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# HIV/AIDS EPIDEMIC IN INDIA AND PREDICTING THE IMPACT OF THE NATIONAL RESPONSE: MATHEMATICAL MODELING AND ANALYSIS

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Abstract. After two phases of AIDS control activities in India, the third phase of the National AIDS Control Programme (NACP III) was launched in July 2007. Our focus here is to predict the number of people living with HIV/AIDS (PLHA) in India so that the results can assist the NACP III planning team to determine appropriate targets to be activated during the project period (2007-2012). We have constructed a dynamical model that captures the mixing patterns between susceptibles and infectives in both low-risk and high-risk groups in the population. Our aim is to project the HIV estimates by taking into account general interventions for susceptibles and additional interventions, such as targeted interventions among high risk groups, provision of anti-retroviral therapy, and behavior change among HIV-positive individuals. Continuing the current level of interventions in NACP II, the model estimates there will be 5.06 million PLHA by the end of 2011. If 50 percent of the targets in NACP III are achieved by the end of the above period then about 0.8 million new infections will be averted in that year. The current status of the epidemic appears to be less severe compared to the trend observed in the late 1990s. The projections based on the second phase and the third phase of the NACP indicate prevention programmes which are directed towards the general and high-risk populations, and HIV-positive individuals will determine the decline or stabilization of the epidemic. Model based results are derived separately for the revised HIV estimates released in 2007. According to revised projections there will be 2.08 million PLHA by 2012 if 50 percent of the targets in NACP III are reached. We perform a Monte Carlo procedure for sensitivity analysis of parameters and model validation. We also predict a positive role of implementation of anti-retroviral therapy treatment of 90 percent of the eligible people in the country. We present methods for obtaining disease progression parameters using convolution approaches. We also extend our models to age-structured populations.

**Abbreviations used:** AIDS—Acquired Immunodeficiency Syndrome, ART—Anti-Retroviral Therapy, BSE—Bovine Spongiform Encephalitis, FSW— Female Sex Worker, HBV—Hepatitis B Virus, HCV—Hepatitis C Virus, HIV—Human Immunodeficiency Virus, HRG—High Risk Group, IDU—Injecting Drug User, MSM—Men having Sex with Men, NACO—National AIDS Control Organization, NACP—National AIDS Control Programme, NGO—Non-Governmental Organization, PMTCT—Peri-natal Mother to Child Transmission, PPS—Positive Prevention Strategy, SARS —Severe Acute Respiratory Syndrome, STI—Sexually Transmitted Infection, VCTC—Voluntary Counseling and Testing Centre

1. **Introduction.** The HIV (Human Immunodeficiency Virus) epidemic has been evolving in India since the first case was detected in Tamil Nadu in 1986. Based on the sentinel surveillance data, the estimated number of HIV-infected persons has gone up from 3.5 million in 1998 to over 5.206 million in 2005 accounting for one eighth of all infections in the world [43]. These estimates indicate that there has been no dramatic upsurge in the spread of HIV infection across the country since 1998. However, state-specific variations in the profile of the epidemic have been observed. Several states in southern India and the north-eastern part of the country have shown higher HIV prevalence and diversity in predominant patterns of HIV transmission. Even low HIV-prevalence states are characterized by the presence of high-risk pockets with potential for increased spread of the epidemic in these states. HIV infection during the 80s and 90s reflects an increase in the number of AIDS (Acquired Immunodeficiency Syndrome) patients and consequent medical, economic, and social implications. The epidemic in India is very heterogeneous with diverse modes of infection, particularly in the southern and western states of Tamil

Nadu, Karnataka, Andhra Pradesh, and Maharashtra, and the two north-eastern states of Nagaland and Manipur. Even within states, there is a wide variance in HIV prevalence between and within districts as evidenced by data from HIV sentinel surveillance sites and Voluntary Counseling and Testing Centers (VCTC). Information from AIDS case reporting indicates that sex continues to be the main route (86 percent) of transmission in most parts of the country. Blood products, injecting drug use, and perinatal transmission from mother to child are the other routes. Injecting drug use is the predominant route of transmission in the north eastern states of India. India has mounted a response to the HIV epidemic through two NACPs (National AIDS Control Programmes, called NACP I and NACP II). The third phase of the program was initiated in early 2007 (we call this NACP III). The modeling exercise is undertaken to assist the NACO (National AIDS Control Organization) and NACP III planning teams to realize a realistic scenario in the setting of the new initiatives undertaken during the project period from 2006 to 2011. One of the novel features of NACP III modeling is to take into account Positive Prevention Strategy (i.e., preventive measures of HIV infected people). Incorporation of this strategy is a major advancement over NACP II strategies.

Models are introduced in Section 3 and details of methods involved are in Appendices I to V.

2. **Background and scope: Third phase policy (2006-2011).** The focus of NACP III is to reduce new infection of HIV by 60 - 80 percent in different regions of India through prevention with care and support. The activities include greater coverage of more than 80 percent of the High Risk Population, which includes female sex workers, MSM (men having sex with men) and IDU (injecting drug user) with preventive interventions including, condom promotion, and STD (sexually transmitted diseases) treatment. This provision of care support and treatment includes first line ART (Anti-Retroviral Therapy) to all infected people, with the target of 300,000 treated over the next five years, with effective linkage of prevention with care and support so that all patients receiving care and support participate in the prevention activities and prevent the spread of HIV. Interventions also include vulnerable and other bridge populations of STD clinic attendees, street children, young men, and migrant workers. There is a programme of general IEC (information, education and counseling) in the general population, which includes special targeting of young people, women, and out of school youths, to increase awareness and knowledge of HIV and risks of transmission. This will be supported through a network of district based infrastructure and effective monitoring to ensure quality of service delivery. The work builds on the success of the earlier programmes in India which have shown that focussed effort on high risk groups (HRG) can control the epidemic, as demonstrated in the state of Tamil Nadu as well as in other international efforts (for example, Thailand and Uganda). Success is best achieved via public-private partnership through TIs (targeted interventions). Currently nearly 50 percent of the population has been successfully targeted and the plan is to increase awareness to 80 percent or more of the population.

2.1. **Major routes of transmission in India.** The major routes of transmission of HIV virus continue to be sexual (86 percent). The other routes are blood products, perinatal transmission, and injecting drug use. The latter is the predominant

route of transmission particularly in the north-eastern states of India [43]. See Figures 1 and 2 for trends of HIV estimates and prevalence in various sub-populations in India [37].

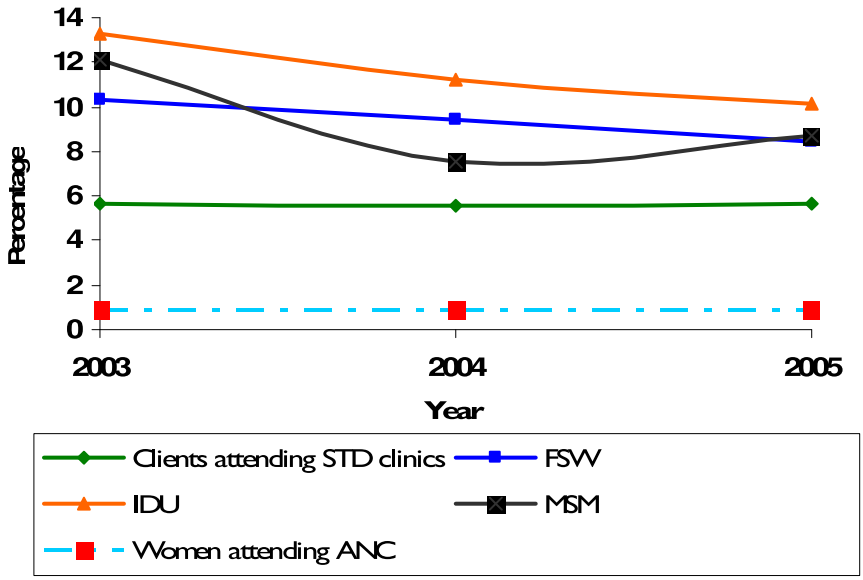


FIGURE 1. Trends of HIV prevalence in various sub-populations. Year-wise HIV prevalence in the five subpopulations, namely, anti-natal care population, STD, female sex workers, IDUs, and MSM, plotted from the data available from the HIV sentinel surveillance report [38].

2.2. **Sex ratio in Indian epidemic.** The infection remained limited to sex workers and their clients in the early part of the epidemic and remains so in many states in India. However, in other states, the infection has spread from sex workers to the general population and women are being infected by their husbands who indulge in high-risk behavior. The male to female ratio of infected people has shifted from 0.55 in 2001 to 0.6 in 2006 [58] (see Figure 3).

2.3. **Groups at high risk of acquiring HIV.** There are groups of individuals who are at high-risk of acquiring HIV infection. These are sex workers, IDUs and MSM including transgender sub-populations. Other groups who are also at-risk, include: women, youth and adolescents, migrants, street children, and transport workers etc. There are statistical issues that need to be addressed for estimating sizes of risk groups [51, 52]. NACO recently constituted an expert group to assess the number of high-risk groups in the country. Table 1 provides the information regarding the high-risk group population based on best estimates and Table 2 provides various population sub-groups considered in our models.

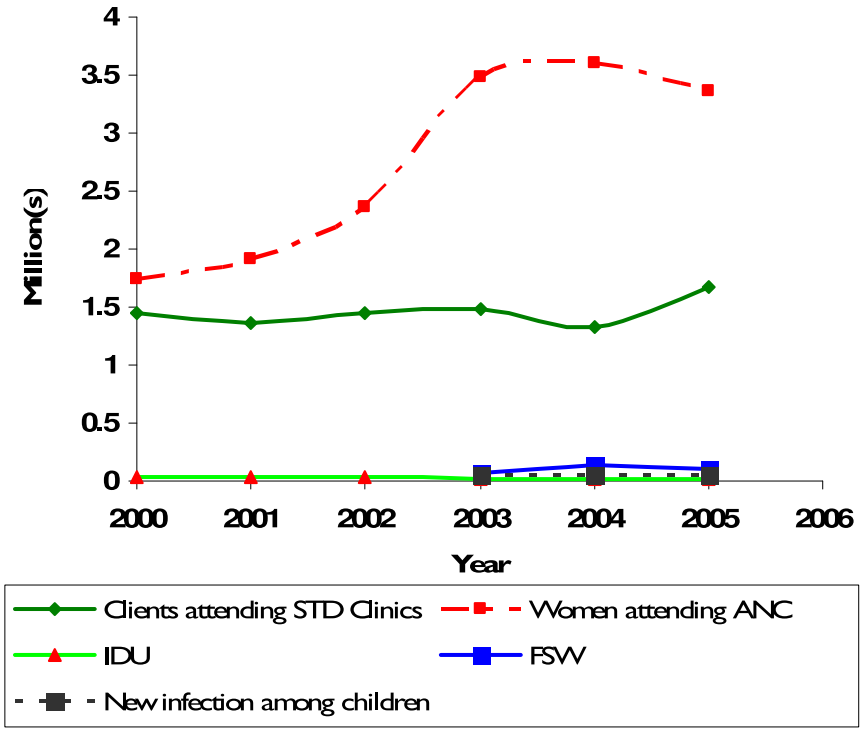


FIGURE 2. Trends of HIV estimates in various sub-populations. Year-wise HIV infection (in millions) during the period 2000 to 2005 for various subpopulations, namely, clients attending STD clinics, women attending anti-natal care clinics, IDUs, female sex workers, and new infection among children, plotted from data in the HIV sentinel surveillance report [38].

TABLE 1. Size of sub-populations

| Female Sex Workers | MSM more than 5 partners | Male Sex Workers | IDU | |
|---|---|---|---|---|
| | | | Male | Female |
| 831677 - 1250115 | 2,352,133 | 235,213 | 96463 - 189729 | 10055 - 33392 |

Data source: see reference 30.

