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What does it take to reduce the rate of new HIV infections by 50% in KwaZulu-Natal, South Africa?

Ramzi Alsallaq - Research Scientist, New York University, New York, USA

Household surveys estimate the proportion of HIV infected persons in KwaZulu-Natal (KZN), South Africa at a pretty high level of ~23% of the population. This number reflects two ever changing quantities: the number of new infections for this year and the number of existing infections who survived from last year. We built a mathematical compartmental model and fitted it to behavioural and epidemiological data from KZN and we estimated the trend in the rate of new HIV infections (called incidence) in this province: we found that currently about 2 out of 100 persons at risk of HIV infection get infected every year (or simply 2/100 person-years). What is urgently needed is to seek ways to reduce HIV incidence while caring for existing infections in KZN; but in what way?

ART alone might not be sufficient for prevention

Ten years ago HIV providers and public health strategists had nothing but antiretroviral therapy (ART) to treat HIV-infected persons and prolong their AIDS-free lives. ART is still the choice for HIV treatment and recent scientific breakthroughs have illustrated that HIV+ persons who are *committed* to the treatment compared to HIV+ persons who are *not* on treatment have substantially less odds of transmitting the infection to their uninfected partners and enjoy a longer and AIDS-free life (1,2). This finding has motivated using ART (primarily intended for treatment) to prevent HIV transmission. Treatment for prevention emerged as the course of action in the fight against HIV spread. Although ART is a great tool for HIV prevention, it might not be exclusively sufficient because: the infectiousness of persons on ART is not 100% eradicated even with perfect commitment to taking the dose; there will always be drop out from treatment either due to side effects, developing resistance, or just abandoning treatment programs; and due to the difficulty of diagnosing early HIV infection. Therefore, the use of additional prevention tools would be needed to avert transmissions from these leaky or left-out pathways. Fortunately, it has been found that circumcised uninfected men are 60% less likely to get the HIV virus from their partners than uncircumcised men (e.g. (3)). Although male circumcision is not a perfect preventer against HIV acquisition, it does elevate the potential for HIV prevention mainly by combining it with ART in one package. The emerging course of action against HIV spread is to use a combination of prevention interventions rather than relying on individual tools.

Large scale HIV testing would be required

The entry point to ART (targeting HIV+ persons) and male circumcision (targeting HIV- males) interventions is HIV testing; thus expansion of HIV testing would be necessary for any large-scale strategy. Home-based counselling and testing (HBCT) is one way to achieve district-wide coverage (4). Also HBCT can generate a direct prevention effect as counselling for behaviour change after knowledge of HIV+ status in the privacy of one's home has been observed to generate changes in sexual risk behaviour in HIV+ individuals in terms of resorting to more condom use and potentially decreasing the partner acquisition rate (5).

Iterating the question raised earlier in the title of this article but rephrasing it in the following way: Can we reduce incidence in KZN by 50% using a package of combined interventions that includes HIV wide-spread testing and associated behaviour change (among HIV+ persons) together with ART and circumcision?

Mathematical modelling forecast for the impact of combined interventions at the short-term

The answer that is indicated by our mathematical modelling exercise is that incidence in KZN can be reduced by almost 50% (i.e. to ~ 1/100 person-year) and actually in *four years* if the following scenario for interventions were to be fulfilled:

a. Testing 90% of the adult population in 1 year and then having every HIV+ person linked to care, so that their CD4 count is monitored at reasonable frequency and whenever their CD4 reaches or drops below 350 they initiate treatment without delay.
b. Assuming that infected persons who know their HIV status as a result of testing and counselling increase condom use (by 25% if man and by 12.5% if woman) and reduce the rate of change of partners (by 25% for all) and they do so for a temporary duration of time (3 years on average); irrespective if they are eligible to ART or not eligible yet.
c. Referring and counselling men who are found HIV- and not circumcised to get circumcised

voluntarily such that 70% of uncircumcised adult men get circumcised in 2-years time and this level is maintained in the future.

For this ~50% incidence reduction estimate we assume that ART reduces infectivity in users by 92%, circumcision reduces risk of infection by 60% for men, and persons on ART leave treatment at a rate of ~14/100 person-years (and therefore return to be more infectious unless they restart treatment).

Community-based randomized controlled trials would be the robust answer to the short-term impact of combined interventions on HIV incidence in the population. Our modelling estimate for the four years can be interpreted as an anticipated scenario of using three evidence-based intervention components to reduce HIV incidence substantially in a time span of typical trials. However, our sensitivity analysis emphasizes the major role of the behaviour change component in the first four years of the intervention. That is to say if behaviour change is sustained for less than 3 years or its extent is less than anticipated above, the ~50% reduction could shrink to as little as ~40%. But why are circumcision and ART (at CD4 count 350) prevention effects not fully present at 4 years? There is a notion called *herd-immunity* behind the absence of the full effects at this short term. Herd immunity develops as HIV transmission dynamics in the community evolves under the interventions resulting in a general reduction in the risk of HIV in the population. It does take longer time until prevalence of HIV in the male population substantially declines (because of circumcision) and until a larger number of persons meeting the treatment guidelines accumulates on treatment.

Long-term predictions

For this herd immunity to accrue we investigated repeating testing 90% of KZN adult population with unknown HIV status (this includes persons tested HIV- previously) every four years after the first wave of testing described above. If the extent and duration of behaviour change and the levels of coverage for ART and circumcision are maintained as above, herd immunity effects could reduce HIV incidence by up to ~60% after 15 years.

Behaviour change plays major role only at the short-term

Further results from our long-term analysis indicate that the lower is the coverage for testing the less is the impact of ART, obviously because less people would be linked to HIV care and be able to start treatment on time if they ever start treatment. If the dropout rate from ART increases, not only less lives would be saved but also the prevention effect of ART in the population becomes less. Short-lived behaviour change following knowledge of HIV+ status does not significantly affect predicted incidence reduction after 15 years of repeated testing, this is mostly controlled by herd-immunity effects of ART and circumcision.

More aggressive ART component in the combination and model predictions

An intriguing question that might come across when considering ART for prevention is what would happen if the ART component in the above combination intervention is changed to immediate treatment irrespective to CD4 count instead at CD4 count of 350 keeping everything else the same as before?

Making the CD4 threshold for treatment higher than 350 (much earlier ART) would speed up the prevention effect of ART because many infected persons (that have been tested and diagnosed with CD4 count above 350) do not have to wait for their CD4 count to drop below a threshold anymore. Unlike before, HIV transmission dynamics becomes less affected by temporary behaviour change at the short-term. The reduction in HIV incidence for this case would be much larger at four years (63% reduction) and even much more (76%) at fifteen years when most of the herd-immunity effects are accrued.

The modelling shows the importance of repeated high coverage of testing, linkage to care, starting treatment on time (at CD4 count 350 or less), and high coverage of circumcision in order to reduce the rate of HIV infection in KZN to below 1/100 person-years. Implementing early treatment, sustainable high retention to care and sustainable high commitment to antiretroviral therapy would make ART the most influential component in combination prevention against HIV.

Ramzi Alsallaq, Research Scientist, New York University, New York, USA. Area of interest: Mathematical modelling of infectious diseases. *ramzi.alsallaq@gmail.com*

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