART treatment. The death rate from AIDS depends on the size of the population and the average time to death for these two groups (with or without HAART treatment).

$$DTH_t = \frac{AIDSH_t}{T_1} \qquad (3)$$

Where

DTH_t: Death rate for individuals with HAART treatment

$AIDSH_t$: AIDS with HAART treatment population

T_1: Average time to death for individuals with HAART treatment

$$DTWH_t = \frac{AIDSWH_t}{T_2} \qquad (4)$$

$DTWH_t$: Death rate for individuals without HAART treatment

$AIDSWH_t$: AIDS without HAART treatment population

T_2**:** Average time to death for individuals with HAART treatment

(Equations 3 and 4 are valid for all tuberculosis states)

Model Parameterisation and Sensitivity Analysis

The model was parameterised using two categories of data. The first category includes the universal parameters related to tuberculosis and HIV epidemiology, drawn from published estimates as they do not depend on the location of individuals. Where some estimates in this category are unavailable, explicit assumptions have been made. The list of parameters in this category is presented in table 1.

The second category of data includes the HIV transmission parameters and the initial values of the stocks in the model. They were estimated from data collected in Samara oblast (from population and health statistics available in the oblast) and from published research conducted in neighbouring oblasts with similar conditions to Samara. The list of parameters in this category is presented in tables 2 and 3.

The data in table 3 regarding individuals in latent states of tuberculosis (that is infected individuals who have not yet shown the symptoms of the disease) were estimated by combining the information available in the Health Ministry and from several surveys conducted in Samara oblast. This estimation method was adopted because it was impossible at the time to detect latently infected individuals with tuberculosis given the widespread use of tuberculosis vaccination during the Soviet era (Drobniewski et al, 2007). Data with regard to HIV latently infected individuals were estimated using surveys conducted in different areas of the Russian Federation (Shaboltas et al, 2006; Rhodes et al, 2002). These sources of information enabled the research team to make informed assumptions, validated by local health authorities, in order to estimate the size of the tuberculosis and HIV latently infected population in Samara oblast.

A sensitivity analysis was conducted to determine the parameters to which the model output was most sensitive (Sterman, 2000). The model parameters selected for sensitivity analysis include those which can be changed in the real world (MDRTB cure rate for example). However, parameters, which cannot be changed in the real world, namely those related to the natural epidemiology of tuberculosis and HIV were not included in this analysis (Average time to develop persistent tuberculosis for example) as these parameters cannot be

influenced by any real world policy. The parameters for which sensitivity analysis was conducted are presented in table 4.

Each parameter was allocated three values: pessimistic, current, and optimistic (See table 4). The model was run by changing the value of every single parameter to its pessimistic and then optimistic values while keeping all other parameters at their current levels. The most sensitive parameters were determined by evaluating the normalised change (in percentage) in each of the four model output indicators of interest in this research (cumulative tuberculosis deaths, cumulative HIV associated tuberculosis deaths, cumulative MDRTB deaths, and cumulative deaths from AIDS in non tuberculosis individuals) when the parameter value changes from its pessimistic to optimistic value.

The results suggest that cumulative tuberculosis deaths and cumulative HIV tuberculosis deaths were sensitive to the parameters “Average number of contact per day with tuberculosis infectious individuals”, “The fraction of IDUs involved in needle sharing”, “DSTB cure rate first time treatment”, and “HAART coverage”. Cumulative MDRTB deaths was sensitive to the parameters “MDRTB cure rate”, “Probability to detect MDRTB”, “fraction of individuals with MDRTB detected” and “The fraction of IDUs involved in needle sharing”. Cumulative deaths from AIDS in non tuberculosis individuals was sensitive to the parameters “The fraction of IDUs involved in needle sharing”, “HAART coverage” and “IDUs density in the general population”.

Model validation

Model validation tests in SD are divided into model qualitative structure, simulation model structure, and model behaviour tests (Sterman, 2000; Barlas, 1996). Qualitative structure tests were performed through checking the qualitative map of the model against available clinical knowledge. The map was revised and updated several times with the research participants in Samara oblast until it was jointly agreed by the research team and these participants. The simulation model structure was tested through rigorous check of equations, parameter values, and dimensions with the involvement of the research team in Samara. The model behaviour was checked against the real world cumulative tuberculosis deaths in Samara between the beginning of 1999 and the end of 2002, which were obtained from the Ministry of Health in Samara Oblast. The model replicated historical data with high accuracy as shown on figure 3 (Coefficient of determination R^2=0.93).

Scenario analysis parameters

Scenario analysis parameters include MDRTB cure rate and HAART population coverage (fraction of AIDS individuals given HAART treatment). MDRTB cure rate is assigned to two levels: 5% and 80% representing situations of non-use and use of second line drugs in MDRTB treatment respectively. HAART population coverage varies from 0% (no coverage) to 100% (full coverage) with increments of 25%. Each scenario included a value for the parameter "MDRTB Cure Rate" and a value for the parameter "HAART Coverage. The time frame for the simulation model is 20 years and is assumed to start at the beginning of 2003 and finish at the end of 2022.

