

# High coverage with HAART is required to substantially reduce the number of deaths from tuberculosis: system dynamics simulation

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**Summary:** We used a system dynamics simulation model of the transmission dynamics of drug-sensitive tuberculosis (DSTB), multidrug-resistant tuberculosis (MDRTB) and HIV to estimate the impact of coverage with highly active antiretroviral therapy (HAART) and different cure rates for MDRTB in settings of explosive HIV epidemics and high MDRTB levels. Population coverage levels at 0%, 25%, 50%, 75% and 100% for HAART, and 5% and 80% of MDRTB treatment cure rates were simulated over a 10-year period and cumulative deaths from tuberculosis and HIV-associated tuberculosis were estimated for populations with latent tuberculosis, DSTB, MDRTB, HIV and HIV-associated tuberculosis.

Depending on levels of HAART population coverage, increasing MDRTB cure rates from 5% to 80% reduces cumulative tuberculosis deaths by 1% and 13%. High population coverage with HAART (75% or higher), allied with high MDRTB cure rates, reduces cumulative deaths by 60%, with limited impact below this level. High coverage with HAART is required to substantially reduce the number of deaths from tuberculosis.

**Keywords:** HIV, tuberculosis, multidrug-resistant tuberculosis, HAART, Russia, system dynamics

## INTRODUCTION

The Russian Federation has experienced marked increases in both HIV and tuberculosis. These diseases pose major threats in their own right, but the interaction between them creates especially serious public health challenges because of the consequences of HIV's immunosuppressant effect on tuberculosis transmission dynamics. There is growing evidence that HIV has become a key driver of tuberculosis infection and subsequent mortality in many parts of the world.<sup>1-4</sup> Indeed, each year, 200,000 deaths from tuberculosis in sub-Saharan Africa are attributable to co-infection with HIV.<sup>2</sup> Where tuberculosis is multidrug-resistant (MDRTB), the challenges are even greater.<sup>5</sup>

Strategies designed to control tuberculosis, such as the World Health Organization (WHO)'s directly observed therapy-short course (DOTS), will have to be adapted if they are to meet the additional challenge of coincident HIV

effectively and there have been calls for greater integration of tuberculosis and HIV control programmes, with the addition of highly active antiretroviral treatment (HAART) to DOTS programmes.<sup>6-8</sup>

This important shift in public health policy demands critical analysis. Yet, to date, there has been little research to quantify the likely impact of provision of HAART in transitional societies, challenged simultaneously with high rates of MDRTB and explosive outbreaks of HIV. The aim of this research article is to determine the potential impact of several policy scenarios on deaths from tuberculosis and so to inform the policy-making process.

## METHODS

We developed a system dynamics (SD) simulation model,<sup>9-11</sup> described in detail elsewhere,<sup>12,13</sup> to represent the transmission dynamics of tuberculosis and HIV. SD methodology was chosen because the transmission of infectious diseases is complex, involving many interacting variables, interconnected feedback loops involving time delays and non-linear relationships, and given the dynamic complexity of these systems, their behaviour is generally difficult to predict. Formal system-based modelling

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approaches, such as SD, can represent these systems to simulate their behaviour and predict the impact of health system interventions to support policy-makers in determining the most appropriate actions to improve health outcomes.<sup>14-16</sup>

## Interventions

The scenarios tested in the model include policies related to the effectiveness of MDRTB treatment and the level of population coverage with HAART treatment. With respect to MDRTB, two effectiveness levels are selected: (i) 5% cure rate and (ii) 80% cure rate. The first level reflects documented outcomes of DOTS programmes implemented in Russia.<sup>17</sup> The second level represents what can be potentially achieved with a well-resourced and well-organized MDRTB control programme with access to second-line drugs.<sup>5,18,19</sup>

With respect to HAART coverage, we included five possible scenarios ranging from no population coverage (0%) to full coverage of all individuals infected with HIV who are likely to benefit (100%) with 25% increments, including 25%, 50% and 75% coverage.

The impact of these scenarios on the cumulative deaths from tuberculosis, MDRTB and deaths associated with AIDS were analysed. Under all the scenarios, we assumed a case detection rate of 70% for cases of infectious tuberculosis and 85% treatment success rate for cases of drug-susceptible tuberculosis (DSTB), in line with targets set by the World Health Organization (WHO).<sup>20</sup>

## Model description

The model was developed in two stages. First, we constructed a tuberculosis transmission dynamics model – including disease, detection and treatment of both DSTB and MDRTB. Second, we extended the model by adding HIV/AIDS, including acquisition and spread of HIV, development of AIDS and the effects of treatment with HAART for individuals with late-stage HIV or AIDS.