2.4. **Knowledge and behavior.** In 2001, a nationwide behavioral surveillance survey [10] was conducted to provide baseline information on the risk behavior patterns in the country, for both the general population and high-risk groups such as female sex workers and their clients, MSM, and IDUs. The survey revealed variations in knowledge of HIV/AIDS between different states and between rural and urban populations. While 76 percent of the Indian population had heard of HIV/AIDS the figure was 93.2 percent for urban males and 65.2 percent for rural women. In Bihar, only 21.5 percent of the adult population and in UP only 27.6

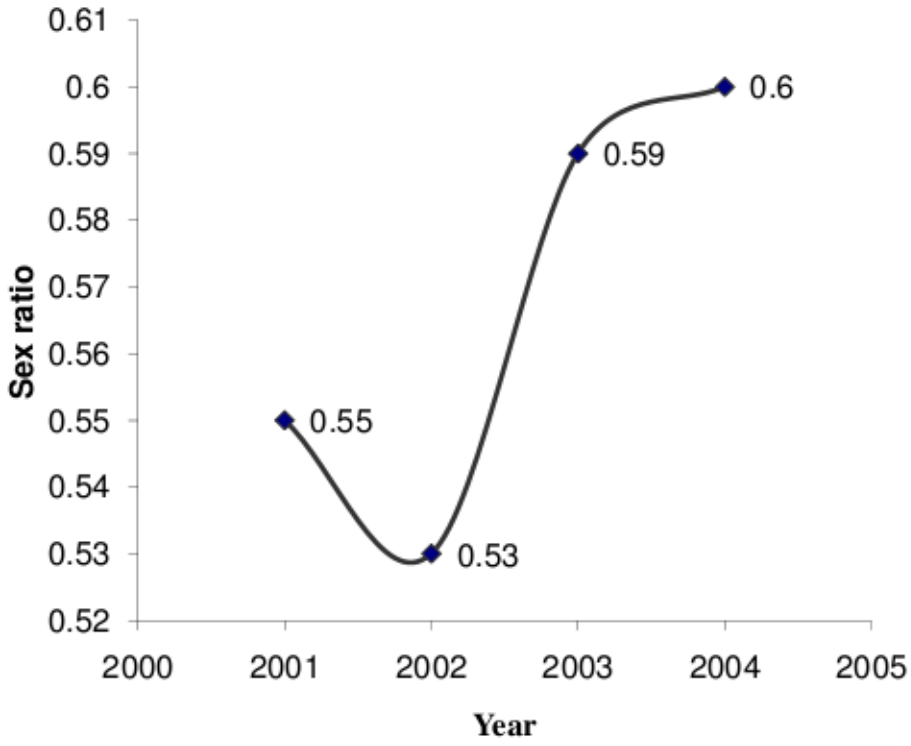


FIGURE 3. Male to female ratios of HIV prevalence among STD clinic attendees. Ratios of male to female prevalence rates plotted against time from the STD data obtained from clinics. This figure is taken from the Project Implementation Plan, NACP III (2006). We have modified the color shades.

percent had heard of HIV/AIDS. While 71.1 percent of Indians were aware of the sexual route of HIV transmission, only 18.6 percent of rural women had heard of the linkage. The knowledge and behavior indicators of high-risk groups showed similar wide gaps.

2.5. **AIDS-related deaths.** There could be moderate to severe impact of AIDS related mortality on the demographic situation in certain populations in India. There were modeling attempts in India that indirectly estimate excess deaths due to AIDS from time series data available at the municipal corporation public health records. Community prevalence surveys also indicate AIDS-related deaths in certain high-risk groups [65]. There are estimates proposed by various groups, but they did not provide the methodology adopted in their estimation procedures. Since records on AIDS-related deaths are not available for India and for each state, it is not clear what is the actual impact during the last decade of AIDS on crude death rate and age specific death rates. Estimations based on back-calculation suggest there were 160,000-200,000 deaths up to 2000 since the beginning of the epidemic [53].

2.6. **Migration impact on HIV.** There have been studies that documented vulnerability to HIV among migrant workers in slum populations in India due to their

lifestyle and living conditions [61]. High migration of the infected population and their mobility could be spreading the disease in some parts of India. There is a need to undertake more substantial studies to quantify the migration-related HIV infections in India and for models to be developed for understanding migration impact at the state level.

3. **Description of the non-linear deterministic models constructed for predicting the number of people living with HIV.** Mathematical and statistical models can serve as tools for understanding the HIV epidemic if they are constructed carefully. In the past two decades dynamical models have provided important insights into infectious disease epidemiology and assisted in designing effective control strategies and cost analysis for HIV/AIDS, BSE (Bovine Spongiform Encephalitis), Foot and Mouth Diseases and SARS (Severe Acute Respiratory Syndrome). The model that we construct here uses the basic principles in AIDS modeling developed by Anderson and May [2, 3] and May and Anderson [33] that have been widely accepted as one of the key strategies to understand the progress and impact of the epidemic in different settings. There have been several modifications to these models over the past decade to account for the impact of vaccines and anti-retroviral therapies. In general, dynamic modeling reflects important epidemiological and behavioral determinants of the disease and are constructed using a mathematical framework.

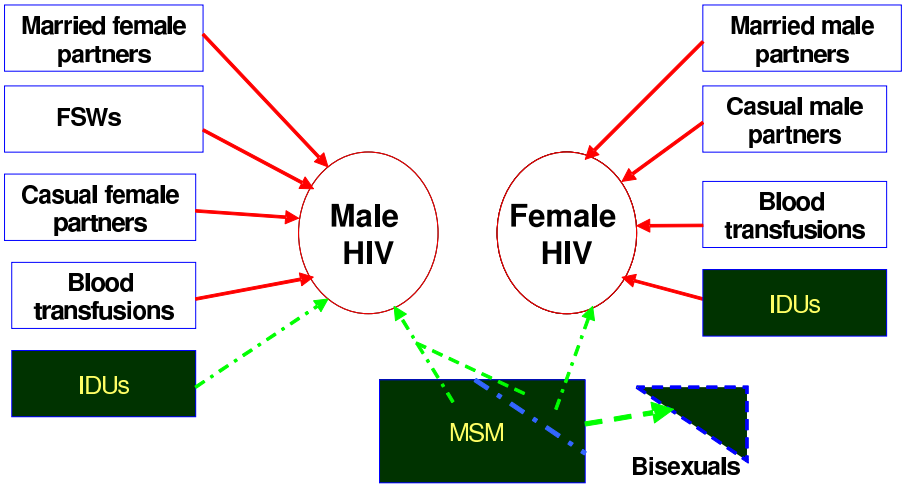


FIGURE 4. Sources of infection by gender. In-flow to the male and female HIV infection classes and route of transmission by sub-population. A male can acquire infection from any of the six infected host populations (or sub-populations) and a female can acquire infection from any of the five infected host or sub-populations.

In this paper, we construct ordinary differential equation models to explain the spread of HIV between male and female and the spread within MSM and within IDUs. Sexual transmission of infection between genders could be due to casual

sex, female sex workers, male sex workers, and within married couples if one of the spouses is infected. For the data in India, it was observed that expanding effective prevention programmes within married couples might also be responsible for controlling the spread between regular partners [34]. For the purpose of the present article, we briefly describe our model equations and explain the parameters and their interactions. General discussions on such model construction and analysis can be found elsewhere [2, 14, 28, 6, 54]. In spite of prevention programmes, which are actively engaged in reducing the disease burden, there is a need to widen them and bring in more effective preventive responses [27].

Our model for NACP III target interventions for the programme period differs from previous models in that it includes prevention measures to be launched for infected people in addition to NACP II policies. We project HIV estimates based on the three levels of targets fixed by NACP III. Various sources contributing to infection for male and female populations are explained in Figure 4. The dynamic compartments in the model are $S_i, G_i, I_i$, and $D_i$, the number of susceptibles, sexually transmitted infections, HIV infecteds and AIDS cases by gender ($i$=*1* for male and $i$=*2* for female), respectively. Male susceptibles can acquire infection from six infected sub-populations ($j$=*1* for female marriage partner, $j$=*2* for female commercial sex partner, $j$=*3* for female casual partner, j=4 transmission through blood, $j$=*5* for MSM, $j$=*6* for IDUs). A detailed description of the variables in the various models in this work and their terminology can also be found in Table 2. MSM transmissions are not acquired from females. Out of the 2,352,113 estimated number of MSM in India [38, 39], 30 per cent participate in bisexual activities and the remaining 70 per cent are predominantly homosexual. We assume that MSM interactions are not particularly relevant in the major mixing of the population. Hence we have separated MSM interactions from the main model and separately studied the spread of HIV among them. Although IDUs exist all over India, spread of infection among them is very high only in a few metropolitan cities and parts of north-eastern India [21, 67]. Very little information is available on IDUs who have sex partners and their role in transmission or acquisition of the virus in addition to that of regular IDU activity. So, we have separately considered the dynamics of IDU infections. Estimating subpopulation sizes and their infection levels is essential for predicting accurately the future course of action for HIV control [51]. To make an accurate prediction, we need to estimate the population at risk of acquiring the infection in various subpopulations, but identifying the representative population is not always straightforward (for example, due to the stigma attached). We make use of the best available data obtained either from the NACP III framework [38] or where applicable we consider expert opinions from the task team. As better data on subpopulation estimates become available, model predictions will become more accurate. By raising the surveillance and spreading the programme to low-risk groups and vulnerable groups, HIV estimates can be made more accurate [50]. The idea of estimating prevalence levels in each subpopulation at risk and summarizing to obtain national estimates in concentrated and generalized epidemics is well documented [68].

Sources of infection by gender are illustrated in Figure 4, where (dark green) shaded regions are those interactions whose dynamics are studied separately. Female susceptibles can acquire infection from five infected sub-populations ($j$=*1* for male marriage partner, $j$=*2* for male bisexual MSM, $j$=*3* for male casual partner, $j$=*4* transmission through blood, $j$=*5* for IDUs). For example, the combination *"1j"* in

TABLE 2. Model variable and description

| Variables | Description |
|---|---|
| $S_i$ | Number of susceptibles of gender $i$ of HIV and STI |
| $G_i$ | Number of individuals of gender $i$ with STI infection |
| $I_i$ | Number of individuals of gender $i$ with HIV infection |
| $D_i$ | Number of individuals of gender $i$ with AIDS disease |
| $S_m$ | Number of MSM who are susceptible to HIV and STI |
| $G_m$ | Number of MSM with STI infection |
| $I_m$ | Number of MSM with HIV infection |
| $D_m$ | Number of MSM with AIDS disease |
| $S_{IDU}$ | Number of IDUs who are susceptible to HIV and STI |
| $I_{IDU}$ | Number of IDUs with HIV infection |
| $D_{IDU}$ | Number of IDUs with AIDS disease |

the model equations represents a given male who acquired infection from the $j^{th}$ sub-population and similarly *"2j"* represents a given female who acquired infection from the $j^{th}$ sub-population. Overall we have three ordinary differential equation models; one for the total dynamics (excluding MSM and IDU), one for MSM infections, and one for IDU infections.