Results

The model outputs we are concerned with are: (i) cumulative deaths from tuberculosis which includes deaths from all forms of tuberculosis and deaths from HIV-associated tuberculosis; (ii) cumulative deaths from HIV-associated tuberculosis, (iii) cumulative deaths from MDRTB, and; (iv) cumulative deaths from AIDS in non tuberculosis individuals. These outputs were selected after discussions with health officials in Samara oblast, who were interested into the number of deaths which could be averted as a result of implementing different MDRTB cure rate and HAART coverage policies.

(i) Cumulative tuberculosis deaths

The results indicate that in the 20 year period of simulation, in the absence of HAART coverage, the cumulative number of tuberculosis deaths will be 13,700 with an MDRTB cure rate of 5% but will decline to 9,840 if MDRTB cure rates reach 80%. With an increase in HAART coverage, the cumulative number of tuberculosis deaths initially declines at a slow rate as long as coverage rates are below 50%. Between 50% and 75% the rate of decline increases but with a coverage rate of 75% and beyond this the rate of decline significantly increases and these observations are valid under scenarios of 5% and 80% MDRTB cure rate.

The evidence for this is shown in figure 4 (under 80% MDRTB cure rate). The cumulative number of deaths decreases if the HAART coverage increases. However, the decline is much more significant when HAART coverage increases from 50% to 100% than from 0% to 50%. Under 5 % MDRTB cure rate, the cumulative number of deaths decreases by around 5% from 0% to 50% HAART coverage and by 40% from 50% to 100% HAART coverage.

Where MDRTB cure rate is 80%, the cumulative number of deaths decreases by around 6% from 0% to 50% HAART coverage and by 48% from 50% to 100% HAART coverage

(ii) Cumulative HIV associated tuberculosis deaths

Cumulative deaths from HIV-associated tuberculosis with no HAART coverage reach 7,270 and 6,570 when MDRTB cure rates are, respectively, 5% and 80%. Cumulative HIV-associated deaths decline in a similar way as cumulative tuberculosis deaths, that is slowly up to HAART coverage of 50%, and then more significantly especially after 75% HAART coverage when the decline is steep (When 100% HAART coverage is achieved, HIV-associated tuberculosis deaths fall by 74% to 1,950 and by 75% to 1,740 respectively for 5% and 80% MDRTB cure rate). The acceleration in the decline in death rates beyond 75% HAART coverage is much faster for HIV-associated tuberculosis deaths than for tuberculosis only deaths.

(iii) Cumulative MDRTB deaths

Cumulative deaths from MDRTB decreases significantly as MDRTB cure rate moves from 5% to 80% and this is valid for all levels of HAART coverage. The cumulative MDRTB deaths decreases from 4,280 deaths to 410 deaths (91% decline) for no HAART coverage and from 3,490 to 290 (92% decline) for full HAART coverage. The behaviour over time of this variable is shown on figure 5 (for 0% HAART coverage) and it gives a clear view of the dramatic reduction of MDRTB deaths when MDRTB cure rate increase from 5 to 80%.

The same observation can be made with regard to the impact of HAART coverage increase on cumulative MDRB deaths. The rate of decline tend to increase significantly beyond the 50% HAART coverage point and becomes significant if HAART coverage is greater than 75%.

(iv) Cumulative deaths from AIDS in non tuberculosis individuals

Cumulative deaths from AIDS in non TB individuals decreases as HAART coverage increases (this is valid for both 5% and 80% MDRTB cure rates). However, as shown on figure 6, the decrease becomes important only beyond 50% HAART coverage and substantial for HAART coverage above 75%. Between 0% and 50%, deaths decrease by 12% from 69,580 to 61,350. At 75% HAART coverage, the reduction is around 30% to

49,530 deaths, whereas at 100% HAART coverage, the reduction is of 79% to 14,970 deaths.

The counterintuitive non-linear relationship between HAART coverage and reduction in HIV associated tuberculosis deaths, hence tuberculosis deaths, could be explained by the feedback processes presented in figure 7. Patients under HAART treatment do not die from AIDS immediately and survive for a longer period of time, a process represented by balancing loop B2. However, as they survive, they are under the risk of getting infected with tuberculosis and consequently die from HIV associated tuberculosis as shown by balancing loop B3. At low HAART coverage, the combined deaths from patients not under HAART treatment (balancing loop B1) and those under HAART treatment infected with tuberculosis and dying from HIV associated tuberculosis (balancing loop B3) offset the reduction in deaths for patients under HAART treatment (balancing loop B2). As HAART coverage increases, the balancing loop B2 gets stronger and, therefore, we witness a shift in loop dominance from balancing loops B1 and B3 to balancing loop B2. In other words, the reduction in deaths for patients under HAART is significantly more important than the combined deaths for patients not under HAART and patients under HAART infected with tuberculosis leading to an overall decrease in the number of deaths from tuberculosis and HIV/AIDS.

Discussion and conclusion

We show that in a setting where there is currently a high prevalence of MDRTB and an immature, contained, epidemic of HIV in IDUs, the epidemic of MDRTB, if left unchallenged, may result in a substantial number of deaths from tuberculosis.

