Managing India's AIDS crisis in the 2000s: quantitative modelling had impact

Younger readers may not be aware of the grave crisis that AIDS posed to India in the late 80s, or the heroic efforts on many fronts that prevented a greater tragedy. In the wake of recent deadly epidemics caused by the Ebola and Zika viruses, this tale bears retelling.

The deadly human immunodeficiency virus (HIV) attacks $CD4^+$ helper T cells. Left untreated, our body fights the virus for up to 12 years after which the concentration of $CD4^+$ cells in the blood starts to plummet, marking the onset of acquired immune deficiency syndrome (AIDS). In early 1982, the Centre for Disease Control in the United States first used the term 'AIDS'. As the syndrome had initially been identified in homosexual men in California, the Indian press wrote about the disease as one prevalent in the West due to the sinful practices of homosexuality and free sex. It was believed that this disease would not touch our country. Nevertheless, by 1985, Jacob John in Vellore, and Suniti Solomon and her student Nirmala in Chennai were looking for such cases. In due course, lo and behold, six samples were found to be positive. After confirmatory tests in the US, the alarming news had to be broken, and the Prime Minister informed (http://www.bbc.com/news/magazine-37183012).

The Government of India (GoI) established the National AIDS Control Organization (NACO) in 1992. The first National AIDS Control Programme (NACP), the prelude to a series of NACPs, was established in 1993. Fast forward to 1998: the number of HIV infections in India was a staggering 3.5 million, roughly one-eighth of the world's infection load. India faced a frightening future.

By 2005, worldwide, 70 million people had become infected and 10 million had died. This led to an infusion of US$ 1 billion a year for 25 years in an attempt to contain the disease. Sujatha Rao (former Union Health Secretary) has written a detailed and rivetting account of NACP-III (*Do We Care; India's Health System*, Oxford University Press, 2017) which she led from 2006 to 2010. Across the country the efforts of a large number of organizations, including 29 international aid agencies, had to be coordinated so that there was a concerted attack on the problem.

The way the virus spreads meant that NACO had the tough task of working with the socially marginalized communities of sex workers, men who have sex with men (MSM) and injectable drug users (IDUs). After months of consultations with a wide range of individuals and organizations, NACP-III adopted a three-pronged strategy that included prevention (55% of the budget), treatment (20%) and – showing great sensitivity – working to reduce the stigma and discrimination against those infected (25%). Despite criticism of the WHO and foreign experts, India started surveillance programmes: Who had HIV and how did they get it? Any strategy to contain the epidemic needed such data. NACO also took the unusual step of making available its raw data to foreign experts for inspection, a fact that was much appreciated.

In a novel plan, NACO classified all the districts of the country into four bands, based on the prevalence of the disease, with some districts requiring more urgent attention than others. Further, all the states had to be on-board, which was not always easy, as health has often not been a priority, and different states also had varying levels of competence to deal with the issue at hand. Organizations had to be strengthened, be it at the Centre, in the States or those working with the affected communities. A large number of professionals, working in a wide range of areas – from virologists on the one hand to communication experts on the other – had to be roped in. In late 2011, over 44,000 personnel were working on the anti-AIDS effort, spread over 182 districts. Fresh recruits had to be trained, and over three dozen guidelines were developed for this. It also had to be ensured that everyone was following these guidelines, and a system of reviews, from weekly to quarterly was drawn up, implemented and the outcomes tracked.

Two seminal events enabled part of the strategy. First, Yusuf Hamied of Cipla announced, in 2000, that he could produce anti-retroviral treatment for US$ 300 per patient per year (down from the then price of US$ 1000, itself a substantially reduced price from the original US$ 30,000). Second, in 2003, Health Minister Sushma Swaraj announced that the Government would fund the treatment of all patients.

Some of the other interesting facets of the programme were: (a) the need to identify the estimated 60,000 HIV+ pregnant women amongst a total of 23 million each year; (b) many of the public sector referral laboratories were able to obtain the coveted National Accreditation Board

for Testing and Calibration Laboratories (NABL) certification due to the standards set for the HIV work; (c) the annual visits of Bill Gates and his father, and their meetings with sex workers, helped destigmatize the disease; (d) workshops were organized that included supreme court judges from South Africa and Australia to help influence Indian Supreme Court judges' views on homosexuality and HIV; and (e) India was the first to develop pediatric dosages of antiretroviral therapy (ART).