The overall schematic structure of the model is shown in Figure 5. We aim to answer questions such as what proportion of reduction in HIV is due to an increase in ART users, an increase in positive prevention strategy or due to an increase in general preventive measures? We base our answers on information on modes of transmission of virus in India, sub-population infection levels, and mixing patterns between susceptibles and infecteds in various sub-populations. The ordinary differential equations that describe the mixing scenario in general population explained above are:

Model 1: Spread of HIV in general population

$$\begin{aligned}
\frac{dS_i}{dt} &= r_i S_i - f(S_i, G_j, I_j; \lambda_{ij}, \beta_{ij}) + \phi G_i \\
\frac{dG_i}{dt} &= f'(S_i, G_j; \lambda_{ij}) - g(G_i, I_j; \alpha_{ij}) - \mu G_i - \phi G_i \\
\frac{dI_i}{dt} &= h(S_i, I_j, G_i; \beta_{ij}, \alpha_{ij}) - \delta_i I_i - \gamma_i I_i \\
\frac{dD_i}{dt} &= \gamma_i I_i - \delta_i D_i.
\end{aligned} \tag{1}$$

Here, $r_i$ is natural growth rate of susceptibles, $\mu$ is average general mortality rate, $\delta_i$ is HIV related mortality rate, $\phi$ is the rate of recovery of sexually transmitted infections (STIs) (excluding HIV), $\lambda'$s, $\beta'$s and $\alpha'$s are, respectively, transmission rates of STI, HIV from susceptibles (without STI) and STI infecteds with HIV from subpopulation $j$ of the opposite gender. $\gamma_i$ is the disease progression parameter indicating the rate at which HIV infected individuals progress to AIDS. Disease progression information is available for hospital based prevalent cohorts [24] and the relation between CD4 counts and clinical manifestations [20] in India. Issues like double censoring (i.e., roughly missing the data from both ends of the study period)

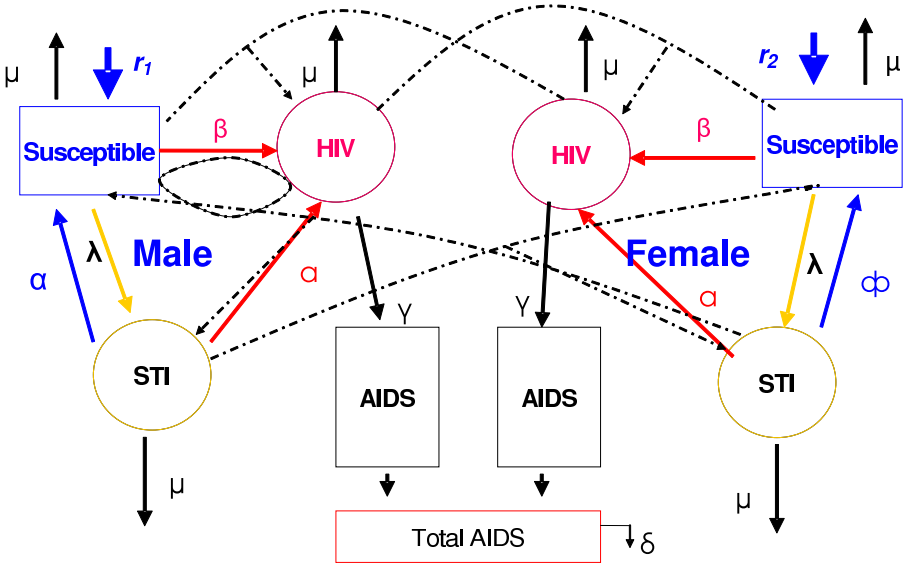


FIGURE 5. Schematic structure of the NACP III model. We show how the infection transmits from male to female and female to male. The dotted lines indicate how the susceptibles become infected from the opposite gender (either STI or HIV). The self loop within the male group indicates infection within MSM. Here, $r_i$ is the input into the susceptibles, $\mu$ is general mortality rate, $\delta$ is HIV related mortality rate, $\phi$ is the rate of recovery of STIs (excluding HIV), $\lambda$'s, $\beta$'s and $\alpha$'s are transmission rates of STI, HIV from susceptibles (without STI) and STI infecteds to HIV from each gender to opposite gender, respectively. $\gamma$ is the disease progression parameter indicating the rate at which HIV infected individuals progress to AIDS. A compartment and corresponding transmission rate are shown in the same color.

need to be taken into consideration, so there were parametric and non-parametric methods developed to estimate incubation periods in such data [55]. A susceptible individual can acquire either STI or HIV. Therefore these susceptibles will enter into either the HIV compartment or the STI compartment as shown in Figure 4, and HIV infected individuals will progress to AIDS. The function $f(S_i, G_j, I_j; \lambda_{ij}, \beta_{ij})$ accounts for transmission of STI and HIV infections to the susceptible class at rates $\lambda_{ij}$ and $\beta_{ij}$, respectively, from subpopulation $j$ (the respective size of the subpopulation $j$ is $N_j$) of opposite gender $i$. The function $f'(S_i, G_j; \lambda_{ij})$ accounts for transmission of STI from susceptibles and $g(G_i, I_j; \alpha_{ij})$ accounts for transmission of HIV to the STI infecteds at a rate $\alpha_{ij}$ and the function $h(S_i, I_j, G_i; \beta_{ij}, \alpha_{ij})$ accounts for transmission of HIV from both STI and general susceptibles class. See Appendix I for more details on these functions and other functions in the following models:

Model 2: Spread of HIV within MSM

$$\begin{aligned}
\frac{dS_m}{dt} &= r_m S_m - f_m(S_m, G_m, I_m; \lambda_m, \beta_m) + \phi G_m \\
\frac{dG_m}{dt} &= f'_m(S_m, G_m; \lambda_m) - g_m(G_m, I_m; \alpha_m) - \mu G_m - \phi G_m \\
\frac{dI_m}{dt} &= h_m(S_m, I_m, G_m; \beta_m, \alpha_m) - \delta_m I_m - \gamma_m I_m \\
\frac{dD_m}{dt} &= \gamma_m I_m - \delta_m D_m.
\end{aligned} \tag{2}$$

The four compartments in Model 2 are $S_m$, $G_m$, $I_m$ and $D_m$ representing, respectively, susceptibles, STI infecteds, HIV infecteds, and full-blown disease individuals. Here, $r_m$ is the recruitment rate into the susceptible MSM, $\phi$ is the rate of recovery of STIs, $\delta_m$ is HIV related mortality rate, $\lambda_m$, $\beta_m$ and $\alpha_m$ are transmission rates of STI, HIV from MSM (without STI) and STI infected MSM to HIV, respectively. $\gamma_m$ is the disease progression parameter indicating the rate at which HIV infected individuals progress to AIDS. The functions $f_m(S_m, G_m, I_m; \lambda_m, \beta_m)$, $f'_m(S_m, G_m; \lambda_m)$, $g_m(G_m, I_m; \alpha_m)$ and $h_m(S_m, I_m, G_m; \beta_m, \alpha_m)$ account, respectively, for transmission of STI and HIV infections to the susceptibles, transmission of STI to the susceptibles, transmission of HIV to the STI infecteds, and transmission of HIV from both STI and general susceptibles. Limited information is available on MSM data and infection rates in the country. The estimates published by various reports are inconsistent. We use demographic, epidemiological data given in Tables 2 and 3 and parameter values in Table 4 (prepared for NACP III) for the present analysis. We calculated the weighted average of prevalence rates from data and used these average values in models for MSM and IDUs. Parameter value selection and related references can be found in Appendix II. However we note that more information on the mixing, behavioral, and epidemiological parameters is required for several time periods before a reliable model and subsequent trend analysis with a greater degree of accuracy can be obtained. Those MSM who are bisexuals will also contribute to infection via their spouses and the corresponding rate is preserved in Model 1. The sex worker population was considered for both males and females. Some of the MSM are considered as sex workers.

Model 3: Spread of HIV within IDU

$$\begin{aligned}
\frac{dS_{IDU}}{dt} &= r_{IDU} S_{IDU} - f_{IDU}(S_{IDU}, I_{IDU}; \lambda_{IDU}) \\
\frac{dI_{IDU}}{dt} &= f_{IDU}(S_{IDU}, I_{IDU}; \lambda_{IDU}) - \delta_{IDU} I_{IDU} - \gamma_{IDU} I_{IDU} \\
\frac{dD_{IDU}}{dt} &= \gamma_{IDU} I_{IDU} - \delta_{IDU} D_{IDU}.
\end{aligned} \tag{3}$$

The three compartments in Model 3 are $S_{IDU}$, $I_{IDU}$, and $D_{IDU}$ representing, respectively, susceptibles, HIV infecteds, and full-blown disease individuals. Here, $r_{IDU}$ is the rate of movement into the susceptible MSM class, $\delta_{IDU}$ is HIV related mortality rate, $\lambda_{IDU}$ is transmission rate from infected IDUs to susceptibles.

TABLE 3. Demographic and epidemiological values in Models 1-3

| Description | Value | References |
|---|---|---|
| 15 – 49 population | 269965931 (M)<br>251431886 (F) | 12 |
| Marriage Rates | 80 (F), 60 (M) | 12 |
| HIV Infecteds gender ratio | 1 M : 0.6 F | 39 |
| FSW population | 1040558 | 41 |
| MSM population | 2352113 | 41 |
| IDUs | 143096(M), 43447(F) | 41 |
| 15 – 49 STI Prevalence | 6%(M), 5%(F) | 42 |
| Blood transfusions | 4.4 million | 41 |
| IDU transmission rate through injections | 30% | 67,<br>expert opinion |
| Prevalence of HIV in IDUs | 16.3% | weighted average calculated from surveillance data |
| HIV transmission through blood | 0.034% | 43 |
| HIV prevalence in MSM | 7.7% | weighted average calculated from surveillance data |
| General condom usage in high risk behavior class | 30%<br>5.0% | 10<br>10 |

TABLE 4. Parameter values used for Models 1-3

| Parameter | Description | Value $year^{-1}$ | References |
|---|---|---|---|
| $r_1$, $r_2$ | Annual natural growth rate | 2% | 12 |
| $\lambda_{1j}, \lambda_{2j}$ $(\lambda_{1j} = \lambda_m, \lambda_{IDU})$ | Female to male and male to female transmission rates of STI | 0.003,<br>0.006 | 5 |
| $\beta_{1j}, \beta_{2j}$ $(\beta_{1j} = \beta_m, \beta_{IDU})$ | Female to male and male to female transmission rates of HIV | 0.006,<br>0.009 | 5 |
| $\alpha_{1j}, \alpha_{2j}$ $(\alpha_{1j} = \alpha_m, \alpha_{IDU})$ | Female to male and male to female transmission rates of HIV among STI | 0.012,<br>0.018 | 5 |
| $\mu_1, \mu_2$ | General mortality rate (15-59) age group per 1000 per year | 0.0041,<br>0.0025 | 63 |
| $\delta_1, \delta_2$ $(\delta_{1j} = \delta_m, \delta_{IDU})$ | Male and Female HIV/AIDS related mortality rate per year | 10.3% | 58 |
| $\gamma_1, \gamma_2$ $(\gamma_{1j} = \gamma_m, \gamma_{IDU})$ | Male and female rate of disease progression per year. (This parameter is the reciprocal of the average incubation period) | 0.125,<br>0.125 | 24,<br>64 |
| $\varphi_1, \varphi_2$ | Male and female STI recovery rates | 0.5, 0.3 | 5 |

$\gamma_{IDU}$ is the disease progression parameter indicating the rate at which HIV infected individuals progress to AIDS. The function $f_{IDU}(S_{IDU}, I_{IDU}; \lambda_{IDU})$ accounts for transmission of HIV infections to the susceptible class. Those IDUs who are bisexuals will also contribute to their spouses and the corresponding rate is considered in Model 1.

When the interventions are triggered, the key parameters of virus transmission in the model equations will be affected. For example, due to an increase in condom usage by infected people, the transmission rate to susceptibles will be reduced. At the same time, due to more preventive measures (as part of knowledge and behavioral intervention) and improved health due to ART there might also be an increase in sexual activity that will again result in increased contact rates between susceptibles and infecteds. We used demographic data acquired from the Census of India and Sample Registration System, India tables [12, 63]. See Table 5 for NACP II target interventions, Table 6 for the ART scale-up plan (also see section 4), and Table 7 for the status of the response in NACP III ART scale-up. For various programme targets that have affected parameters, see Tables 8 and 9 (details can be obtained from the NACO [40, 41, 42]). Our models developed here give spread of the virus in the total population. In Appendix V, we present extensions of the above models that can be useful in predicting age-specific prevalence. Spread is not uniform in all the age groups, and unless reliable age-specific incidence and prevalence estimates, and epidemiological and clinical parameters are available, it is difficult to assess the disease spread within various age-groups.