Many deaths from tuberculosis, HIV-associated tuberculosis, and HIV-associated MDRTB can be averted with effective tuberculosis and MDRTB control strategies that achieve high MDRTB cure rate and coverage of HIV-infected people with HAART. However, the rate of decline in the cumulative number of deaths is not linearly proportional to the rate of increase in HAART coverage. Instead, we observe a slow change in the rate of decline for cumulative deaths from tuberculosis, HIV-associated tuberculosis and HIV-associated MDRTB up to 50% HAART coverage rates. The rate of decline increases between 50 and 75% HAART coverage and more substantially between 75% and 100% coverage. This relationship holds for both 5% and 80% MDRTB cure rates.

Our findings have important policy implications. At low HAART coverage rates the impact on cumulative deaths is minimal but increases substantially at coverage rates above 50% but particularly above 75%. Population coverage with HAART needs to be very substantial if avoidable excess deaths from tuberculosis are to be averted.

Current policy recommendations for HAART coverage focus on scaling up but do not explicitly identify an optimal population coverage target (WHO, 2005). We demonstrate that, in the epidemiological setting described above (where HIV epidemics is mainly driven by IDUs and where HIV and TB have similar epidemiology) scaling up HAART coverage to levels up to 50% is likely to achieve minimal impact, with an appreciable impact on mortality only becoming apparent at 50-75% coverage and becoming substantial only at 75% coverage level and beyond.

The non-linear relationship between increased HAART coverage and decline in cumulative deaths is an example of the counter-intuitive behaviour of systems due to complex interactions at play between their elements (Sterman, 2000). The application of System Dynamics modelling in this research has been extremely fruitful to understand the complexity of tuberculosis and HIV transmission systems and help design policies to tackle these diseases.

Our analysis is limited in a number of ways. First, the model assumes a static age structure such that younger cohorts of individuals, who may be at risk of tuberculosis and HIV, are not included in the model. The extent of the HIV epidemic may be underestimated in the model because the population at risk of HIV, that is the IDU population, remains static. In reality, it is likely that new young people will enter this population, swelling its ranks. Work is continuing to include age structure and wider transmission of HIV in this model. Similarly, the model does not include the consequences of population migration to and from the region. Samara region, however, has a relatively stable population and was chosen as the population to model, in part, for this reason. Any changes in this pattern of population movement could impact upon predictions. We have assumed that HIV spread will be contained within the IDU population, which is a further limitation. In future it is likely that there will be significant sexual spread that will lead to ‘leakage’ outside this population. These factors are expected to lead to an underestimate of the likely epidemic of HIV in the region and, consequently, of the impact with tuberculosis dynamics.

In practice, both HIV and tuberculosis tend to cluster in certain sub-populations and micro-epidemics may occur, for example, through institutional spread within prison settings or in

tuberculosis hospitals. Our model does not predict such scenarios and consequently may, again, underestimate the likely impact of such enhanced transmission dynamics.

The most recent medical information suggests that HIV transmission risks are lower in individuals under HAART treatment (Wilson et al, 2008; Garnett & Gazzard, 2008). This contradicts the assumption made in our model that individuals with HIV have the same transmission risks regardless of whether they are under HAART treatment or not as this information was not available when the current research was conducted. As a result, our model may have over estimated HIV infections and deaths in scenarios of high HAART coverage. However, we believe that our policy recommendation that high HAART coverage is required to reduce HIV deaths still stand given that benefits of reduced transmission risks are only applicable to individuals under HAART treatment.

The model does not take into account possible policy changes. In our model, for example, the number of contacts per unit time between tuberculosis-susceptible and tuberculosis-infected individuals is assumed to be constant and the model does not account for quarantine or isolation policies or changes in, for example, contact rates due to reactions from susceptible individuals to perceived risks in infected groups. The same assumptions hold regarding the rate of acquiring HIV. The rate of movement from the HIV negative state to the HIV positive state is assumed to be constant regardless of the individual's tuberculosis state, a factor that might be influenced, for example, by institutional care practices and patients' behaviour within institutions. Notwithstanding these limitations, we believe that the findings are sufficiently robust to inform policy.

Our findings have implications for governments, the WHO, the Word Bank and the Global Fund who are investing significant funds to control the tuberculosis, MDRTB, and HIV epidemics in post Soviet countries. The investment in HAART should be large enough to scale up coverage to 75% of the HIV positive population to have a significant impact on tuberculosis and HIV-associated deaths. Incremental scale up at low levels of coverage will have limited success in averting deaths. For HIV-associated tuberculosis deaths, provision of HAART alone is likely to be more effective public health strategy than provision of effective MDRTB treatment alone.