## Model of DSTB transmission

The natural history of tuberculosis transmission is represented by a stock and flow structure in which individuals move from the state of 'susceptible individuals' to the state of 'latently infected individuals'. From the latently infected state, some individuals progress to the 'DSTB disease' state rapidly, whereas others progress slowly.<sup>21,22</sup> Without therapeutic interventions, individuals with disease may die, develop persistent disease or 'self-cure'.<sup>23-26</sup>

The model incorporates a therapeutic intervention for individuals who have progressed to the 'DSTB disease' state. These individuals, when detected, enter a drug treatment phase for the first time. They may die, be cured or develop persistent disease. Those with persistent disease may remain in that state, die or return to treatment at a later stage, a state from which, again, they may remain, die or be cured.

## Model of MDRTB transmission

Two processes drive the spread of MDRTB. First, individuals with DSTB entering treatment for the first time may develop MDRTB – a process known as *secondary* or *acquired* infection. Second, susceptible individuals who come in contact with individuals with acquired MDRTB may develop tuberculosis with a multidrug-resistant strain of *Mycobacterium tuberculosis*<sup>19,27,28</sup> – a process known as *primary* MDRTB. These individuals progress to the 'MDRTB disease' state rapidly or slowly, in a similar fashion to DSTB.

Individuals with MDRTB enter a treatment phase from which they may progress to three states: death, cure or persistent MDRTB. A stock and flow diagram that represents the combined transmission dynamics of DSTB and MDRTB is presented in Figure 1.

## Model of HIV transmission

The HIV transmission sub-system model assumes individuals will be in one of three states: (i) HIV seronegative, (ii) HIV seropositive or (iii) AIDS. Any individual represented in any of the states described in the tuberculosis model will also be represented in one of the three states described in the HIV transmission model. Figure 2 presents the HIV transmission process for one specific tuberculosis state, 'latently infected DSTB'. Given that, in the Russian Federation, a very high proportion of HIV-seropositive individuals acquired HIV through intravenous drug use and a small proportion through secondary sexual spread, the model restricts transmission to the intravenous drug use route.<sup>29</sup> The transmission risk of moving from HIV-seronegative to HIV-seropositive state depends on: (i) the average number of injections per unit time, (ii) the probability that the injection equipment is contaminated with HIV, (iii) the probability of HIV transmission and (iv) the prevalence of intravenous drug users (IDUs) in the overall adult population.<sup>30-32</sup> For the purposes of our model, the proportion of the population who are IDUs is assumed to remain constant.

Individuals who become HIV seropositive are assumed to progress over a period of 10 years to develop AIDS. Because of the breakdown in the immune system that results, co-infection with DSTB or MDRTB means that these individuals will progress faster to the corresponding disease states than individuals without AIDS.

If an individual with AIDS is not treated with HAART, it is assumed that they will die within two years. However, individuals treated with HAART may live for a period of 10 years after reaching the AIDS disease state. Furthermore, if an individual co-infected with AIDS and tuberculosis is treated with HAART, their disease progression is similar to that of an individual without HIV/AIDS.

## Parameter estimation and model validation

The parameters in the model have been drawn from published estimates and, where these are unavailable, explicit assumptions have been made. We identified studies