## 4. **Progamme interventions.**

### 4.1. **Different levels of future response.**

The four levels of response considered in this paper are the following:

1. Interventions to continue at NACP II Level
2. Rapid scale-up anti-retroviral therapy without positive prevention
3. Expanded coverage of high-risk groups with integration of prevention with care support (50 percent target)
4. Expanded coverage of high-risk groups with integration of prevention with care support (100 percent target)

### 4.2. **Interventions considered in NACP II model.**

While NACP II has been a successful programme in its strategy, the level of success in implementation of the programme has varied in different states of India. As a result the coverage of high-risk groups with intervention programmes has been less than adequate (30 percent). Even though some states have achieved a high level of behavioral change in the high-risk group population, the national average is that only 50 percent of individuals use condoms regularly during sexual activity with non-regular partners. Targets used in the NACP II model are summarized in Table 4.

### 4.3. **Anti-retroviral therapy (ART) interventions.**

In NACP III there is a special emphasis on increasing ART and improving the knowledge base for those who are taking treatment. There could be an increase of three to four years in the median incubation period due to the availability of ART [64]. The NACP III model captures the impact of ART interventions by decreasing the transmission rates. When ART is introduced the interaction between CD4 cells and viral particles reduces and as a result viral load in the body sometimes reaches a sufficiently low level such that the infected CD4 count is undetectable by normal diagnostics. Viral

TABLE 5. NACP II - Status of response

| | |
|---|---|
| Condom use in HRG | 50% |
| Condom use in causal sex | 30% |
| Condom use with regular partners | 5% |
| Transmission through blood | 2% |
| IDU coverage with needle exchange | 2% |
| PMTCT programme coverage | 11% |
| Protection rate in PMTCT | 48% |
| ART provided to eligible subjects | 10% of AIDS patients |
| Positive prevention strategy in PLHA on ART | Same as general population |

TABLE 6. The ART scale-up plan

| **Year** | **2006** | **2007** | **2008** | **2009** | **2010** | **2011** |
|---|---|---|---|---|---|---|
| Total AIDS cases estimated | 508200 | 501800 | 493000 | 486000 | 478000 | 473500 |
| AIDS cases diagnosed 15% - 18% | 102000 | 151000 | 247000 | 291000 | 382000 | 379000 |
| Government commitment | 30000 | 100000 | 125000 | 150000 | 184000 | 200000 |
| ART by private sector | 40000 | 51000 | 122000 | 141000 | 198000 | 179000 |

TABLE 7. Status of response in rapid ART scale-up model

| | |
|---|---|
| Condom use in HRG | 50% |
| Condom use in causal sex | 30% |
| Condom use with regular partners | 5% |
| Transmission through blood | 2% |
| IDU coverage with needle exchange | 2% |
| PMTCT programme coverage | 11% |
| Protection rate in PMTCT | 48% |
| ART provided to eligible subjects | 10% - 100% patients |
| Positive prevention strategy in PLHA on ART | As in general population |

load reduction lowers transmission rates from infecteds to susceptibles per sexual interaction. The reduction in transmission rates also depends on the proportion of infected individuals undergoing ART. Through our model, we have estimated the impact of implementing a targeted ART number (see Table 6) to the overall reduction in infection rates in the population. Optimizing the benefits of ART to the overall infected and susceptible populations is a challenging issue for the government. It was expected that the HIV number in the general population will decline if ART is introduced systematically. It was predicted that an unstructured

TABLE 8. NACP III targets for prevention strategies

| **NACP III projections** | **50%Target** | **75%Target** | **100%Target** |
|---|---|---|---|
| Condom use in FSW | 65% | 72.5% | 80% |
| IDU and MSM coverage | 65% | 72.5% | 80% |
| Condom use in causal sex | 40% | 45% | 50% |
| Condom use with regular partners | 7.5% | 8.75% | 10% |
| Transmission through blood | 0.25% | 0.375% | 0.5% |
| IDU coverage with needle exchange | 40% | 60% | 80% |
| PMTCT programme coverage | 40% | 60% | 80% |
| Protection rate in PMTCT | 90% | 90% | 90% |
| ART provided to eligible subjects | 10% - 100% patients | 10% - 100% patients | 10% - 100% patients |

ART programme may reverse the declining trend and increase the disease burden [49].

4.4. **Rapid scale-up of ART without positive prevention.** This scenario predicts the outcome if NACP II activities are continued along with rapid scale-up of ART delivery. Currently approximately 40,000 AIDS patients are on ART. Nearly 15,000 are from the public sector programme and the rest have been initiated by different private sector units in the country. The government is committed to rapidly scale-up the ART services to those in need to 100,000 by 2007 and 184000 by 2010 as given in Table 6.

ART influences the epidemic in different ways and its net response is complex. For example,

a) ART will reduce both the viral load and transmission rate in PLHA (people living with HIV/AIDS)

b) ART will prolong the life of PLHA and increase the chance of spread

c) Improved quality of health can increase sexual activity of PLHA receiving ART.

The net effect of this intervention will depend on whether preventive strategies target PLHA to produce behavioral change. This scenario illustrates the potential negative effect of ART on the HIV epidemic if positive prevention strategies are not initiated while scaling up is accomplished. These assumptions result in decreasing protection to susceptibles, increasing partners, increased contact rate (due to improvement in health due to ART), and eventually an increase in transmission rates from infecteds to susceptibles.

4.5. **Integrating care and support in NACP III.** Three scenarios (50 percent, 75 percent, and 100 percent targets) are analyzed to investigate the possible outcome if expanded coverage of high-risk groups including female sex workers, IDU, MSM to 90% with targeted intervention is achieved along with integration of care support and treatment with prevention strategies. The scale-up of ART is achieved with focus on positive prevention. See Table 6 for details.

5. **Revised estimation of HIV burden (2007).** The surveillance system has also provided an excellent opportunity for NACO to estimate the HIV burden in India. The assumptions and analytical tools have also evolved over the years and

the NACO's programmatic initiatives have expanded substantially. This process has helped to gain better understanding of the epidemic and make necessary adjustments. Additional information on high-risk groups, data from health care delivery points, and other behavioral studies have also provided greater insights in understanding the patterns and trends of the epidemic at national and state levels. Accordingly, the NACO has been estimating the total number of people living with HIV/AIDS in India since 1998 and sharing the information nationwide. In 2005, the NACO had projected the total number of PLHA at 5.2 million. The results of the HIV sentinel surveillance round of 2006, National Family Health Survey-3 (NFHS-3) and Integrated Behavioral and Biological Assessment (IBBA) have enabled the programme to create a robust database, conduct sophisticated analysis, and interpret the trends in a more realistic and accurate way. This composite approach has enriched the data quality and accuracy of the analysis mainly due to coverage spread over 1122 sites, the population based NFHS-3 conducted in 2005-06 covering a sample size of over 100,000 people for HIV testing, and the targeted surveillance system focusing on high-risk population groups in high burden states with HIV/AIDS by IBBA. Based on the results from these major initiatives and the modified assumptions, the estimates have been revised by adjusting the prevalence figures since 2002. The earlier estimate was 5.2 million with a range of 3.4 million to 9.4 million. As per the recent estimates by NACO, there are 2.4 million (with a range of 2 million to 3.1 million) people living with HIV/AIDS at the end of 2006 [45]. Out of these, 0.97 million (39.3 percent) are women and 0.09 million (3.8 percent) are children. The estimated adult prevalence in the country is 0.36 percent (range: 0.27 - 0.47 percent). This essentially indicates a declining trend from 0.45 percent in 2002 to 0.36 percent in 2006. Accordingly, the total number of PLHA has also declined from 2.73 million in 2002 to 2.47 million in 2006 [45, 44]. There are other reports which show that fewer people are being infected by HIV and that the HIV burden in India is declining [32, 15, 16, 17, 36, 62]. Other studies indicate decline of HIV in subgroup populations [35, 22]. The recent estimates also highlight the existence of wide-ranging differences in prevalence rates across geographical regions in India. The antenatal clinic sites have shown that HIV prevalence has remained around 1 percent in previously designated high burden states and a few states such as Tamil Nadu and Maharashtra have reported declining trends moving to less than 1 percent HIV prevalence. The HIV prevalence trends among high-risk groups continues to be high though a marginal decline was noticed among FSWs in select states. IDU and MSM groups require greater attention. Disaggregated district level data analysis also indicates that HIV prevalence is increasing in previously designated low burden states. Districts have been categorized based on HIV burden as evidenced by sentinel surveillance data either as category A (based on ANC prevalence), B (prevalence among high-risk groups), C (migration and other potential features), or D (very low prevalence and inadequate data). The estimation procedures and processes have been validated by a panel of national and international experts representing agencies such as UNAIDS, WHO, and CDC. The panel also interacted and consulted with local institutions in fine-tuning the methodologies and refining the assumptions.

6. **Results.** Figure 6 depicts the national projections for various levels of intervention. The five scenarios depicted show the outcome by 2011. The starting point of intervention is based on the national estimate of 5.34 million for 2006. It is

important to note that the current projections take the present epidemic in India as a single epidemic while in reality this is really composed of multiple epidemics of different character in different regions/states of India. Therefore there are some limitations in interpretation of these results.

6.1. **Model validation and sensitivity analysis.** We have compared the estimated values of HIV given by the NACO with our model predictions for the period 2000-06 (see Table 10 for both of these values in millions). In Figure 6, actual estimates obtained by the NACO are shown, connected by dotted lines. Interestingly, model predictions are higher throughout except for 2003, where predictions are lower than the estimates, and in 2004 the difference is negligible. There is the possibility that, due to relatively few surveillance centers in 2000-01, the prevalence obtained from the national level survey might have under-estimated the total numbers. Remarkably, the number of sentinel surveillance sites increased to a sufficiently high number in the recent past and for 2005 this number is 625 across the country. We used a Monte Carlo algorithm for model validation and defined an objective function as suggested by Ciupe et al [13]. See Appendix IV for details.

6.2. **NACP II model.** If the NACP II level of intervention is continued during the project period of 2006 to 2011, then from the 2004 estimate of 5.134 million the projected number of PLHA is expected to be 5.06 million. Stabilization occurs with the current levels of PLHA on ART (10 percent), thus AIDS related mortality would continue at the present levels and its implications on health burden, development, and poverty will need to be addressed by the country. The projected trends based on our mathematical modeling are similar to the model using spectrum software that showed that by 2011 there would be 4.73 million PLHA in India [58]. While the differences in the projections based on mathematical and statistical projections are minor in terms of overall implications, this must be understood. It is felt that the main reason for the difference is because the mathematical model used the overall country average of the sentinel surveillance while the statistical model used the state level estimates and obtained the final projection from summation of the state projections. The majority of sentinel sites are in the southern regions of the country where the prevalence is higher and this would bias the country projections to be over-estimated when national estimates are used for overall projections.

6.3. **Scale-up of ART with NACP II level of interventions.** There is a commitment by the government to provide ART to all those who need it. This translates to approximately 10 percent of all HIV patients of whom 80 percent will be identified as shown in Table 5. The increased number of PLHA on ART will reduce AIDS mortality over the immediate project period and also speed up the development and poverty reduction objectives of the country. However if the rapid scale-up of ART is associated only with current NACP II levels of prevention and poor integration of care and support without focused attention on identified PLHA participating in positive preventive living, then the probability of having a worsening situation is predicted by the model with the total number of PLHA increasing from 5.13 million to 5.96 million over the next five years. If this scenario develops it is likely to compromise the project objectives of stabilizing and reversing the epidemic.

