

Stopping HIV: Treatment as prevention

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We cannot afford to allow the AIDS epidemic to ruin the realization of our dreams ... we are at the beginning of the AIDS epidemic in our country. Unattended ... this will result in untold damage and suffering by the end of the century.
- Chris Hani, Maputo AIDS Conference, 1990.

HIV ranks among the great plagues in the history of our species: 33 million people infected, 2 million dying each year (1). The scientific response has been fast and furious. In 1981 the US Centres for Disease Control reported the first five cases of young gay men suffering from what came to be known as AIDS. Within two years, scientists at the Institut Pasteur in Paris had identified the virus responsible for AIDS, within four the genome had been sequenced and the first test for HIV was available. In the early 1980s anti-viral drugs were almost unknown and viral epidemics were contained with vaccines; hopes were high that a vaccine would save the world from this new threat. The reality was different and unexpected. An effective vaccine is still years, possibly decades, away but within six years of the start of the epidemic, the first effective drug for treating HIV had been developed. By 1996 triple drug therapy was available, at a cost of about ten thousand dollars a year, and by 2006 the price of first line therapy had fallen to a few hundred dollars per year. Now more than 30 drugs are available in four classes with two new classes under development.

No behavioural change

For those that can access them the drugs are life-saving, but transmission of the virus continues unabated. And yet condoms, the oldest method of prophylaxis both against pregnancy and disease, are cheap, widely available and effective. So all that was needed was for people to change their behaviour, ever so slightly, and a combination of condom use and perhaps 'zero grazing' or other kinds of behaviour change would contain the epidemic. But people's behaviour has not changed and the death toll mounts.

There is much that we still do not understand and, in particular, the reason why one quarter of all the people with HIV in the world live in nine countries in southern Africa, and two thirds of these live in South Africa. But there is also much that we do understand. In South Africa, at the start of the epidemic, the prevalence of HIV doubled every 1.5 years, so that each person infected with HIV infected only one person every 1.5 years. Young adults, infected with HIV will live for an average of 10 years without treatment. Therefore, at the start of the epidemic each HIV-positive person must have infected 10/1.5 or 7 other people in his or her

lifetime of infection. So to eliminate HIV we need to reduce transmission by 7 times.

Behaviour change interventions have not brought about a sufficient reduction in transmission; treating curable sexually transmitted diseases have not had the impact that it was believed it might have; empowering women, mobilizing communities, providing support to sex-workers have not changed the course of the epidemic. The only proven intervention is male circumcision (2), but this reduces transmission, averaged over male-to-female and female-to-male transmission, by a factor of 2 which is important and significant, but not sufficient to halt transmission.

Treatment as prevention

So we return to the one great success: the development of cheap and extremely effective anti-retroviral therapy (ART). The drugs keep people alive, could they also be used to stop transmission? In 1995 David Ho argued in an editorial in the *New England Journal of Medicine* that we should 'hit HIV early and hard' using triple combination therapy (3). He reasoned that this would both limit the damage that HIV does to the immune system, even before clinical symptoms are manifest, and reduce the likelihood that the virus would develop resistance. In 2006 Julio Montaner and colleagues argued, in a paper in *The Lancet* that it might be possible to use ART to stop the transmission of HIV (4). They reasoned that if ART substantially reduces the level of the virus in a person's body it would also reduce their infectiousness to others. In 2009 scientists from the WHO published a dynamical model in *The Lancet* to explore the impact that that ART might have on the transmission of HIV (5). To decide if treatment-as-prevention is feasible we need to determine the extent to which ART reduces the infectiousness of HIV-positive people. To decide if treatment-as-prevention is realistic we need to consider the levels of acceptance and compliance that might be achieved, the cost of the drugs, the rate of development of resistance, drug delivery and patient management (6).

Feasible?

To determine feasibility we note that if people are fully compliant with triple combination therapy it is possible to reduce their plasma viral load by 10,000 times. For reasons that remain obscure,

infectiousness declines roughly as the cube-root of the viral load so that this reduction in viral load only reduces infectiousness by 20 times but this is still much greater than the factor of 7 that we need to eliminate the infection. Since people live for an average of about ten years after being infected with HIV starting them on ART within a year of being infected would reduce their infectious period by up to ten times. A 20-fold reduction in infectiousness on ART over 9 years gives us an overall reduction of close to 7 times. The margin for error is not great and for treatment-as-prevention to be effective will require high levels of coverage and compliance, effective viral load suppression, and low drop-out rates. So it may be possible to eliminate transmission of the virus in the five years or so that it would take to roll-out a programme of annual testing and immediate treatment. But this would only be the beginning of the end as there would still be about 6 million South Africans, 30 million people world wide, who would need to be kept and maintained on ART until they die, hopefully at a ripe old age, in 40 or 50 years. So whatever we do we are in it for the long term.

Realistic?

So is treatment-as-prevention realistic? This is an empirical question and demands an empirical answer but we can, and indeed must, consider some of the potential pit-falls. Unpleasant side effects will lower compliance and the choice of a few standard drug regimens that are well tolerated will be essential. The development of resistance could compromise the effectiveness of the drugs while constant and close monitoring would be expensive and difficult to implement widely. Fortunately, there is increasing evidence from developed countries that where compliance is good and drug regimens are chosen carefully, both acquired and transmitted drug resistance are declining. It will be important to ensure that residual transmission is low and this will best be done by monitoring transmission between discordant couples in which the HIV-positive partner is on ART. Cost and cost effectiveness calculations suggest that while this will require a substantial initial investment, amounting to 1 or 2 percent of the gross domestic product, at least in South Africa, the cost to the health services of managing AIDS related diseases will roughly balance the cost of providing drugs. And over the next forty years the cost of treatment-as-prevention will be much the same as the cost of continuing with the present levels of drug provision. If we include the financial cost to society of killing mainly young adults in their most productive years treatment-as-prevention may well be cost saving from the very beginning. The stigma associated with HIV is of great concern and is, in some cases, life-threatening. It will be essential to ensure that an intervention of this kind is strictly voluntary and carried out with the full support and engagement of the people living in the affected communities.

But there are also additional benefits and ways in which the intervention could be made more effective. The most common AIDS-related opportunistic infection is tuberculosis and HIV has increased the already high incidence of TB in South Africa by three times. Fortunately, the available data suggest that ART reduces the risk of developing TB disease in HIV-positive people by about 60% so that as soon as full coverage is achieved there would be a substantial reduction in the incidence of TB. The elimination of AIDS-related TB would require the elimination of HIV, which would take 40 to 50 years as shown above. One might also consider using ART to provide pre-exposure prophylaxis to ensure that people who are HIV-negative but at high risk of infection remain HIV-negative. The analytical problem is then to determine how best to target the provision of ART, both as treatment and as prophylaxis, in order to maximize the impact while minimising the cost.

Joseph Needham, the doyen of the study of science in Ancient China observed that ‘the difference between modern and ancient or medieval science is the mathematization of hypotheses about nature combined with rigorous experimentation’. We have done the mathematics, now we need to do the experiments. In South Africa a generation of children were lost to Apartheid; we must not lose another generation to HIV/AIDS.

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