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Monitoring progress towards ending AIDS in South Africa

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In 2008, The Lancet medical journal published a study that used a mathematical model to investigate a bold new initiative in the fight against HIV/AIDS (1). The paper suggested that if all adults in South Africa were tested annually for HIV, and if all HIV positive cases were started immediately on anti-retroviral therapy (ART), then we could reduce the rate of occurrence of new HIV infections, that is, the HIV incidence, to less than one case per 1000 people per year by 2016. Moreover, it would be possible to reduce the proportion of people infected with HIV – that is, the HIV prevalence – to less than one case per 100 people within 50 years. The senior author on the paper was SACEMA's founding father, Brian Williams, who was at that time working for the World Health Organisation (WHO) in Geneva. Two years later, in March 2010, Williams, by then working for SACEMA, addressed the American Association for the Advancement of Science (AAAS) in San Diego and, for reasons that are not entirely clear, the international press suddenly woke up to the importance of Williams' model, reporting it worldwide in the press and on radio and television, and we at SACEMA were flooded with enquiries. The idea that it really could be possible to end the HIV epidemic quickly captured the attention of many decision makers and there was an unstoppable move towards more aggressive use of what has become known as "Treatment as Prevention" or TasP.

The ideas behind TasP are quite simple.

With the revolutionary development of anti-retroviral (ARV) drugs it became possible to reduce the amount of virus in a patient's blood to undetectably low levels. The drugs had been used initially for the immediate and all-important task of reducing HIV mortality. Until quite recently the prevailing view about the treatment of HIV in the Third World was that cases should only be started on ART when damage to the immune system, as measured by a decline in the number of CD4 cells in the blood, had progressed to the point that the patient's life was threatened. There were several reasons for promoting this policy of deferred treatment. It was argued that starting people on ART when, for example, they were still feeling healthy, with no symptoms of disease, would result in a lack of adherence to treatment and undoubtedly increase the risk of the evolution of resistant strains of HIV. This problem would be made worse by the unpleasant side-effects of some of the early ARVs, and by the fact that, initially, it was only possible to offer treatment consisting of a single drug, making it essentially inevitable that a resistant strain of the virus would eventually survive and become dominant in a patient. There was also the issue of cost: in the early years of the rollout, ART was prohibitively expensive, and this was a major reason for limiting treatment to the sickest individuals. The costs of treating all HIV positive cases would have been overwhelming for most developing countries.

In the developing world this generally meant that, even theoretically, patients only became eligible for ART when their CD4 counts dropped below a level of 200 cells/mm^3. In practice, given peoples' reluctance to get tested for HIV, the real starting point was often tragically lower than 200, and patients were often irretrievably ill by the time they started treatment. During all of the time that these cases were untreated, they of course remained infectious and continued to spread infection. On the other hand, most people who were on effective ART had viral loads that were so low that they were not infectious – and they would become part of the solution, rather than part of the problem. The idea of TasP is as simple as that: use ART to drop the total viral load of the population and you switch off the tap of new HIV infections. It took the use of mathematical models to demonstrate, however, just how big an impact TasP could have on the epidemic.

Selling the idea of TasP to policy makers

In an earlier, similar, development, the French scientist Bertran Auvert had been the first to demonstrate, in a randomised control trial (RCT) conducted in Orange Farm near Johannesburg, that male circumcision approximately halves a man's risk of acquiring HIV infection (2). The resulting effect on population level HIV incidence, among males and females, was, however, unclear until Auvert, Williams and other colleagues at SACEMA, carried out mathematical modelling which predicted that safe medical male circumcision applied at scale in Africa could avert two million new HIV infections and 300,000 deaths over a 10–year period in sub-Saharan Africa. (3) The clear-cut results of the Orange Farm trial, confirmed by independent trials in Kenya and Uganda, and supported by estimated population-level effects suggested by mathematical modelling, convinced policy makers of the wisdom of promoting voluntary safe medical male circumcision as a public health measure.