We come now to an angle that may be of particular interest to scientists, that is the use of mathematical modelling in controlling the crisis. Historically, epidemiologists were at the forefront of embracing mathematical modelling in understanding the dynamics of disease transmission. Ronald Ross, an early proponent, used such models to understand the spread of malaria in the 1900s. Expanding on his work, Kermack and McKendrik pioneered a simple model of host–pathogen interaction in three seminal papers around 1930 (Kermack, W. O. and McKendrik, A. G., *Proc. R. Soc. London Ser, A*, 1927, **115**, 700–721; 1932, **138**, 55–83; 1933, **141**, 94–122). Their work inspired the next generation of quantitative modellers to work hand in hand with traditional epidemiologists.

From the 1990s onwards, mathematical modelling proved to be essential in understanding the transmission dynamics of HIV. Yet it was only in 2005 that the government, via NACP, decided to commission mathematical modellers to shape preventative strategies. NACP-I and NACP-II were completed but had met with limited success, and things had to be done differently. Amongst other steps, the planning committee commissioned mathematical modeller Srinivasa Rao (a fellow at the Indian Institute of Science – to make recommendations regarding feasible prevention strategies (Research Excellence Framework 2014; Impact case study, REF3b). Specifically, the government sought a recommendation on the comparative efficacy of four courses of action, namely (i) maintaining NACP-II level intervention, (ii) rapid scale-up of ART among high-risk groups without the integration of preventative care support, (iii) expanded targeting of high-risk groups, integrating both prevention and care (50% target of high-risk groups), and (iv) the same strategy as in (iii) but with a 100% target.

Drawing from the established model of Anderson and May (Anderson, R. M. and May, R. M., *Nature*, 1988, **333**, 514–519; and Oxford University Press, 1991), Rao and his colleague Maini at Oxford University, UK started to develop a detailed model of HIV transmission. They built a four-compartment model where the population was split among individuals who are susceptible (S); infected with a sexually transmitted infection other than HIV (G); infected with HIV (I); and living with AIDS (D). As there is gender variability in the routes of HIV transmission, each of these sub-groups was further differentiated by gender. The IDUs and MSMs were treated separately as the modellers assumed that they are isolated communities in India. In order to predict the future course of the disease, it was also essential to obtain information regarding intra- and inter-compartment interactions, and model them faithfully. Through extensive literature survey and by mining surveillance, census and publicly available data, followed by fitting model outcomes to known scenarios, these factors were determined. Then using ordinary differential equations they interrogated the model to generate strategy-specific predictions for infection burden. It is worth noting that the four potential strategies mentioned above entailed modifying different factors that contributed to the change of sub-populations in different compartments. For example, ART (strategy ii) would decrease the rate of transmission by reducing the viral load, but would certainly increase the rate of sexual encounter between the infected and the susceptible population as the former would stay healthier for longer. Taking all these moving parts into account, Rao and Maini predicted that achieving 100% target with ART treatment, along with integrative prevention and care support, would fulfil the objective of reversing the AIDS epidemic. It would reduce the total number of people living with HIV/AIDS (PLHA) from 2.4 million in 2006 to 1.7 million in 2011. Achieving the 50% target would also reduce the overall burden from 2.4 million to 2.08 million by 2011. Interestingly, their model predicted that the use of ART without integrated care support would lead to an increase in overall infection from 2.4 million to 3.1 million in 2011, with a worse outcome than just maintaining NACP-II level interventions (Rao, A. S. R. S. *et al.*, *Math. Biosci. Eng.*, 2009, **6**(4), 779–813).

The key impact of this work was to inform policy decisions and influence outcomes. India is still waging its protracted battle with the AIDS epidemic and while we feel deep regret for those who did not receive treatment in time, we should celebrate the fact that GoI did ultimately extend support to the millions affected by this deadly disease. By 2011 the infection burden plummeted to 2.089 million individuals, remarkably close to the predictions made by the Rao and Maini model. This was the first time that modelling had been used to help tackle the spread of a disease in India.

Despite severe criticism and resistance from various quarters to the actions taken under NACP-III, over a few years India saw a huge drop in incidence, in fact, the largest drop in any country, and was applauded world-over. Thus, this piece is a story of the invaluable inputs of mathematical modellers to Indian policy makers and how it ushered in a new era in the prevention and integrative care of PLHA. It is also a grand story in the area of 'implementation science'.

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