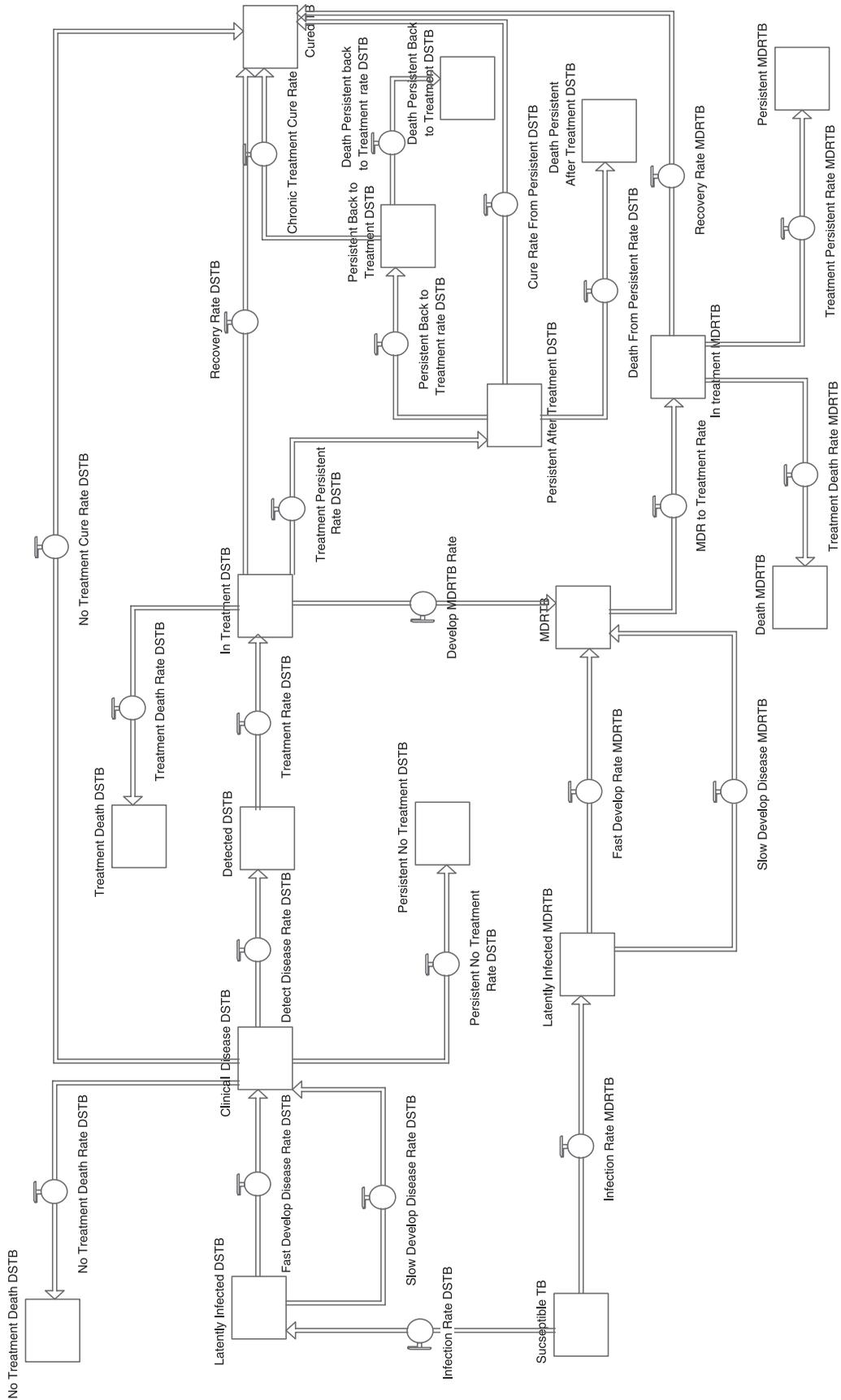


Figure 1 The drug-sensitive tuberculosis and multidrug-resistant tuberculosis transmission model

through a systematic Medline search and obtained data from locally collected routine statistics. Tables showing tuberculosis transmission parameters corresponding to the HIV-seronegative, HIV-seropositive and AIDS states are not shown but are available from the authors on request.

To validate the model before its use for scenario analysis, trends were compared against available data regarding cumulative tuberculosis deaths in Samara Oblast from 1997 to 2002. The model replicated, with a high level of accuracy, the real world dynamics of the most important variables such as tuberculosis prevalence and cumulative deaths.<sup>12</sup>

## Scenario analysis parameters

Scenario analysis parameters include MDRTB cure rate and HAART population coverage. MDRTB cure rate is assigned to two levels: 5% and 80%. HAART population coverage varies from 0% (no coverage) to 100% (full coverage) with increments of 25%. The time frame for the simulation model is 10 years and is assumed to start at the beginning of 2003 and finish at the end of 2012. The initial values in the simulation correspond to the number of adults in each of the tuberculosis and HIV states represented in the model at the beginning of year 2003. These values are presented in Table 1.

## Model outputs

The model predicts the following outcomes: (i) cumulative deaths from tuberculosis that includes deaths from all forms of tuberculosis and deaths from HIV-associated tuberculosis; (ii) cumulative deaths from HIV-associated tuberculosis and (iii) cumulative deaths from HIV-associated MDRTB.

## RESULTS

Samara Region has a total population of 3.3 million people, of whom 1.6 million are adults. In January 2003, the estimated prevalent number of individuals with tuberculosis was 2690, of whom 40% had MDRTB (Table 1). The

region has experienced an explosive epidemic of HIV, and by January 2003 there were an estimated 17,000 prevalent cases (Table 1).