It is probably fair to say, however, that efforts aimed at promoting voluntary safe medical male circumcision have been rather overshadowed by the advances in the more proactive use of ART as a means of reducing HIV incidence. What made the idea easier to sell by 2010 was the development of a much larger range of ARV drugs, and the use of combinations of these drugs in what is called "triple therapy". That is to say, patients were taking a cocktail of three different drugs, which made the likelihood of the emergence of drug-resistant strains of HIV much less likely. The drugs were also much more effective, the dosing was simplified and the side-effects were much less severe. Moreover, in a parallel development in Canada, Julio Montaner and co-workers had already started, with considerable success, TasP programmes aimed at reducing the HIV problem among injecting drug users on the streets of Vancouver. Montaner was able to show that, between 1996 and 2008, as more and more people were started on TasP, the transmission of drug-resistant strains actually dropped by a factor of 10, and there was a significant increase in the proportion of HIV infected people who had extremely low or even undetectable levels of virus in the blood. In other words, TasP was resulting in a less severe resistance problem, rather than the opposite.

The game was also changed as a consequence of declining drug prices. Annual drug costs per person, for triple therapy in South Africa, dropped from US$10,000 in 1995, to $1700 in 2003, then to $730 in 2006, to $188 in 2009 and $100 by 2014. Drug costs thus declined by a factor of 100 in just under 20 years. With these much lower drug prices, the same mathematical models which suggested that TasP could be used to massively reduce HIV incidence, now also suggested that such an approach would also actually save money in the long run.

The sums of money required to carry out TasP are admittedly huge, but to misquote Oscar Wilde: "the only thing more expensive than treating HIV is not treating it".

Mathematical modelling clearly played an important part in persuading policy makers that there should be a change in the guidelines for initiating ART. Demonstrating a good idea is, however, not at all the same thing as having that idea put into practice and it is noteworthy that eight years after the publication of the The Lancet paper we have only recently got to the point where the WHO has revised the guidelines for the initiation of ART to state that: "antiretroviral therapy (ART) should be initiated in everyone living with HIV at any CD4 cell count". Perhaps predictably, the move towards universal ART for all HIV positive cases has happened more slowly in the developing world than, for example, in the United States and Europe.

Reaching 90-90-90 in South Africa

In 2014, UNAIDS proposed the so-called 90-90-90 targets. That is to say, the aim is to ensure that, by 2020, 90% of all HIV positive cases will have been diagnosed as such; and that 90% of those diagnosed will be on ART; and that 90% of all people receiving ART will be virally suppressed.

Progress towards the 90-90-90 targets has varied between situations and, predictably, poorer countries in Africa often have a long way to go. Nonetheless, UNAIDS reported recently that "in at least 10 countries from diverse regions, HIV treatment coverage either doubled or almost doubled from 2012 to 2015, reinforcing the feasibility of rapid scale-up".

In South Africa, the Department of Health rapidly took up the WHO recommendation of making ART available to all HIV positive cases – regardless of their CD4 count, and is making progress towards meeting the 90-90-90 targets. In 2016, UCT's Leigh Johnson estimated that about 85% of HIV positive cases in South Africa have been diagnosed, which is already tolerably close to the 2020 target. When it comes to the percentage of HIV cases on ART we are doing rather less well – with only an estimated 57% receiving treatment. When people are on treatment, however, the results appear to be rather better, with an estimated 78% virally suppressed.

Clearly, we still have some way to go if we wish to achieve the 90-90-90 targets by 2020. Nonetheless, one should not diminish South Africa's efforts, resulting in the country having the biggest ART programme in the world. Moreover, it should be emphasised in this regard that the South African taxpayer foots the bill for 75% of the current figure of nearly 30 billion rand spent annually on HIV, as opposed to the situation in most states in the region which have an almost total dependence on donor funding for their fight against HIV.

