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# Universal testing and immediate treatment could cut HIV infections by 95% in 10 years

## WHO publishes modelling study

Universal HIV testing and immediate antiretroviral therapy for everyone diagnosed with HIV in a country with very high HIV prevalence could reduce new infections from 20 per thousand to 1 per thousand within ten years, according to findings from a mathematical modelling exercise carried out by the World Health Organization, published on November 26<sup>th</sup> by *The Lancet*.

The findings suggest that HIV transmission could be virtually eliminated by 2020 in countries with high levels of HIV prevalence, such as South Africa, if it were possible to persuade everyone in the community to test for HIV infection once a year and then provide antiretroviral therapy to all who test HIV-positive. Transmission is expected to decline if more people are treated because antiretroviral treatment reduces the amount of HIV in semen and vaginal fluids, reducing the risk of transmission.

Currently only around 20% of people with HIV in sub-Saharan Africa know their HIV status, and antiretroviral therapy in most countries is available only to those with symptoms of HIV disease or severe immunosuppression (a CD4 count below 200 cells/mm<sup>3</sup>).

Expanding treatment to all those who need it under current guidelines will be a substantial undertaking. Three million people are currently receiving antiretroviral therapy worldwide, but an estimated 6.7 million are still in need of treatment and a further 2.7 million became infected during 2007, according to WHO's 2008 report on progress towards universal HIV treatment access.

Expanding treatment and testing to reach everyone with HIV, particularly in southern Africa, would be a massive undertaking that would require vastly greater human resources than currently available for health care.

Dr Kevin de Cock, WHO's HIV department director says that universal testing and treatment regardless of immune system status could not become an official WHO recommendation without further research into the feasibility, safety, acceptability, impact and cost-effectiveness of the approach, as well as extensive consultation.

Nevertheless the findings are likely to stoke interest in expanding access to antiretroviral therapy in order to limit the long-term impact of the HIV epidemic in the most severely affected countries, those in the southern African region where HIV prevalence in the adult population ranges from 15 to 35%.

Treating everyone with HIV infection in order to reduce the number of new HIV infections has been advocated previously by Professor Julio Montaner of the University of British Columbia in Canada. Prof. Montaner and colleagues [published the results of their own mathematical modelling in 2006](#), which projected that new HIV cases would decline from 7 per [thousand](#) to 0.1 per thousand over 50 years if universal testing and treatment were implemented.

The introduction of door-to-door HIV testing and counselling and antiretroviral therapy for all who qualified under Ugandan treatment guidelines [reduced new cases of HIV infection by around 90%](#) over a

three-year follow-up period, according to findings from a US Centers for Disease Control study carried out in rural Uganda over the past five years.

So far no country or region in the world has adopted a strategy of universal testing and treatment. Current treatment guidelines in the United States and Europe recommend treatment for everyone with a CD4 cell count below 350 cells/mm<sup>3</sup>, although there is [some evidence](#) that starting treatment at a CD4 count below 500 cells/mm<sup>3</sup> reduces the risk of serious non-AIDS-defining illnesses when compared to starting treatment at a CD4 count below 350 cells/mm<sup>3</sup>.

Encouraging treatment uptake in order to reduce HIV transmission is an explicit public health goal in only one region of the world at present, the Canadian province of British Columbia, where Professor Montaner's research group [has persuaded the provincial government](#) to adopt a more aggressive approach towards identifying everyone currently eligible for treatment at a CD4 count of 350 cells/mm<sup>3</sup> or below. [The group's modelling suggests](#) this policy could avert more than two-thirds of projected infections in the province between 2008 and 2030.

The WHO model used South Africa as an example, taking data on infection rates and disease progression to model the effects of expanding knowledge of HIV status and a growing uptake of antiretroviral treatment. The model assumed that with a baseline HIV prevalence of 16%, a 99% decline in infectiousness when individuals started treatment, and 90% coverage of treatment in the HIV-infected population by 2016, 104,000 deaths would be averted in 2015 alone when compared to starting treatment at a CD4 cell count of 350 cells/mm<sup>3</sup> (in itself an optimistic threshold).

The model assumed an annual treatment cost (including drugs, monitoring and patient management) of \$727 a year for first-line treatment and \$3290 for second-line treatment, with antiretroviral drugs accounting for 30% of the cost.

The model showed that HIV transmission would decline very steeply as HIV treatment coverage expanded, falling from around 15 new infections per thousand adult and adolescent inhabitants today to 1 per thousand by 2016.

Although the universal treatment strategy would cost three times more than treating everyone with a CD4 cell count below 350 cells/mm<sup>3</sup> in 2015 (\$3.4 billion a year), the yearly cost would begin to fall after this point, and by 2030 the approach would become less expensive than treating only those with CD4 counts below 350 cells/mm<sup>3</sup> (approximately \$1.8 billion).