The cumulative deaths from tuberculosis, with two levels of MDRTB cure rate of 5% and 80% and the five levels of HAART coverage (from 0% to 100%), are presented in Figure 3. The results indicate that, in the 10-year period of simulation, in the absence of HAART coverage, the cumulative number of tuberculosis deaths will be 6650 with an MDRTB cure rate of 5%, but will decline to 4888 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 increases significantly. Hence, the cumulative number of deaths from tuberculosis at 5% and 80% MDRTB cure rates decline: (i) with 25% HAART coverage by 3% to 6473 at 5% MDRTB cure rate and 3% to 4721 at 80% MDRTB cure rate, respectively; (ii) with 50% HAART coverage by 7% to 6162 and 9% to 4428; (iii) with 75% HAART coverage by 17% to 5505 and 22% to 3808 and (iv) at 100% HAART coverage declines substantially by 46% to 3595 and 60% to 1993, respectively (Figure 3).

Cumulative deaths from HIV-associated tuberculosis with no HAART coverage reach 3686 and 3473 when MDRTB cure rates are, respectively, 5% and 80% (Figure 4). At 5% and 80% MDRTB cure rates, cumulative HIV-associated deaths decline in a non-linear manner: (i) at 50%

Table 1 Initial conditions for the simulation model reflecting estimated state in Samara Oblast, January 2003

Stock (variable state)	Initial value
Susceptible TB-HIV seronegative	1,608,596
Susceptible TB-HIV seropositive	12,044
Latently Infected DSTB-HIV seronegative	681,408
Latently Infected DSTB-HIV seropositive	4862
Disease DSTB-HIV seronegative	1400
Disease DSTB-HIV seropositive	100
Disease MDRTB-HIV seronegative	1146
Disease MDRTB-HIV seropositive	44

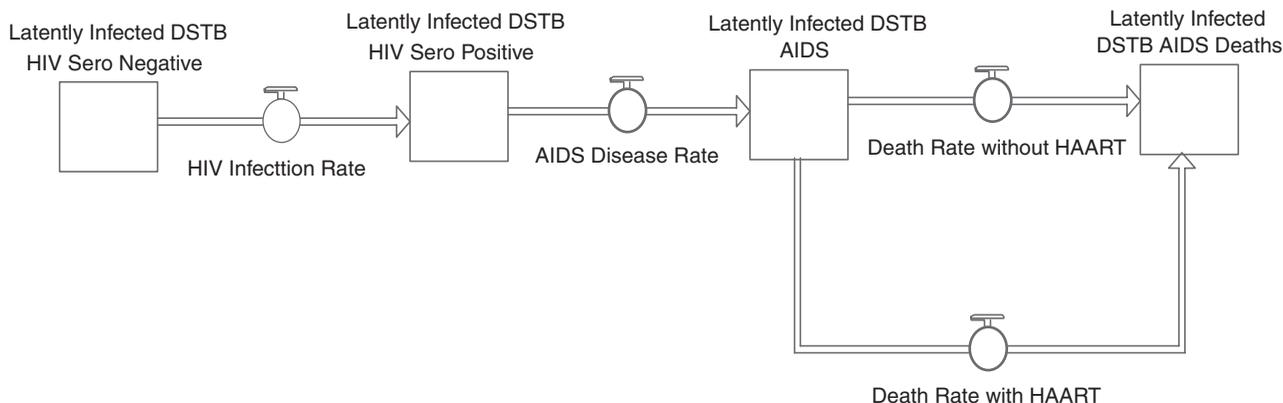


Figure 2 The HIV/AIDS transmission sub-system for the tuberculosis state 'Latently Infected drug-sensitive tuberculosis'

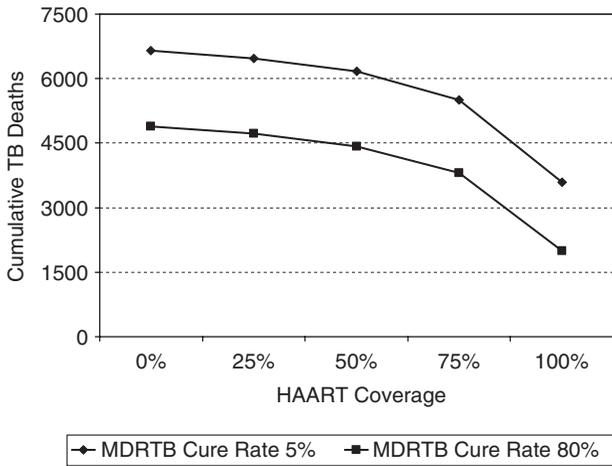


Figure 3 Cumulative deaths at 10 years from tuberculosis at varying HAART coverage levels and multidrug-resistant tuberculosis cure rates of 5% and 80%