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Table 1

Parameter	HIV Sero-negative	HIV Sero-positive	AIDS
Probability of HIV transmission (HIV infectiousness)	n/a	0.01	0.01
Probability of DSTB transmission –1st time infection-	0.1	0.1	0.1
Average period for slow breakdown DSTB	25 years	25 years	5 years
Fraction of slow breakdown DSTB	0.05	0.05	0.2
Average period for fast breakdown DSTB	2.5 years	2.5 years	1 year
Fraction of fast breakdown DSTB	0.05	0.15	0.6
Fraction developing persistent TB – No treatment-	0.25	0.25	0.25
Average time to develop persistent TB – No treatment-	2 years	2 years	1.5 years
Fraction of deaths – No treatment -	0.5	0.5	0.75
Average time to death – No treatment -	2 years	2 years	1.5 years
Fraction of self-cure – No treatment-	0.25	0.25	0
Average time to self-cure – No treatment-	2 years	2 years	--
Fraction of DSTB population screened	0.7	0.7	0.7
Fraction developing persistent TB – 1st time treatment-	0.01	0.01	0.01
Average time to develop persistent TB –1st time treatment-	6 Months	6 Months	6 Months
Fraction of deaths – 1st time treatment -	0.03	0.03	0.03
Average time to death –1st time treatment -	5.5 years	5.5 years	2 years
Fraction of cure – 1st time treatment-	0.95	0.95	0.95
Average time to cure – 1st time treatment-	2 Months	2 Months	2 Months
Fraction developing MDRTB –1st time treatment-	0.01	0.01	0.01
Average time to develop MDRTB –1st time treatment-	3 Months	3 Months	3 Months
Probability of DSTB transmission – re-infection-	0.04	0.04	0.04
Fraction of death -persistent after 1st time treatment -	0.5	0.5	0.5
Average time to death - persistent after 1st time treatment -	2 years	2 years	2 years
Fraction of cure -persistent after 1st time treatment -	0.25	0.25	0.25
Average time to cure -persistent after 1st time treatment -	2 years	2 years	2 years
Fraction of cure -Persistent back to treatment-	0.95	0.95	0.95
Average time to cure -Persistent back to treatment-	3 Months	3 Months	3 Months
Fraction of death -Persistent back to treatment-	0.05	0.05	0.05
Average time to death -Persistent back to treatment-	5.5 Years	5.5 Years	2 Years
Probability of MDRTB transmission	0.1	0.1	0.1
Average period for slow breakdown MDRTB	25 years	25 years	5 years
Fraction of slow breakdown MDRTB	0.05	0.05	0.2
Average period for fast breakdown MDRTB	2.5 years	2.5 years	1 year
Fraction of fast breakdown MDRTB	0.05	0.15	0.6

Table 2

Parameter	Value	Reference
Average number of drug injections per day	1.40	(Rhodes et al, 2002)
IDUs density in the general population	0.01	(Rhodes et al, 1999)
Probability of HIV transmission	0.01	Hamers and Downs, 2003; Grassly et al, 2003)
The fraction of IDUs involved in needle sharing	0.40	(Hamers and Downs, 2003; Grassly et al, 2003)
Probability an injection is HIV positive	0.33	(Hamers and Downs, 2003; Grassly et al, 2003)

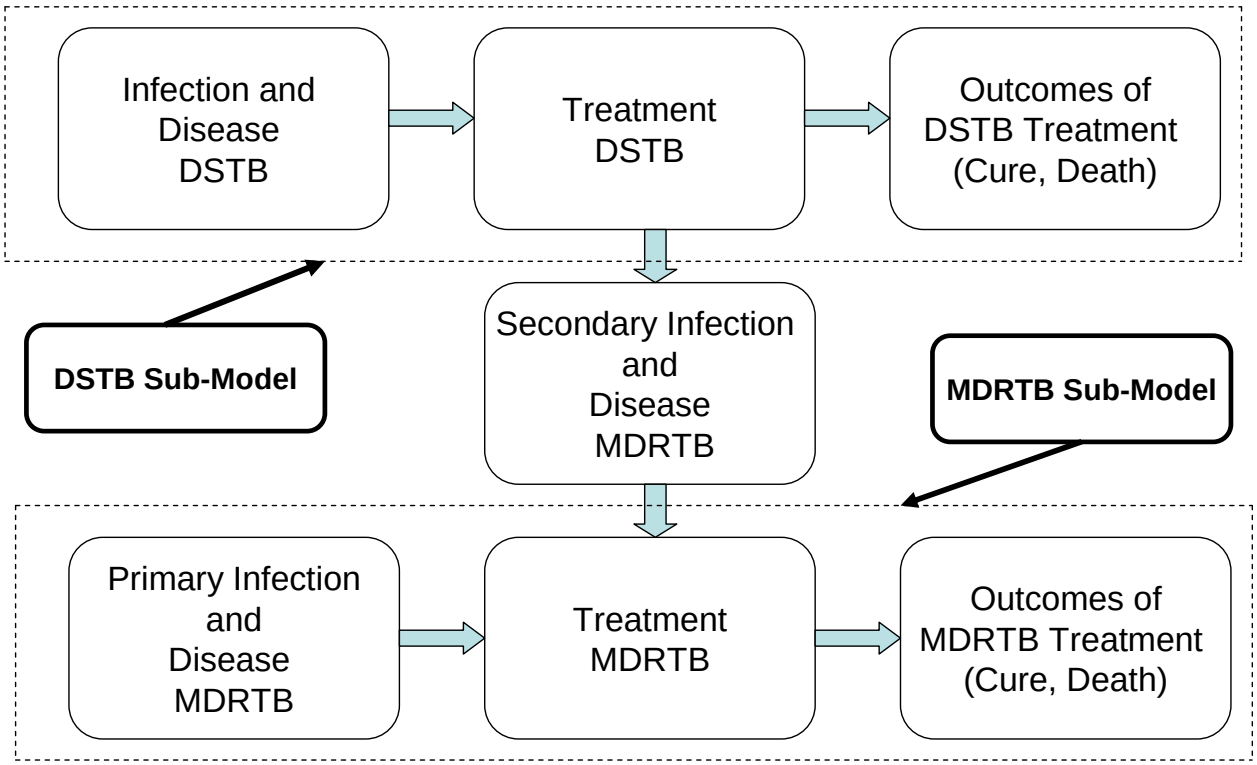
Table 3

Stock	Initial Value
Susceptible TB –HIV-negative	1,608,596
Susceptible TB –HIV-positive	12,044
Latently Infected DSTB –HIV-negative	681,408
Latently Infected DSTB –HIV-positive	4,862
Disease DSTB –HIV-negative	1400
Disease DSTB –HIV-positive	100
Disease MDRTB –HIV-negative	1,146
Disease MDRTB –HIV-positive	44