6.4. **Achieving 50 percent of target of NACP III.** NACP aims to expand coverage of high risk group to 80 percent over the project period. The programme

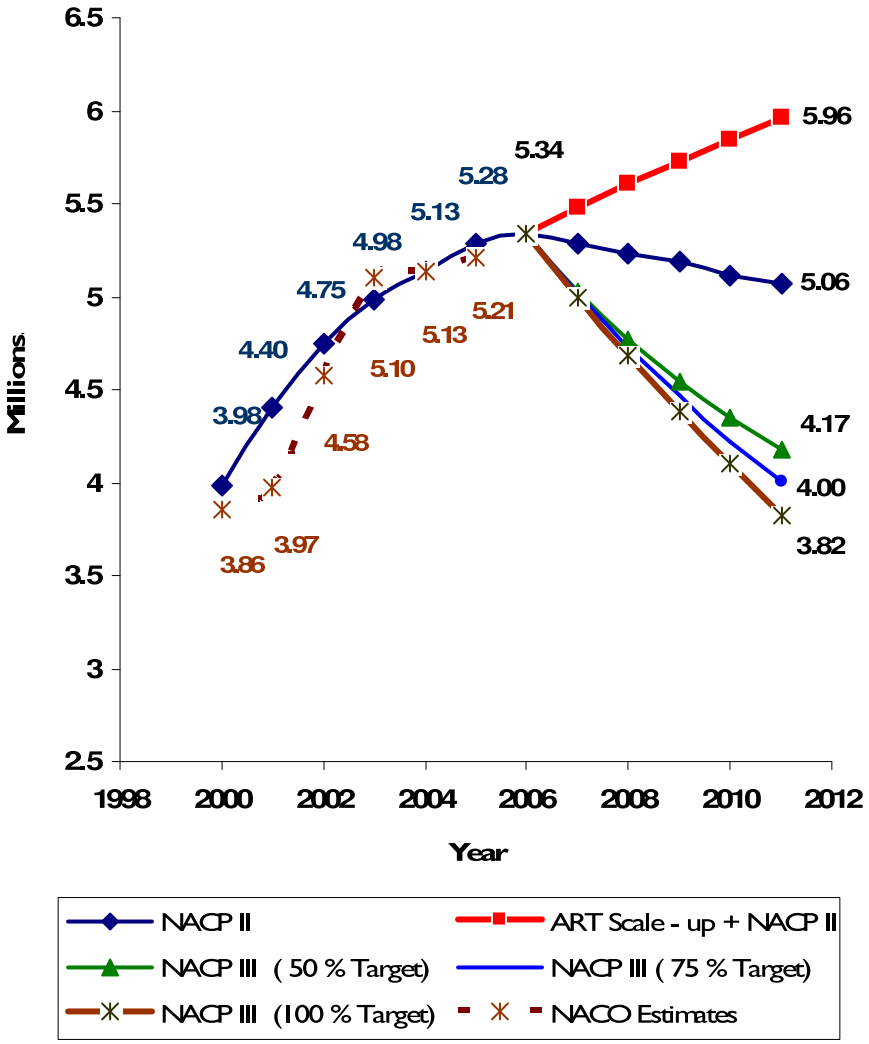


FIGURE 6. NACP III projections for PLHA. Five sets of projections for HIV estimates are shown by summing the predictions of Models 1-3. Three lines are drawn for the cases where the NACP III model assumes, respectively, 50 percent, 75 percent and 100 percent targets and one line for HIV estimates if NACP II is continued. In the initial years of the NACP III period, the impact of positive prevention strategies implemented will be moderate but by the end of 2009 this impact will be larger. When ART scale-up is implemented as discussed in Section 3, we predict the dynamics to follow the uppermost line in the figure.

TABLE 9. Annual percentage of NACP III targets in positive prevention strategy

| **Year** | **2007** | **2008** | **2009** | **2010** | **2011** |
|---|---|---|---|---|---|
| 50% Target for condom use in FSW, MSM | 53 | 56 | 59 | 62 | 65 |
| 50% Target for condom use in causal sex | 32 | 34 | 36 | 38 | 40 |
| 50% Target for condom with regular partners | 5.5 | 6 | 6.5 | 7 | 7.5 |
| 75% Target for condom use in FSW, MSM | 54.5 | 59 | 63.5 | 68 | 72.5 |
| 75% Target for condom use in causal sex | 33 | 36 | 39 | 42 | 45 |
| 75% Target for condom with regular partners | 5.75 | 6.5 | 7.25 | 8.0 | 8.75 |
| 100% Target for condom use in FSW, MSM | 56 | 62 | 68 | 74 | 80 |
| 100% Target for condom use in causal sex | 34 | 38 | 42 | 46 | 50 |
| 100% Target for condom with regular partners | 6.0 | 7.0 | 8.0 | 9.0 | 10.0 |

TABLE 10. Estimated and model predicted HIV numbers during 2000-2006

| Year | NACO estimates(millions) | | Model Predictions(millions) | |
|---|---|---|---|---|
| | Old | Revised | Old | Revised |
| 2000 | 3.86 | - | 3.98 | - |
| 2001 | 3.97 | - | 4.4021 | - |
| 2002 | 4.58 | 2.73 | 4.75 | 2.86 |
| 2003 | 5.1 | 2.67 | 4.9824 | 2.72 |
| 2004 | 5.134 | 2.61 | 5.1366 | 2.65 |
| 2005 | 5.21 | 2.54 | 5.281 | 2.50 |
| 2006 | - | 2.47 | - | 2.45 |

Data source: NACO estimates are taken from the HIV sentinel surveillance report 2 and references 35 and 36.

TABLE 11. Sensitivity of parameters in model predictions

| Parameter | Year | % reduction PLHA(mil.) | | % increase PLHA(mil.) | |
|---|---|---|---|---|---|
| | | Old | Revised | Old | Revised |
| Disease progression | 2007 | 10 - 80 | 2.5 - 1.8 | 10 - 80 | 2.7 - 3.1 |
| Transmission rate of HIV | 2007 | 10 - 80 | 2.2 - 1.3 | 10 - 80 | 3.0 - 3.6 |

will focus on female sex workers, MSM and IDU subpopulations with targeted interventions. The government is committed to scale-up the ART programme. All those who need ART (10 percent of PLHA) will be accessing treatment through effective public-private partnership. The scale-up ART will be associated with integration of care support and treatment. Expansion of voluntary counseling and testing centers, information education and counseling for generating demand and reduction in stigma and discrimination along with facilities for female sex workers, will help to identify the majority of PLHA who will participate in positive living. Transmission through blood will be reduced to 0.5 percent. Expansion of the Perinatal Mother to Child Transmission programme will provide improved ART to 90 percent of the 27 million deliveries in the country. Even with 50 percent of NACP III targets being achieved, the total PLHA load will be reduced to 4.4 million from 5.13 million by 2011.

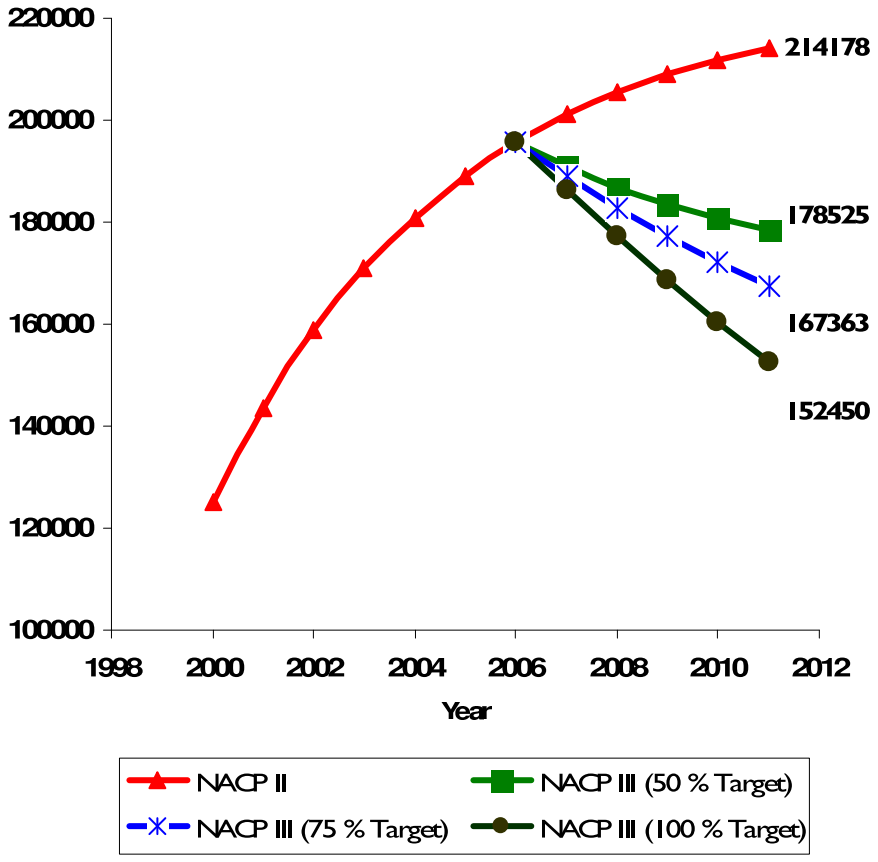


FIGURE 7. NACP III projections for PLHA in MSM. Four sets of projections for HIV estimates among MSM are shown for cases where, respectively, 50 percent, 75 percent and 100 percent targets are achieved, and when NACP II is continued.

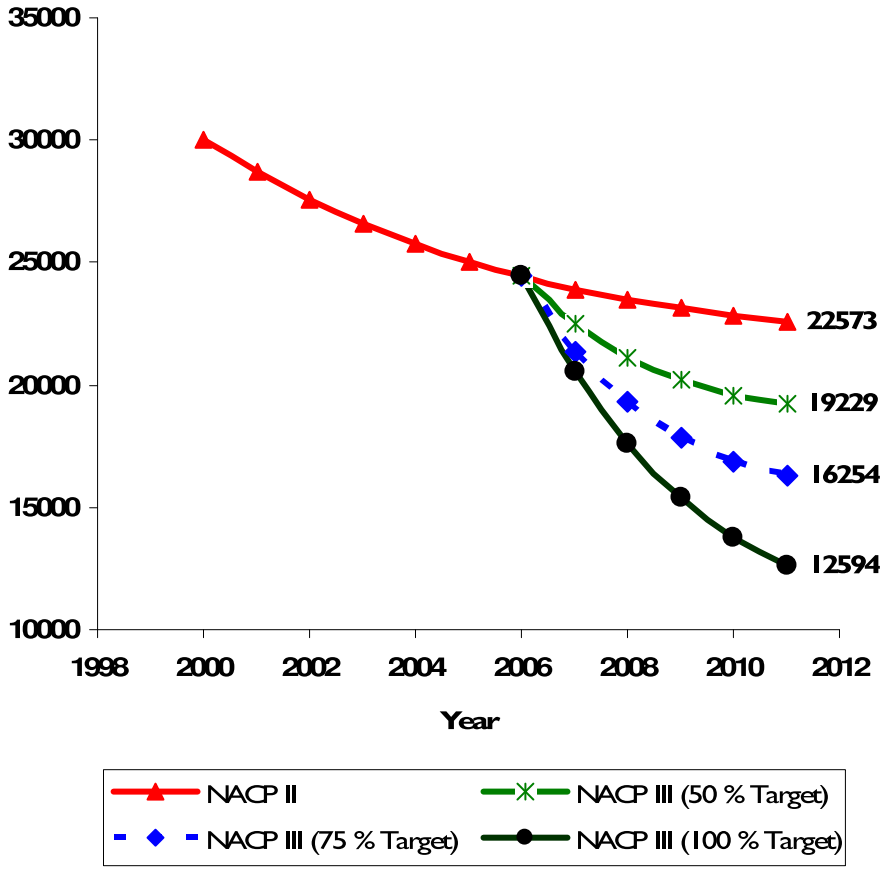


FIGURE 8. NACP III projections for PLHA in IDUs. Four sets of projections for HIV estimates among IDUs are shown.