## Reactions

Professor Geoffrey Garnett of London's Imperial College, an HIV epidemiologist, said in an accompanying commentary: "[The] suggested strategy would be extremely radical, with medical intervention for public health benefits rather than individual patient's benefits. Because screening and treatment would be for the public good, resources would have to come from the public purse. The suggested strategy would reflect public health at its best and its worst"

"At its best the strategy would prevent morbidity and mortality for the population, both through better treatment of the individual and reduced spread of HIV. At its worst, the strategy will involve over-testing, over-treatment, side-effects, resistance and potentially reduced autonomy of the individual in their choices of care...It is easy to see how enforced testing and treatment for the good of society would follow from such an argument. Partial success would lead to infection becoming concentrated in those with a high risk,

with an increased danger of stigma and coercion. The history of the control of sexually transmitted infections documents several examples of compulsory screening and treatment of stigmatised populations, and there is a danger of a well-meaning paternalistic medical model following such a route."

There was [strong advocacy for achieving universal treatment coverage on prevention grounds at this year's](#) International AIDS Conference in Mexico City. Professor Julio Montaner, who is also President of the International AIDS Society, said: "We believe there is now enough evidence to say to policymakers that if you roll out HIV treatment with 100% coverage, you will see a reduction in HIV transmission."

The study was endorsed as an important step forward by several advocacy groups. GNP+, the global network of people living with HIV and AIDS, said that the study represented a breakthrough in thinking by WHO, but urged the agency to work closely with PLWHIV networks to increase access to testing and treatment while protecting human rights.

The International Treatment Preparedness Coalition (ITPC), a global network of community-based HIV treatment advocacy groups, also welcomed the publication.

"This article can help put an end to false debates pitting HIV treatment against HIV prevention," said Aditi Sharma, Co-Coordinator of the Treatment Monitoring and Advocacy Project (TMAP) of ITPC. "If additional research supports this model, it could signal a paradigm shift in the public health response to HIV," Sharma said.

"The WHO study confirms what those of us working on the frontlines of the epidemic know from personal experience: HIV prevention and treatment are mutually reinforcing," Sharma added.

"We need research to determine the feasibility and long-term implications of this change in the way HIV treatment is managed," said Gregg Gonslaves, a member of ITPC. "Starting therapy at high CD4 counts may not have clinical benefits for a person living with HIV and since ART comes with long term toxicities, very early initiation may be problematic."

## Unanswered questions

WHO will convene a meeting early next year bringing together ethicists, funders, human rights advocates, clinicians, prevention experts and AIDS programme managers to discuss this and other issues related to the wider use of antiretroviral therapy for HIV prevention.

However, there will be no early change in guidelines based on a modelling exercise alone.

WHO says it needs to know more about the following questions in order to determine whether its modelling is accurate:

- What is the acceptability of universal HIV testing and will it be genuinely universal?
- How infectious are people receiving antiretroviral therapy, especially in settings where the rate of sexually transmitted infections is high?
- How well do people adhere to antiretroviral therapy in the long-term?
- What are the long-term failure rates for antiretroviral therapy and what are the subsequent resistance patterns? To what extent will these restrict the response to second-line therapy?
- What are the effects of universal testing and antiretroviral availability on sexual behaviour? In particular, would the greater availability of treatment, alongside the message that treatment reduces the risk of transmitting HIV, lead to a generalised

increase in risk behaviour during the early phase of treatment scale-up leading to a paradoxical increase in HIV incidence?

The feasibility of the approach also needs to be tested in a real health system, in order to determine the level of health personnel and health system strengthening required, as well as the effects of the approach on other public health goals.

Better data are urgently needed from real-life settings, but there are several problems in obtaining them:

- Researchers are not altogether satisfied with the accuracy of assays designed to capture HIV incidence in biomedical prevention trials, leaving us reliant on combined antibody/antigen tests that have [varying levels of accuracy](#). Better assays are urgently needed.
- Measuring incidence at the community level is expensive and requires a national or regional surveillance programme; treatment programmes are not set up to measure incidence at present (surprising though that may seem). These data could eventually be gathered quite comprehensively for meta-analysis if major donors such as the Global Fund and PEPFAR **mandated** the measurement over time of HIV incidence in communities where treatment becomes available as a result of their funding.