Table 4

Parameter	Pessimistic	Current	Optimistic
Average number of drug injections per day	2.00	1.40	0.80
IDUs density in the general population	0.05	0.01	0.004
The fraction of IDUs involved in needle sharing	0.80	0.40	0.15
Probability an injection is HIV positive	0.66	0.33	0.15
HAART Coverage	0.00	0.00	0.75
Average number of contacts per day with tuberculosis infectious individuals	0.90	0.40	0.20
Average time to detect an individual with DSTB (Weeks)	16	8	4
Average time to detect an individual with MDRTB (Weeks)	16	8	4
Fraction of individuals with DSTB detected	0.50	0.70	0.90
Fraction of individuals with MDRTB detected	0.50	0.70	0.90
Fraction of individuals with persistent DSTB detected	0.50	0.70	0.90
Probability to detect DSTB	0.50	0.75	0.90
Probability to detect MDRTB	0.50	0.70	0.90
Probability to detect persistent DSTB	0.50	0.75	0.90
DSTB cure rate (First time treatment)	0.50	0.95	0.99
DSTB cure rate (Persistent back to treatment)	0.50	0.95	0.99
MDRTB cure rate	0.05	0.15	0.80

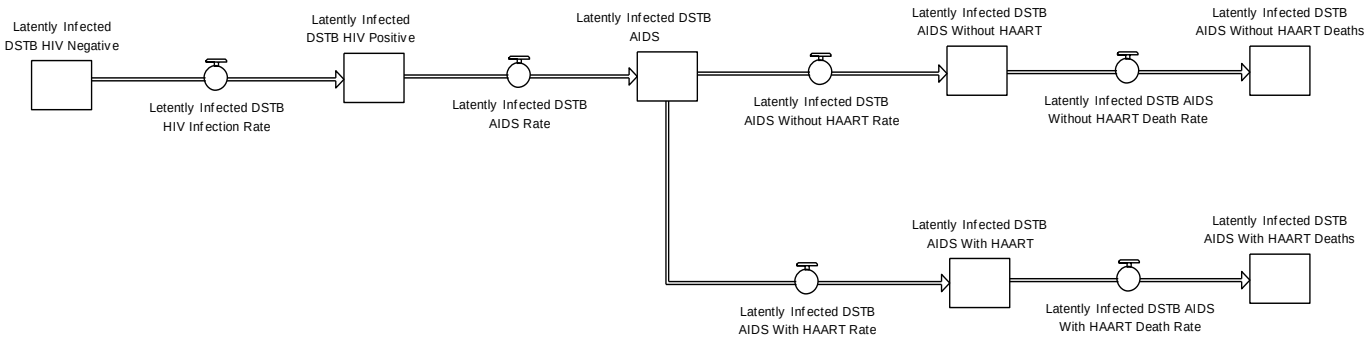
Figure 1



DSTB: Drug Sensitive Tuberculosis

MDRTB: Multi Drug Resistant Tuberculosis

Figure 2



DSTB: Drug Sensitive Tuberculosis

Figure 3

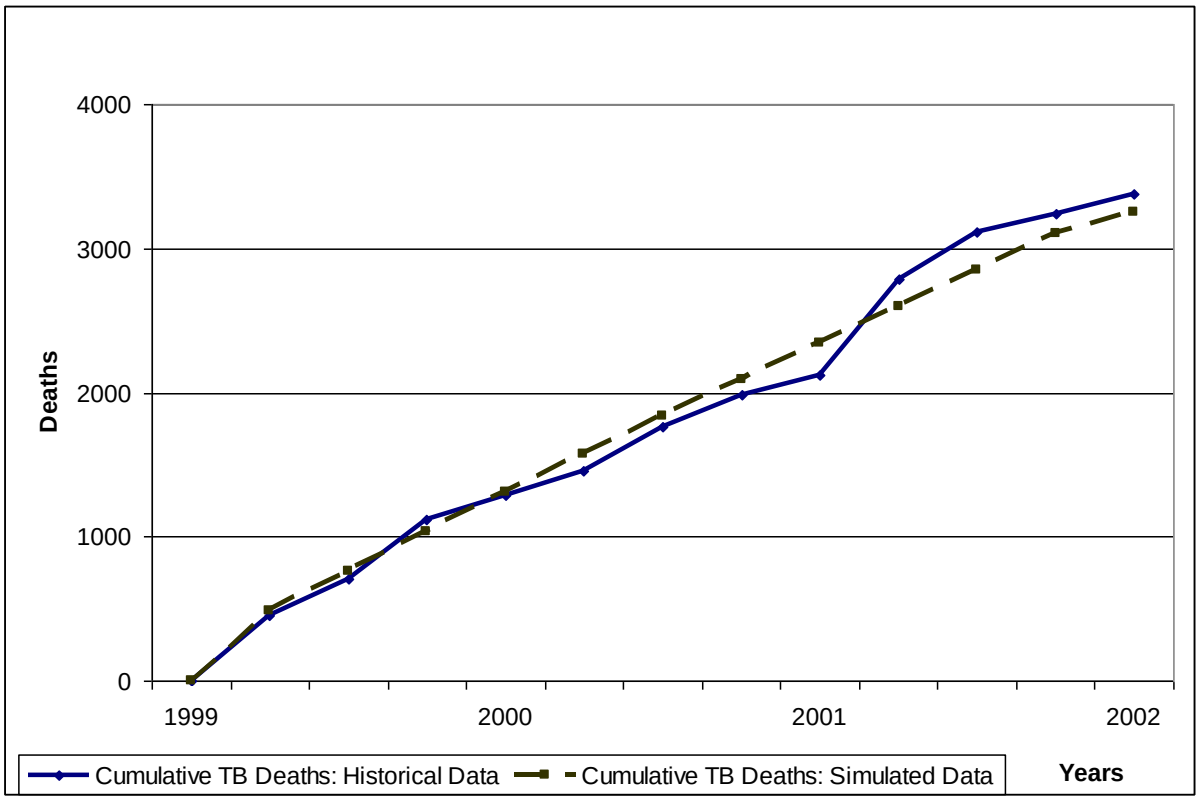

4000
3000
2000
1000
0
Deaths
1999
2000
2001
2002
Years
Cumulative TB Deaths: Historical Data
Cumulative TB Deaths: Simulated Data

Figure 4

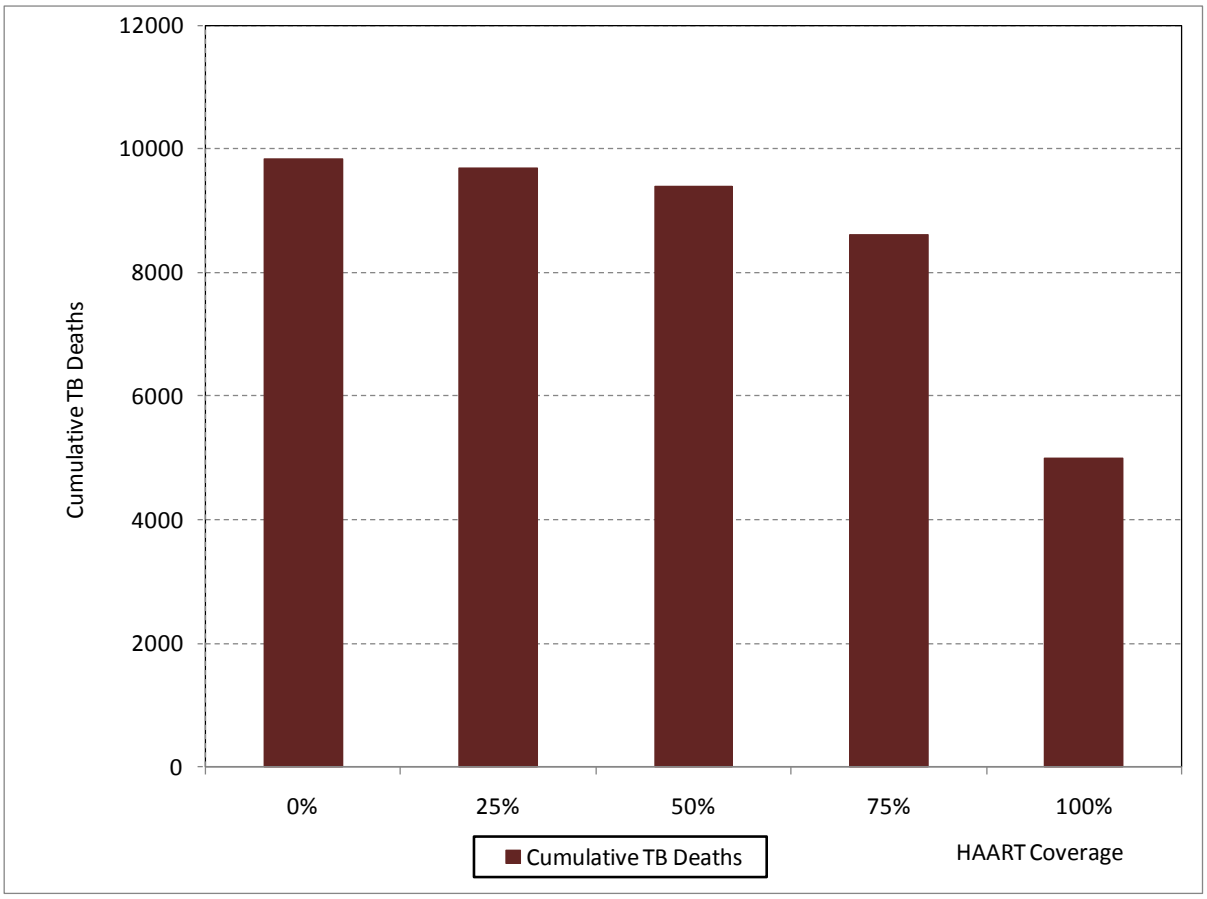

12000
10000
8000
6000
4000
2000
0
Cumulative TB Deaths
0%
25%
50%
75%
100%
HAART Coverage
Cumulative TB Deaths