6.5. **Achieving 100 percent of target set by NACP III.** If the programme is able to achieve 100 percent of the targets set by NACP III, the objective of reversing the epidemic in India will be fulfilled. The total number of PLHA is projected to reduce from 5.13 million to 3.8 million by 2011.

6.6. **IDU-related epidemic in India.** Our model predicts that the MSM population will continue to grow if NACP II interventions are continued and growth of MSM can be controlled in the future through NCAP III interventions (see Fig. 7). Needle exchange and drug substitution is a well-validated strategy for preventing transmission of HIV, Hepatitis B virus, and Hepatitis C virus infections in IDUs. While the proportion of IDUs is of great significance in some regions of the country, the total number is relatively low in terms of the overall population of India. Figure 8 shows the effect of increased coverage of the IDU population with planned interventions. This would result in a projected reduction of infected IDUs from 24,000 in 2006 to 12,000 by 2011. However the benefit is seen to reduce over time due to the small numbers of the population. The effect can be improved only if the primary problem of IDU itself is addressed. It must be noted that there is a

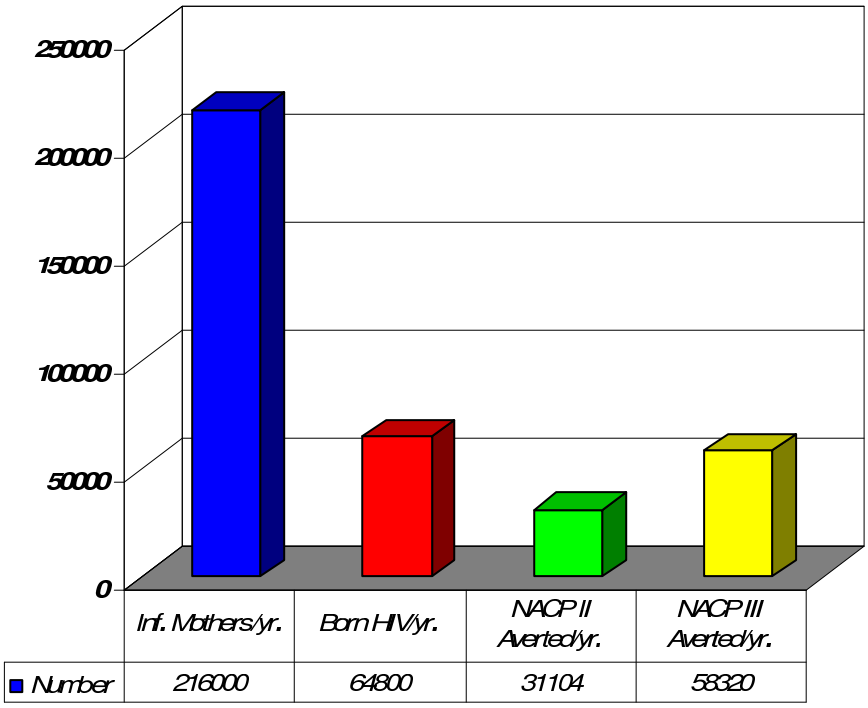


FIGURE 9. PMTCT estimates. Out of 216,000 HIV infected mothers, 64,000 are born with the virus. Among these infected births, 31,000 can be averted according to NACP II and if we achieve the 90 percent target of NACP III then this averted number could rise to 58,000.

need to model the IDU-related HIV epidemic for the north eastern region and other focused regions of the country to understand the implications. We also predict that 60,000 mother to child HIV infections can be averted during the NACP III period (see Fig. 9).

7. **Discussion.** Both spectrum analysis based results and results derived from our mathematical models show that the HIV/AIDS epidemic in the country is likely to stabilize and reverse over the next five years. By 2012, if the NACP II levels of intervention were to continue, the total number of PLHA in the country would vary from 4.73 million (spectrum analysis) [58] to 5.06 million (mathematical model). It is likely to further reduce to a number between 3.8 million and 4.2 million if interventions in positive prevention and female sex work are initiated under NACP III, successful to 100 percent or 50 percent of the expectations, respectively. One of the salient features of NACP III is prevention through behavioral change among high-risk groups. Increase in condom usage for female sex workers, causal sex, and MSM, and changing behavior among IDUs, and controlling transmission through blood have been shown to be effective in terms of reducing HIV rates. The 100 percent target of the NACP III includes, intervention of 80 percent of the high-risk

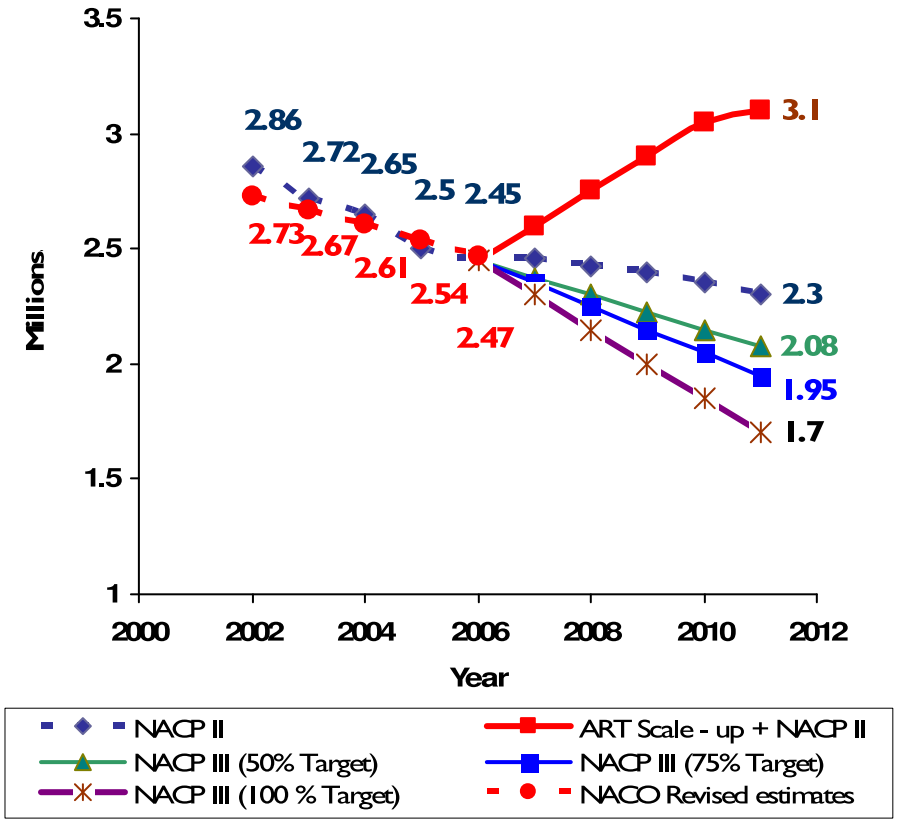


FIGURE 10. NACP III projections for number of PLHA (based on revised estimates). Five sets of projections for HIV estimates are shown based on revised estimates by NACO released in 2007. Other explanations are as in Figure 6.

group, 50 percent of individuals within the casual sex group, 80 percent of the IDU coverage with needle exchange. Various targets of NACP III can be found in Table 8. Incidentally, declining HIV trends due to behavioral intervention were observed in adults of certain age groups in southern parts of India [30], in some countries in Africa [1, 4], and in Thailand. Declining mortality due to ART is also expected from modeling studies [49]. New reasons and determinants behind ART adherence are available [59]. Population projection models by the UN in 2006 have revised assumptions on the impact of ART and assumed longer survival time after HIV infection due to ART than in their previous models [66]. We hope our study will help to initiate further modeling attempts targeting specific sub-populations and further simulations to study sensitivity and specificity of parameters of interest. In addition to the conventional back-calculation methods for predicting the past HIV trend, there are discrete time multistage back-calculation methods available that employ various stages of HIV and AIDS diagnosis. In Appendix III we explain the back-calculation methods that we implemented in estimating parameters. Multi-stage models, hidden Markov models based on Markov processes, are employed in

estimating transition rates between two or more stages of the disease. Such methods are more useful for natural history studies in HIV. In the present work, stages of the epidemic are not included in projecting the number of people living with HIV. For application of the multi-state approach in AIDS see [23] and for general ideas on multi-stage life-table methodology see [25]. There have been attempts to develop non-parametric probabilistic methods to study disease progression from one stage to another stage when the data are censored [55]. There is a major concern and potential threat of rising numbers of PLHA if the ART programme is rapidly expanded without taking into account integration of prevention and care. If this happens even with intervention continuing at NACP II levels, the total number of PLHA is likely to increase to 5.96 million by 2011. The present analysis uses information available on mixing structure in the general as well as high-risk group populations in the country to assist NACP III. NACP III model based predictions are also computed using the revised NACO estimates. These revised predictions are provided in Figure 10. As more data become available from various studies and surveys that are underway and with the launching of new surveys, we expect that future modeling will be more accurate. Programme management implications are based on revised estimates. The new estimates underscore the need for sustained programmatic action since India is among the top three countries in terms of HIV burden. The HIV epidemic is concentrated and localized among the high-risk population sub-groups across the country. Initial risk assessments of districts indicate that new geographical areas with lower HIV prevalence have started showing increasing trends. Developmental initiatives by the public and private sectors have also resulted in increasing migration of the skilled and unskilled workforce in search of employment for longer periods away from home. An increase in disposable income, peer influence towards high-risk behavior, and inadequate health care delivery mechanisms have also contributed to this phenomenon. In this scenario, the national programme is faced with the dual challenge of consolidating the gains resulting from the work done so far and scaling up the interventions substantially to achieve the goal of halting and reversing the HIV epidemic. The structure and composition of the Indian population is very diverse. Studies indicate that sexual and health protection behaviour of individuals across the states/regions in India significantly vary [10]. There is a significant variation in the HIV spread and infection levels in the population [43]. For example, heterosexual activity is the major mode of transmission for highly populated states in the northern, the central and the southern regions. Transmission through needle sharing is prevalent in a few north-eastern states and some other states in India. HIV incidence levels and mixing patterns, might be responsible for variations in the prevalence levels among states. There is a need to study HIV spread through mathematical models of dynamics of HIV at state-level. Such models are expected to provide a range of estimates for incidence in the population by taking into consideration the state-level targeted interventions in NACP III.

Another challenge is that of striking the right balance between prevention and treatment initiatives. Since the epidemic is still concentrated, the interventions need to be target oriented and location specific. The district level planning and intervention strategies will greatly help to achieve this objective. Considering the size and magnitude of the country, the resources required to meet the programmatic demands are substantial and call for sustained partnerships at all levels.

In this context, a more accurate estimate of the HIV burden will help in strategic evidence-based planning and designing more effective programmes at national, state, and district levels. In addition, this approach will also strengthen the decentralized target oriented interventions in select locations. Accordingly, the national programme will have to invest more in public and NGO sector service delivery mechanisms and infrastructure; capacity building of public sector, civil society, and private sector; and a robust strategic information management system. To achieve this complex set of objectives and the overall goal of halting and reversing the epidemic, the national programme will have to strengthen partnerships with donors, civil society and the private sector.