Monitoring and evaluation of the ART programme

The above numbers do, however, tell only half of the story. If the TasP programme is to be successful we need to carry out intensive monitoring and evaluation of that programme. This needs to happen at two levels: first we need detailed follow-up of all individuals who test HIV positive and who initiate ART. We need to keep up-to-date records of all of the information relating

to the treatment history of such patients: What rates of drop-out are we seeing? What are the rates of failure of viral suppression? What is the reason for each failure? Are new variants of the virus implicated? It is only with this level of information, which needs to be continuously and rapidly up-dated, that we can hope to locate any shortcomings in the system – and move rapidly to address the problems.

The second level of judging the success of the interventions lies in monitoring and evaluating observed changes in population levels of infection and disease – and here we need to be careful about how we interpret HIV survey results. A successful TasP programme will, as a first beneficial effect, reduce mortality among HIV positive cases. Moreover, if the people on treatment have negligible levels of virus in their blood, they will not pass on their infection to other people. We therefore expect to see a reduction in the rate at which new infections are occurring.

Paradoxically, however, we do not expect to see an early reduction in the total proportion of people who are infected with HIV. That is to say we do not expect to see HIV prevalence declining in the short run. This is a simple consequence of the reduction in HIV mortality among people on effective ART. So the fact that HIV prevalence among women attending antenatal clinics in South Africa hardly changed from a level a little under 30% between 2003 and 2013 largely reflects the successful reduction of HIV mortality due to ART.

What we do expect to see is a decrease in the rate at which new infections are occurring. In other words, we need to be concentrating on estimating the changes in the HIV incidence rather than in the HIV prevalence. It is generally agreed among HIV workers that the proportion of the population infected with HIV, is anyway not the most appropriate or informative measure of what is happening in an HIV epidemic. HIV is a very long-lived infection: even prior to the availability of ART, HIV positive cases survived for an average of 10 years. So if we test 1000 women at an antenatal clinic and find that 300 of them are HIV positive, then we say that we have an HIV prevalence of 300/1000 or 30%. Clearly this is not a happy state of affairs under any circumstances – but the statistic hides a huge amount of important detail. For example, if all of the 300 HIV positive cases have been infected for at least 8 years then, actually, it looks as if there are very few new infections and we are looking at an epidemic that is in decline, with a very small proportion of new infections. On the other hand, if all 300 HIV positive cases have been infected for less than a year then we have a much more serious situation: this is an epidemic that is exploding, with huge numbers of new infections, and we need to take drastic measures to halt that explosion.

These are, of course, two extreme examples, but they serve simply to make the point that what we really need from the antenatal clinic surveys is not just the prevalence (the proportion of women who are HIV positive) – but also the incidence (that is, the rate of occurrence of new infections). Mathematical modelling can be used to extract HIV incidence estimates from series of the annual antenatal clinic data: Rob Dorrington, Leigh Johnson and co-workers at UCT have had good success in doing just that with their Actuarial Society of South Africa (ASSA) and Thembisa models. And the good news is that while prevalence continues to maintain high levels, for reasons we have discussed, HIV incidence has been declining steadily in South Africa ever since 1998/1999, when it peaked among 15 – 49 year-olds at about 2.4% per year. Johnson estimates that, by 2012/2013, that incidence had halved to about 1.2%.

The mathematical and computational methods used to make these estimates are by no means simple to negotiate and, of course, they rely on the existence of a series of entirely comparable HIV prevalence surveys. Moreover, there is always a considerable delay in generating acceptable data sets from the antenatal clinic survey process that is required to make the estimates. A combination of all of these reasons is responsible for the fact that the 2012/2013 HIV incidence estimates are the last national estimates available from the antenatal clinic data: so we are always running 3 – 4 years behind the clock. We do not know what has been happening more recently and do not have, therefore, the most recent information on how well, or how badly, we are doing in bringing the epidemic under control.