Figure 5

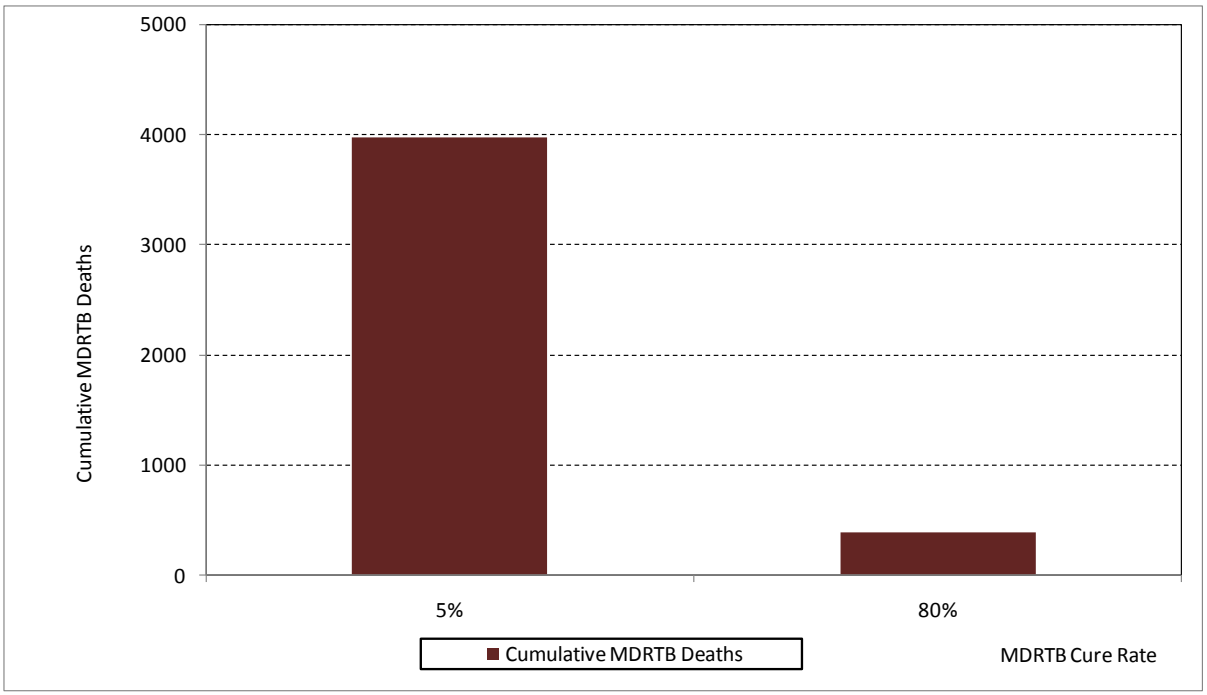

5000
4000
3000
2000
1000
0
Cumulative MDRTB Deaths
5%
80%
Cumulative MDRTB Deaths
MDRTB Cure Rate