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**APPENDIX I.** The infection functions of STI and HIV for general mixing, MSM, and IDU are taken as below. The suffix $ij$ indicates transmission of infection from the $j^{th}$ subpopulation to the gender $i$. We consider subpopulation sizes to take account of proportionate mixing between susceptibles and infecteds.

$$
\begin{aligned}
f(S_i, G_j, I_j; \lambda_{ij}, \beta_{ij}) &= S_i \left( \sum_{j=1}^{4} \frac{\lambda_{ij} G_j}{N_j} + \sum_{j=1}^{4} \frac{\beta_{ij} I_j}{N_j} \right) \\
f'(S_i, G_j; \lambda_{ij}) &= S_i \sum_{j=1}^{4} \frac{\lambda_{ij} G_j}{N_j} \\
g(G_i, I_j; \alpha_{ij}) &= G_i \sum_{j=1}^{4} \frac{\alpha_{ij} I_j}{N_j} \\
h(S_i, I_j, G_i; \beta_{ij}, \alpha_{ij}) &= f(S_i, G_j, I_j; \lambda_{ij}, \beta_{ij}) - f'(S_i, G_j; \lambda_{ij}) + g(G_i, I_j; \alpha_{ij}) \\
f_m(S_m, G_m, I_m; \lambda_m, \beta_m) &= S_m \left( \frac{\lambda_{ij} G_j}{N_j} + \frac{\beta_{ij} I_j}{N_j} \right) \\
f'_m(S_m, G_m; \lambda_m) &= S_m \frac{\lambda_m G_m}{N_m} \\
g_m(G_m, I_m; \alpha_m) &= G_m \frac{\alpha_m I_m}{N_m} \\
h_m(S_m, I_m, G_m; \beta_m, \alpha_m) &= f_m(S_m, G_m, I_m; \lambda_m, \beta_m) - f'_m(S_m, G_m; \lambda_m) \\
&\qquad + g_m(G_m, I_m; \alpha_m) \\
f_{IDU}(S_{IDU}, I_{IDU}; \lambda_{IDU}) &= S_{IDU} \frac{\lambda_{IDU} I_{IDU}}{N_{IDU}}.
\end{aligned}
$$

The description of various transmissions in the population and main models are available in Section 3. All the functions above were used in Models 1, 2, and 3 to estimate the number of people living with HIV/AIDS.

**Appendix II: Parameter values.** All the parameter values used in Models 1, 2, and 3 are given in Tables 3 and 4. Census data for the period 1991-2001, sample registration system data, various publications, and reports are used to select suitable parameters on the assumption that they explain well the current level of HIV epidemiology in India [43, 51, 2, 68, 24, 20, 5]. Studies on the estimation of transmission parameters for HIV and STI were not specifically carried out in India, unlike in Japan, Thailand, and several African, American, and European countries [48, 31, 46, 9, 60, 26, 29, 47]. However there are very useful studies on natural history, estimation of high-risk population, prevention impacts available in India (for example see [43, 33, 54, 27, 24, 55]). Estimation of key epidemiological parameters requires longitudinal cohort studies and cross-sectional studies on incidence and prevalence surveys. We make use of published information wherever applicable and use the expert reports and opinions where the actual value is not available in the literature.

*Natural growth rate (r):* The decadal natural growth rate, $r_{10}$ is assumed to be exponential and is estimated from the equation $S_{2001} = S_{1991} e^{r_{10} \cdot 10}$, where $S_{2001}$ and $S_{1991}$ are susceptible populations aged 15-49 in 2001 and 1991, respectively. From decadal growth, the annual growth rate is calculated as $0.1 * r_{10}$. Separate

studies for the growth rates on MSM and IDUs are not available, so we assumed that the natural growth rates of these sub-populations will follow that of general susceptibles. The values are approximately $r_i = r_m = r_{IDU} = 0.02$ per year.

*General mortality rate ($\mu$):* Sample registration system-based adult mortality rates for 2006 are used. The sample registration system publishes rates for the population aged 15-59 by gender with $\mu_1 = 0.0041$ per year and $\mu_2 = 0.0025$ per year.

*HIV related mortality ($\delta$):* This parameter is estimated as the proportion of deaths from the HIV infected class from the data provided by Reddy et al [58]. We assume there is no gender based differential in HIV related mortality. It is also assumed that this mortality rate will be the same for MSM and IDUs. The values used in the model are $\delta_1 = \delta_2 = \delta_m = \delta_{IDU} = 0.103$.

*Disease progression rate ($\gamma$):* This parameter was estimated for the Indian data from cohort methods [24] and from other statistical methods using prevalence data on HIV and AIDS [55]. The UN AIDS reference team suggests that the median time of progression from HIV to AIDS is 9 years. The estimates range from 7 to 11 years. We choose 8 years as the mean of duration (from the NACP III modeling framework) and assume there are no differentials due to gender or behavior. The parameter values are $\gamma_1 = \gamma_2 = \gamma_m = \gamma_{IDU} = 0.125$. See Appendix III for further technical details on disease progression.

*STI recovery rate ($\phi$).* We assume male recovery rate is faster than that for females as more males attend STD clinics and their health seeking behavior is relatively higher. We choose $\phi_1 = 0.5$ per year and $\phi_2 = 0.3$ per year based on the background modeling report for NACP III [64].

*Transmission rates ($\lambda$, $\beta$, $\alpha$):* We make the following assumptions which are consistent with published studies. The rates of transmission of HIV and STI for males to females are higher than for females to males. In addition, the rates of transmission of HIV are greater when susceptibles are infected with STI. Transmission rates of STI are lower than that of HIV. We choose $\lambda_{1j} = \lambda_m = \lambda_{IDU} = 0.003$, $\lambda_{2j} = 0.006$; $\beta_{1j} = \beta_m = \beta_{IDU} = 0.006$, $\beta_{2j} = 0.009$, and $\alpha_{1j} = \alpha_m = \alpha_{IDU} = 0.012$, $\alpha_{2j} = 0.018$ based on the background modeling report for NACP III [5]. All these rates are annual rates.

**Appendix III: Disease progression rates.** The procedures used for estimating the parameters for incubation period distribution are described in this section. Further methodological detail and discussion can be found elsewhere [56, 57, 7, 8]. The annual rate of disease progression is considered here as a reciprocal of the average incubation period of AIDS (from the time of HIV infection). We use a convolution relation between the distribution of reported AIDS cases, HIV density, and incubation period distribution [56, 57], and then the rate of disease progression was estimated by de-convoluting this relation.

Suppose X and Z are distribution functions of cumulative AIDS cases and incubation period distribution, respectively, and $w$ is the HIV density function then, by [7, 8], we have

$$X(t) = \int_0^{t_n} w(s)Z(t-s)ds \tag{4}$$

where $t_n$ is the last available time point (year) of AIDS cases. The above convolution is fundamental in the back-calculation method. In equation (4), $w$ was assumed to be a quadratic exponential function parameterized by $a_0$, $a_1$, and $a_2$ as shown below (see [52] for details in considering such a function for Indian data):

$$w(t) \quad = \quad exp(a_0 + a_1 t + a_2 t^2). \tag{5}$$

HIV prevalence in sub-populations during the recent past has been declining with a peak, so equation (5) is justified. $a_0$, $a_1$, and $a_2$ are estimated from the sero-prevalence data. The most widely accepted functional form for the incubation period is the Weibull distribution [56, 57], although there are other functions, for example, the gamma, and logistic distributions were also demonstrated to be appropriate [57]. The functional form for $Z$ is assumed to follow the Weibull function with parameters $b_0$ and $b_1$ as shown below:

$$Z(b_0,\ b_1;\ t) \quad = \quad 1 - exp\left\{ - \left( \frac{t}{b_0} \right)^{b_1} \right\}. \tag{6}$$

Assuming that the reported AIDS cases will follow a multinomial distribution [26], the likelihood equation is $L = \prod_{i=1}^{n} p_i^{X_i}$ , where $p_i$ is the conditional probability given by

$$p_i \quad = \quad \frac{X(t_i) - X(t_{i-1})}{X(t_n)}. \tag{7}$$

Equations (4) and (5) are used to de-convolute $Z$ and estimate parameters in (6) by the maximum likelihood estimation on $L$. $X(t_*) = \int_0^{t_*} w(s) Z(t_* - s) ds$ in equation (7). $X_1, X_2, ..., X_n$ are reported AIDS cases from the beginning to the latest available calender years. We applied a bootstrap method [19] to calculate 95 percent confidence interval for the estimated parameters.

The incubation periods are estimated for the sub-population disease progression rates by considering reported AIDS cases among the individuals with or without STDs, IDUs, and MSM. Suppose $X(t_i, 1)$, $X(t_i, 2)$, $X(t_i, 3)$, and $X(t_i, 4)$ represent the distribution functions of cumulative AIDS and $Z_1(t)$, $Z_2(t)$, $Z_3(t)$ and $Z_4(t)$ are incubation period distribution for four sub-populations, namely, individuals with STDs, individuals without STDs, IDUs, and MSM, respectively. Then the four conditional probabilities are computed as follows:

$$p_{ji} \quad = \quad \frac{X(t_i, j) - X(t_{i-1}, j)}{X(t_n, j)}, \quad (j = 1, 2, 3, 4).$$

The parameters are estimated by maximizing the likelihood functions,

$$L_j \quad = \quad \prod_{i=1}^{n} p_{ji}^{X_i(j)}, \quad (j = 1, 2, 3, 4).$$

Substituting the value of $p_{ji}$ and expanding the product of terms in $L_j$ will lead to,

$$
\begin{aligned}
L_j &= \prod_{i=1}^{n} \{X(t_i,j) - X(t_{i-1},j)\}^{X_i(j)} \{X(t_n,j)\}^{-X_i(j)} \\
&= \{X(t_1,j) - X(t_0,j)\}^{X_1(j)} \{X(t_n,j)\}^{-X_1(j)} \times \\
&\quad \{X(t_2,j) - X(t_1,j)\}^{X_2(j)} \{X(t_n,j)\}^{-X_2(j)} \times ... \\
&\quad \times \{X(t_n,j) - X(t_{n-1},j)\}^{X_n(j)} \{X(t_n,j)\}^{-X_n(j)} \\
&= \left\{1 - \frac{X(t_0,j)}{X(t_1,j)}\right\}^{X_1(j)} \{X(t_1,j)\}^{X_1(j)} \{X(t_n,j)\}^{-X_1(j)} \times \\
&\quad \left\{1 - \frac{X(t_1,j)}{X(t_2,j)}\right\}^{X_2(j)} \{X(t_2,j)\}^{X_2(j)} \{X(t_n,j)\}^{-X_2(j)} \times ... \\
&\quad \times \left\{1 - \frac{X(t_1,j)}{X(t_2,j)}\right\}^{X_n(j)} \{X(t_n,j)\}^{X_n(j)} \{X(t_n,j)\}^{-X_n(j)}.
\end{aligned}
$$

**Appendix IV: Model predictions and sensitivity analysis.** We adopt the Monte Carlo procedure of Ciupe et al [13] for model validation and sensitivity analysis. Consider three vectors of parameters, $A1$, $A2$, and $A3$. Let $I_1(A_1, t_i)$, $I_2(A_2, t_i)$, and $I_3(A_3, t_i)$ be the predicted individual levels from the model and $I_1(t_i)$, $I_2(t_i)$, and $I_3(t_i)$ be, respectively, the corresponding observed values for infecteds in the general population, MSM population, and IDU population at time $t_i$. We define three objective functions (as in [13]) as follows:

$$
\begin{aligned}
J_1(A_1) &= \left\{\sum_{i=1}^{n} I_1(A_1,t_i) - log\left(I_1(t_i)\right)\right\}^{\frac{1}{2}} \\
J_2(A_2) &= \left\{\sum_{i=1}^{n} I_2(A_2,t_i) - log\left(I_2(t_i)\right)\right\}^{\frac{1}{2}} \\
J_3(A_3) &= \left\{\sum_{i=1}^{n} I_3(A_3,t_i) - log\left(I_3(t_i)\right)\right\}^{\frac{1}{2}}.
\end{aligned}
$$

The three vectors in the above equations are represented as follows:

$$
\begin{aligned}
A_1 &= [r_i, \lambda_{ij}, \beta_{ij}, \phi, \alpha_{ij}, \mu, \delta_i]^T \\
A_2 &= [r_m, \lambda_m, \beta_m, \phi, \alpha_m, \mu, \delta_m]^T \\
A_3 &= [r_{IDU}, \lambda_{IDU}, \beta_{IDU}, \phi, \alpha_{IDU}, \mu, \delta_{IDU}]^T.
\end{aligned}
$$

We then follow the method in Ciupe et al [13] for further analysis. For the sensitivity analysis, our focus is to study the impact of two parameters namely, disease

| | 1 | . | . | . | n |
|---|---|---|---|---|---|
| 1 | $\lambda_{ij}{}^{(1)}$ | | | | |
| ⋮ | | $\ddots$ | | | |
| k | | | $\lambda_{ij}{}^{(k)}$ | | |
| ⋮ | | | | $\ddots$ | |
| n | | | | | $\lambda_{ij}{}^{(n)}$ |

| | 1 | . | . | . | n |
|---|---|---|---|---|---|
| 1 | $\beta_{ij}{}^{(1)}$ | | | | |
| ⋮ | | $\ddots$ | | | |
| k | | | $\beta_{ij}{}^{(k)}$ | | |
| ⋮ | | | | $\ddots$ | |
| n | | | | | $\beta_{ij}{}^{(n)}$ |

FIGURE 11. Schematic diagrams representing the various age-dependent transmission rates.

progression and transmission rate of HIV with STI. In addition to this, we alter numerical values of these parameters and obtain model predictions. By removing the disease progression parameters from Model 1, individuals with full-blown disease disappear from the infected population and by removing the parameter responsible for transmission rate of HIV with STI, the resultant number of HIV and AIDS individuals from 2007 to 2011 declined from 2.2 to 1.3 million. By simultaneously removing both the above parameters from the model, the epidemic looks very much under control (i.e., growth of infections is controlled). We have tested the sensitivity of the model predictions to the above two parameters by varying them by 10 percent to 80 percent of their original values. The results are shown in Table 11.