This is a serious situation. Currently, about 30 billion rand is being spent annually by South Africa and international partners on the HIV programme. A very large proportion of that is now spent, quite rightly in our view, on TasP. But what is the effect of all of this spending, and all of the increased level of treatment? Is it resulting in an improvement in the HIV situation? In particular, are we seeing decreases in HIV incidence rates that in any way correspond to what we expect, given our efforts? Unless we are in a position to provide rapid and accurate measures of HIV incidence we are in no position to answer those questions, and thus in no position to decide whether or not we are spending our money to best advantage. HIV data from antenatal clinics are of prime importance in this regard, and it is equally important that these data

are released as swiftly as possible to the analysts who can use them, together with results from earlier surveys, to provide up-to-date HIV incidence estimates as described above.

Tests to identify HIV recent infections

What we would also like is a stand-alone method of estimating HIV incidence that does not require a long series of HIV prevalence estimates but, instead, calculates HIV incidence estimates directly from the results of a single HIV survey, particularly such as those carried out at antenatal clinics.

Recall that, in estimating incidence, we are essentially trying to answer a very simple question: "What is the rate at which new infections are occurring?" Unfortunately, while the question is simple, the answer has turned out to be remarkably elusive – for the simple reason that we do not have a reliable method for determining whether a given HIV positive individual has become infected recently or has a long-standing infection. The tests used, for example, in all of the antenatal clinic surveys to date have only told us whether or not a person is HIV positive or HIV negative: the result of the test says nothing about the recency of the infection.

Various teams of scientists around the world have, however, devised new tests which are able to identify HIV recent infections. Such tests rely, essentially, on the fact that levels of antibodies against HIV increase with time since HIV infection. Unfortunately, none of these tests is perfect and there is always a small proportion of cases that are incorrectly identified as having been infected recently. Early test systems made errors of this kind in at least 5% of cases and this level of error was sufficient to mean that HIV incidence was badly over-estimated. New improved test systems have, however, reduced the so-called "false-recent rate" to the order of 1%, and SACEMA is playing an important role in the evaluation of such tests, and in the development of the methods and mathematical theory required to use them to provide rapid, reliable estimates of HIV incidence.

The road ahead

I have argued here that the proactive use of ART provides a powerful weapon for combatting the HIV epidemic, and that we also have the tools for monitoring and evaluating the progress of that campaign. Mathematical modelling has played an important role, both in suggesting appropriate interventions, and in developing new monitoring methods.

We need to acknowledge, however, that we are still in for a long journey. It is a sobering thought that, even if all new HIV infections were stopped with immediate effect, there would still be about 7 million people living with HIV in South Africa, and we have an estimated 2 million AIDS orphans in need of care and support. Moreover, we still need to address the question of quite why it is that the HIV epidemic is so much worse in southern Africa than it is anywhere else in the world. If, as various authors have suggested, the answer relates to sociological issues such as labour-hiring practices, oscillating migration and the resultant destruction of the family unit, then the underlying problem will not be solved by medical interventions alone, no matter how effective.

So, yes, we are in for a long journey. But every journey starts with a first step and, with the proactive rolling out of TasP we have taken the very important first step towards turning off the tap of new HIV infections. The continued success of this campaign depends ultimately on leadership and commitment from the Department of Health. They have brought us to this point where victory is in sight. With their continued leadership there is no doubt that we can end this terrible scourge.

It bears repeating, also, that South Africa currently spends about 30 billion rand a year on HIV. This massive spending on a single disease has a negative effect on the economy in general, and seriously compromises the Department of Health's efforts to address health issues other than HIV. Moreover, it also robs other arms of government of the chance to use part of that 30 billion rand in other ways – such as in making desperately needed improvements in the nation's primary and secondary school education and, yes, in the increased support for disadvantaged students at our universities.

For all of these reasons we need to see an end to the HIV epidemic in South Africa. Putting an end to that epidemic is not a sufficient condition for a better and a happier South Africa, but I would argue that it is a necessary, even an essential, condition.

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