Figure 6

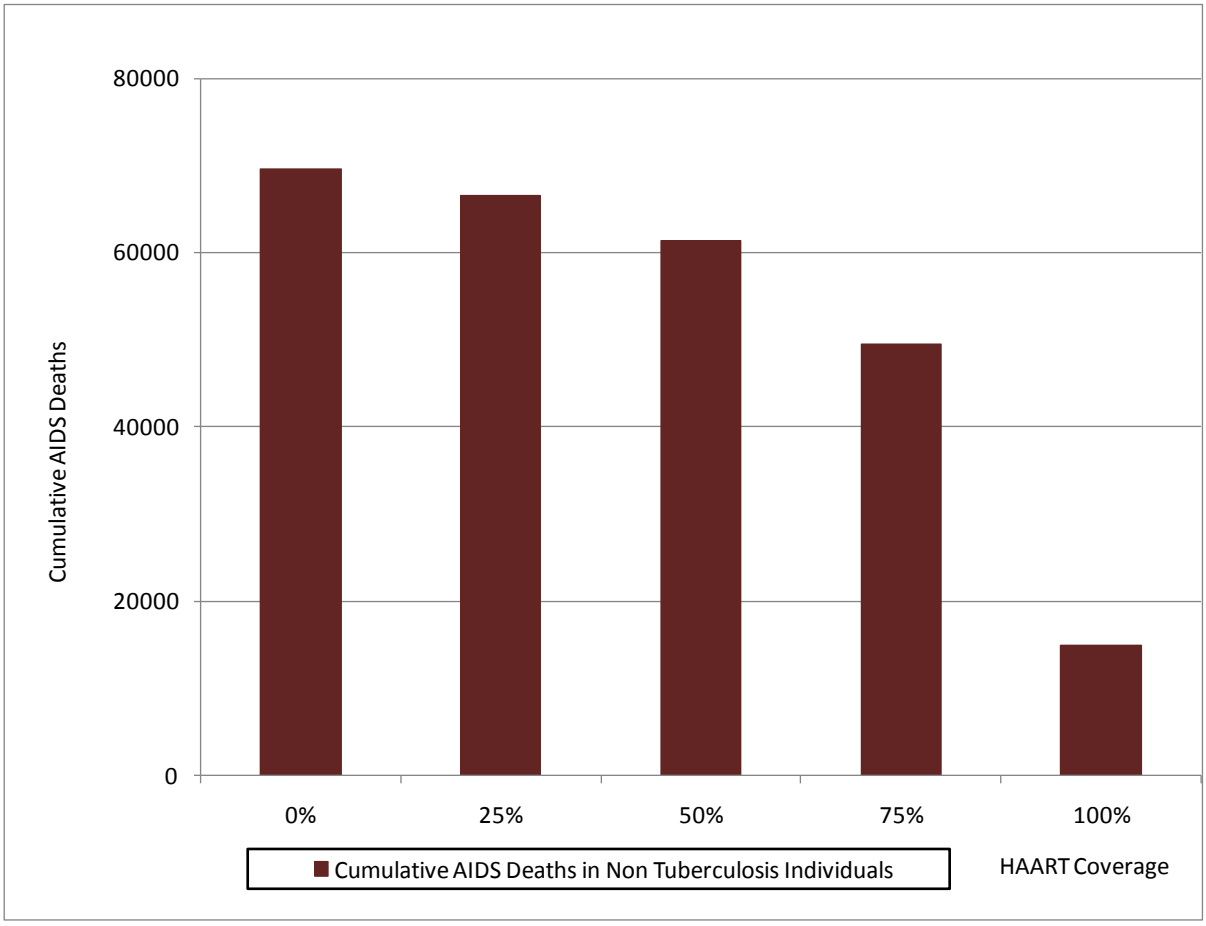
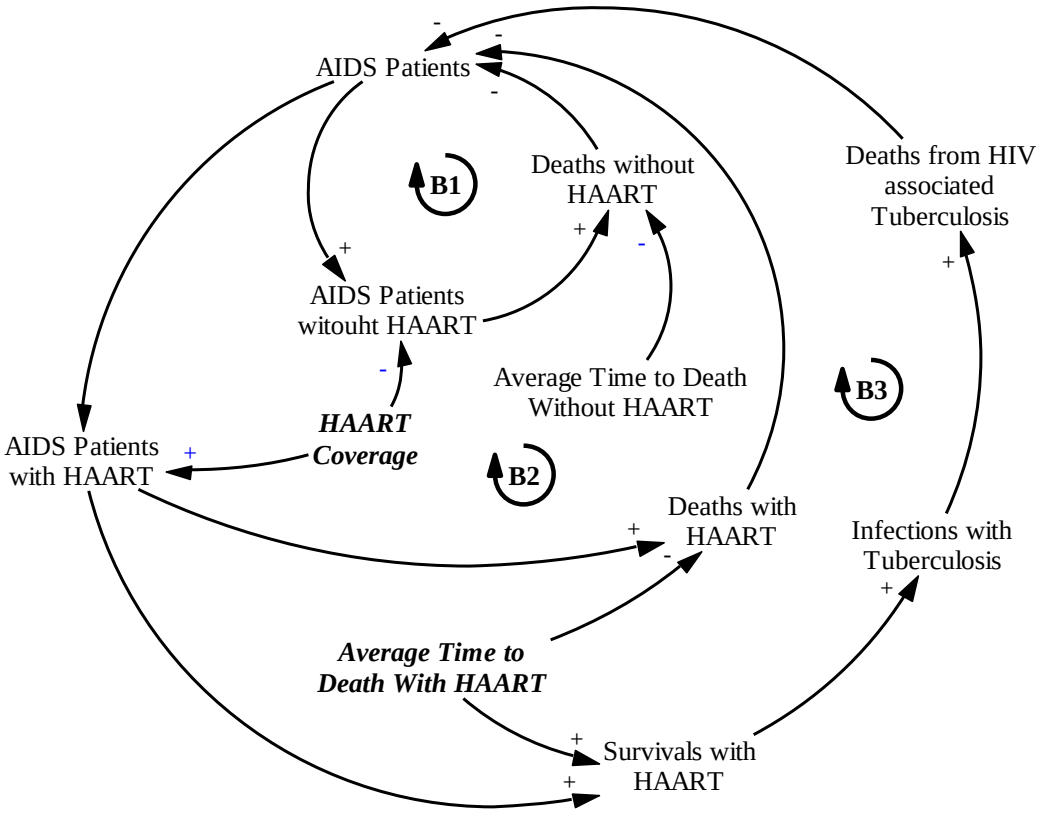

80000
60000
40000
20000
0
Cumulative AIDS Deaths
0%
25%
50%
75%
100%
HAART Coverage
Cumulative AIDS Deaths in Non Tuberculosis Individuals

Figure 7


AIDS Patients
Deaths without HAART
Deaths from HIV associated Tuberculosis
B1
AIDS Patients witouht HAART
Average Time to Death Without HAART
B3
HAART Coverage
AIDS Patients with HAART
B2
Deaths with HAART
Infections with Tuberculosis
Average Time to Death With HAART
Survivals with HAART

Captions for Figures and Tables