**Appendix V: Virus spread models with age-structure.** Here we construct age-structured models for the spread of HIV. These are extensions of the models explained in section 3, where homogeneous mixing is considered. In practice, our study does not attempt to project age-specific projections of PLHA. Suppose $\lambda_{ij}^{(k)}$, $\beta_{ij}^{(k)}$, and $\alpha_{ij}^{(k)}$ are, respectively, the transmission rate of sexually transmitted infections, the transmission rate of human immunodeficiency virus (without STI in the host), and the transmission rate of human immunodeficiency virus (with STI in the host) from a gender $j$ of any age group to the gender $i$ of age group $(k)$. Here, by age-dependent transmission rate we mean the transmission rate from infected to susceptible (host) by considering the age of the host. Hence within each host age group the transmission rates are the same and are independent of the age group of the infecteds (see schematic description in Fig. 11).

If the parameters and variables described in section 3 are extended for the age-dependent notation, then the three models describing the HIV transmission for various age groups will be as follows:

Model A1. Age-dependent model for general population

$$\begin{aligned}
\frac{dS_i^{(k)}}{dt} &= r_i^{(k)} S_i^{(k)} - S_i^{(k)} \left( \sum_{j=1}^{4} \frac{\lambda_{ij}^{(k)} G_j}{N_j} + \sum_{j=1}^{4} \frac{\beta_{ij}^{(k)} I_j}{N_j} \right) + \phi G_i \\
\frac{dG_i^{(k)}}{dt} &= S_i^{(k)} \sum_{j=1}^{4} \frac{\lambda_{ij}^{(k)} G_j}{N_j} - G_i^{(k)} \sum_{j=1}^{4} \frac{\alpha_{ij}^{(k)} I_j}{N_j} - \mu G_i^{(k)} - \phi G_i^{(k)} \\
\frac{dI_i^{(k)}}{dt} &= S_i^{(k)} \sum_{j=1}^{4} \frac{\beta_{ij}^{(k)} I_j}{N_j} + G_i^{(k)} \sum_{j=1}^{4} \frac{\alpha_{ij}^{(k)} I_j}{N_j} - \delta_i^{(k)} I_i^{(k)} - \gamma_i^{(k)} I_i^{(k)} \\
\frac{dD_i^{(k)}}{dt} &= \gamma_i^{(k)} I_i^{(k)} - \delta_i^{(k)} D_i^{(k)}.
\end{aligned} \tag{8}$$

In the model (8), $S_i^{(k)}$, $G_i^{(k)}$, $I_i^{(k)}$ and $D_i^{(k)}$ are variables corresponding, respectively, to susceptibles to HIV, infecteds with STI, infecteds with HIV, and AIDS cases for the age group $(k)$, $k = 1, 2, ..., n$, where $n$ is the last effective age group. The above ordinary differential equations describe the spread of the virus in the general population. Spread among homosexual men and injection drug users is explained separately in Models A2 and A3 with corresponding sets of variables $S_m^{(k)}$, $G_m^{(k)}$, $I_m^{(k)}$and $D_m^{(k)}$ and $S_{IDU}^{(k)}$, $I_{IDU}^{(k)}$ and $D_{IDU}^{(k)}$ respectively. Other parameters used in the age-structured models in this section are defined similarly to those in section 3, except that they are now for a specific age group $(k)$. It is not easy to obtain many of the parameters for each age group even though there is evidence for age dependency in the infection process. The rate of disease progression is age dependent and there is an advantage in using age-specific rates in predicting the disease, as individuals with higher age at the time of infection tend to progress to full disease quicker than those who are infected at a younger age [18, 11]. Detailed studies are needed to estimate such age-related issues for disease progression, transmission rates, and death rates in India in the era of anti-retroviral therapies. A stochastic age-dependent model that predicts the number of PLHA by using the above information could be an alternative when the size of the population under anti-retroviral therapy is small.

Model A2. Age-dependent model for homosexual men

$$\begin{aligned}
\frac{dS_m^{(k)}}{dt} &= r_m^{(k)} S_m^{(k)} - S_m^{(k)} \left( \frac{\lambda_m^{(k)} G_m}{N_m} + \frac{\beta_m^{(k)} I_m}{N_m} \right) + \phi G_m \\
\frac{dG_m^{(k)}}{dt} &= S_m^{(k)} \frac{\lambda_m^{(k)} G_m}{N_m} - G_m^{(k)} \frac{\alpha_m^{(k)} I_m}{N_m} - \mu G_m^{(k)} - \phi G_m^{(k)} \\
\frac{dI_m^{(k)}}{dt} &= S_m^{(k)} \frac{\beta_m^{(k)} I_m}{N_m} + G_m^{(k)} \frac{\alpha_m^{(k)} I_m}{N_m} - \delta_m^{(k)} I_m^{(k)} - \gamma_m^{(k)} I_m^{(k)} \\
\frac{dD_m^{(k)}}{dt} &= \gamma_m^{(k)} I_m^{(k)} - \delta_m^{(k)} D_m^{(k)}.
\end{aligned} \tag{9}$$

Model A3: Age-dependent model for injection drug users

$$\begin{aligned}
\frac{dS_{IDU}^{(k)}}{dt} &= r_{IDU}^{(k)} S_{IDU}^{(k)} - S_m^{(k)} \frac{\lambda_{IDU}^{(k)} I_{IDU}}{N_{IDU}} \\
\frac{dI_{IDU}^{(k)}}{dt} &= S_m^{(k)} \frac{\lambda_{IDU}^{(k)} I_{IDU}}{N_{IDU}} - \delta_{IDU}^{(k)} I_{IDU}^{(k)} - \gamma_{IDU}^{(k)} I_{IDU}^{(k)} \\
\frac{dD_{IDU}^{(k)}}{dt} &= \gamma_{IDU}^{(k)} I_{IDU}^{(k)} - \delta_{IDU}^{(k)} D_{IDU}^{(k)}.
\end{aligned} \tag{10}$$

The age-structured incubation period parameters in the dynamical models are captured using the following methodology. See Appendix III for the basic introduction to the notation.

Suppose $\mathbf{Z}^l$, $\mathbf{w}^l$ are probability distribution functions of incubation period and HIV infection density, respectively, for individuals who were infected at age $l$. We assume the incubation period for all the individuals at age $l$ is a variable. $\mathbf{Z}^l$ and $\mathbf{w}^l$ are computed by estimating the parameters $\mathbf{a_1}^l$, $\mathbf{a_2}^l$, $\mathbf{a_2}^l$, $\mathbf{b_0}^l$, and $\mathbf{b_1}^l$ as explained in Appendix III. If $\mathbf{X_i}^l$ denotes the reported AIDS cases at time $i$ and infecteds at age $l$, then the conditional probabilities would become,

$$\mathbf{p_i}^l = \left\{\mathbf{X(t_i)}^l - \mathbf{X(t_{i-1})}^l\right\}\left\{\mathbf{X(t_n)}^l\right\}^{-1}$$

where $\omega$ is the maximum age of the individual at the time of HIV infection and who later developed AIDS. Then the age-structured likelihood equations, $AL$, are

$$\begin{aligned}
AL &= \left(p_1^l\right)^{X_1^l}\left(p_2^l\right)^{X_2^l} \ldots \left(p_n^l\right)^{X_n^l} \\
&= \left\{X^l(t_1) - X^l(t_0)\right\}^{X_i^l}\left\{X^l(t_2) - X^l(t_1)\right\}^{X_i^l} \ldots \left\{X^l(t_n) - X^l(t_{n-1})\right\}^{X_n^l} \\
&\qquad \times \left\{X(t_n)\right\}^{-X_1^l}\left\{X(t_n)\right\}^{-X_2^l} \ldots \left\{X(t_n)\right\}^{-X_n^l}.
\end{aligned} \tag{11}$$

Suppose $\mathbf{Y}^l$ is the convolution of $\mathbf{Z}^l$ and $\mathbf{w}^l$, then $\mathbf{X}^l$ in equation (11) can be expressed in terms of a single integral for notational convenience. Equation (11) will now become:

$$
\begin{aligned}
AL \quad = \quad & \left[ \left\{ \int_{\tau:\tau\in[t_0,t_1]} Y^l(\tau)d\tau \right\}^{X_i^l} \left\{ \int_{\tau:\tau\in[t_0,t_2]} Y^l(\tau)d\tau - \int_{\tau:\tau\in[t_0,t_1]} Y^l(\tau)d\tau \right\}^{X_i^l} \right. \\
& \left. \ldots \left\{ \int_{\tau:\tau\in[t_0,t_n]} Y^l(\tau)d\tau - \int_{\tau:\tau\in[t_0,t_{n-1}]} Y^l(\tau)d\tau \right\}^{X_n^l} \right] \times \\
& \left[ \left\{ \int_{\tau:\tau\in[t_0,t_n]} Y^l(\tau)d\tau \right\}^{-X_1^l} \left\{ \int_{\tau:\tau\in[t_0,t_n]} Y^l(\tau)d\tau \right\}^{-X_2^l} \ldots \right. \\
& \left. \left\{ \int_{\tau:\tau\in[t_0,t_n]} Y^l(\tau)d\tau \right\}^{-X_n^l} \right].
\end{aligned}
$$

The method of finding the age-structured disease progression for the $j$ subpopulations is based on the following likelihood equations:

$$
\begin{aligned}
AL_j \quad = \quad & \left[ \left\{ \int_{\tau:\tau\in[t_0,t_1]} Y_j^l(\tau)d\tau \right\}^{X_i^l} \left\{ \int_{\tau:\tau\in[t_0,t_2]} Y_j^l(\tau)d\tau - \int_{\tau:\tau\in[t_0,t_1]} Y_j^l(\tau)d\tau \right\}^{X_i^l} \right. \\
& \left. \ldots \left\{ \int_{\tau:\tau\in[t_0,t_n]} Y_j^l(\tau)d\tau - \int_{\tau:\tau\in[t_0,t_{n-1}]} Y_j^l(\tau)d\tau \right\}^{X_n^l} \right] \times \\
& \left[ \left\{ \int_{\tau:\tau\in[t_0,t_n]} Y_j^l(\tau)d\tau \right\}^{-X_1^l} \left\{ \int_{\tau:\tau\in[t_0,t_n]} Y_j^l(\tau)d\tau \right\}^{-X_2^l} \ldots \right. \\
& \left. \left\{ \int_{\tau:\tau\in[t_0,t_n]} Y_j^l(\tau)d\tau \right\}^{-X_n^l} \right].
\end{aligned}
$$

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