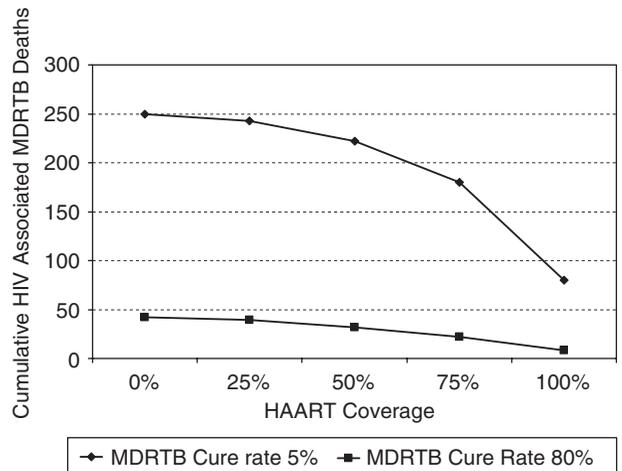


Figure 5 Cumulative HIV-associated multidrug-resistant tuberculosis deaths at 10 years

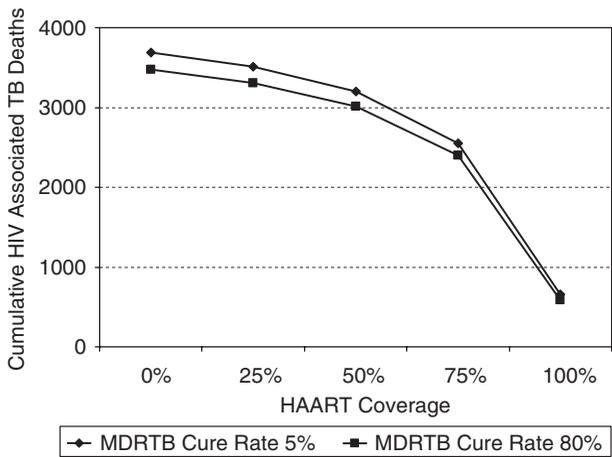


Figure 4 Cumulative HIV-associated tuberculosis deaths at 10 years at varying HAART coverage levels and with multidrug-resistant tuberculosis cure rates of 5% and 80%

HAART coverage by 13% to 3204 and 14% to 3014; (ii) at 75% coverage by 31% to 2552 and 32% to 2396 and (iii) beyond 75% coverage, the number of deaths declines substantially so that when 100% HAART coverage is achieved, HIV-associated tuberculosis deaths fall by 83% to 657 and by 84% to 585, respectively (Figure 4). The acceleration in the decline in death rates beyond 75% is much faster for HIV-associated tuberculosis deaths than for tuberculosis only deaths.

In the absence of any HAART coverage, the cumulative number of deaths from HIV-associated MDRTB is 250 at 5% and 42 at 80% MDRTB cure rates, respectively. The cumulative number of HIV-associated MDRTB deaths declines substantially with HAART coverage of 75% and beyond, and at 100% HAART coverage these deaths

diminish by 68% to 80 and by 80% to eight with 5% and 80% MDRTB cure rates, respectively (Figure 5).

## DISCUSSION

We show that in a setting where there is currently a high prevalence rate of MDRTB and an immature, contained epidemic of HIV in IDUs, the epidemic of MDRTB, if left unchallenged with effective MDRTB treatment but in particular high HAART coverage, 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 good 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% and particularly above 75%.

Current policy recommendations for HAART coverage focus on scaling up but do not explicitly identify an optimal coverage target.<sup>33</sup> We demonstrate that, in the epidemiological setting described above, 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 death rates can be explained by the complex interactions at play between different elements of the tuberculosis and HIV transmission systems. Systems with complex relationships, which include feedback loops, behave in a non-linear manner and may respond in counter-intuitive ways to interventions, which are designed to influence system elements.<sup>9,12,34-37</sup> This may result in 'policy resistance'.<sup>11,38</sup> One way to reduce this policy resistance is to adopt 'systems thinking', which requires a detailed analysis of these system elements and the ways they interact.<sup>39</sup>

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, do not enter the model. As cohorts age, they are likely to influence the transmission dynamics of these two infections. The extent of the HIV epidemic may be underestimated in the model because the population at risk of HIV, which 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 underestimation 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 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 good regarding the rate of acquiring HIV. The rate of movement from the HIV-seronegative state to the HIV-seropositive 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 the patient's behaviour within institutions. Notwithstanding these limitations, we believe that the findings are sufficiently robust to inform policy.

Our findings have implications for the governments, the WHO, the World 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-seropositive 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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