The most convincing long-term data are likely to come from long-term randomised studies however. A study of the effects of earlier initiation of antiretroviral therapy in HIV-discordant couples is currently taking place in Malawi, Brazil, India, Thailand, and Zimbabwe and is due to report around 2013. [That study, HPTN 052](#), is recruiting HIV-positive people with CD4 counts between 350 and 550 cells/mm<sup>3</sup> and their HIV-negative partners. The HIV-positive partner is randomised either to begin treatment immediately or to start treatment according to national guidelines (at a CD4 count of 250-200 cells/mm<sup>3</sup>). The study will measure the effect on incidence of the two treatment strategies, and is powered to detect a greater than 35% reduction in HIV incidence in the early treatment arm.

However, many of the operational questions about this approach might be addressed in a community-randomised trial, in which geographically separate districts within the same country are randomised either to carry out treatment and testing according to current guidelines, or to adopt the universal testing and treatment approach. Such a study might take five to seven years to provide a robust answer by the time it was funded, set up and allowed to run for long enough to assess the operational difficulties inherent in the new approach.

Several research groups based in the United Kingdom, Canada and France are already working on ideas for studies.

Ultimately, Reuben Granich of WHO's HIV department told HATIP, WHO will need a variety of sources of information on this topic before it could issue a recommendation.

"WHO has a fairly rigorous guidelines process in order to make recommendations. In that context randomised controlled trials are usually the gold standard, but other types of data can be brought into that process, and all that evidence would be weighed."

Other types of data might include a meta-analysis of incidence data from communities with various levels of treatment coverage, as well as operational research. Countries with good antiretroviral coverage and a relatively well developed infrastructure, such as Botswana and Namibia, could yield useful data relatively soon.

## Feasibility

But will it be possible to sustain almost universal annual HIV testing in a population over many decades? Such a seismic shift would

undoubtedly require a shift to community-level testing initiatives, which might in themselves have prevention benefits. As noted above, the US Centers for Disease Control (CDC) has demonstrated that almost universal uptake of HIV testing is feasible in its Home Based AIDS Care study in rural Uganda, by going door to door.

On the other hand a national campaign to promote knowledge of HIV status in Lesotho fell far short of its targets, probably due to the fact that lay counsellors were poorly trained and there was insufficient linkage between testing and treatment (unlike in the CDC model). By August 2007 just 25,000 people had been tested through the Know Your Status campaign. The target was 1.3 million by the end of 2007. A [qualitative research study](#) by Human Rights Watch and the AIDS and Rights Alliance for Southern Africa (ARASA) found “a clear disconnect between planning on paper and the capacity to implement what was planned.” Counsellors had inadequate training, particularly in the importance of informed consent and confidentiality, and there was no training in couples counselling, which was key to the CDC approach in Uganda.

Another concern is that there is no evidence at present of what is necessary in order to achieve and sustain high levels of HIV testing, particularly in urban and periurban settings. This issue is of particular relevance to South Africa, the most urbanised country in southern Africa, but growing urbanisation will make it equally pertinent in other countries in sub-Saharan Africa.

Health system capacity to deliver treatment on the scale envisaged is the big, unanswered question. More information is needed about the level of health system strengthening that would be required in order to facilitate such a level of testing and treatment, together with evaluation of any distortionary effects on other health system priorities. Such an approach would inevitably require a huge devolution of care to the primary care and community level, together with the adoption of a chronic disease management model within primary health care, which in turn will require substantial investment and training. Although some models of task-shifting within HIV care have shown positive outcomes, not all task-shifting results in a consistent standard of care or comparable outcomes (see [issue 116 of HATIP, published in September 2008](#), for more on this topic).

## Toxicity

More information is also needed about the trade-off between earlier treatment and drug toxicity. In many developing countries first-line treatment includes drugs with quite high rates of toxicity, including d4T (stavudine) and AZT (zidovudine). Using these drugs, which are much cheaper than the better tolerated first-line regimens now used in Europe and North America, could have significant long-term disadvantages if they cause a high rate of serious side-effects in otherwise healthy people. [Some data suggest](#) up to one in five people may need to switch as a result of toxicity. On the other hand, [there is also evidence](#) that the side-effects of these drugs appear less frequently in people who start treatment earlier.

These drugs are used because they cost around \$100-\$150 a year, compared with \$270-\$400 a year for less toxic drugs. When considering the cost of first-line treatment it is important to be aware of the fact that the cheapest combinations all contain nevirapine. However nevirapine is not suitable for use in women with CD4 counts above 250 cells/mm<sup>3</sup> or men with CD4 counts above 400 cells/mm<sup>3</sup>, due to the increased risk of life-threatening liver toxicity above these thresholds. So, a substantial proportion of

treated people would need to receive other less toxic, more expensive drugs if universal treatment was the aim.

It is unlikely that less toxic drugs will ever be as cheap as the current first-line options, because they require more raw materials and more complex chemistry, in the view of the Clinton HIV/AIDS Initiative.

## Affordability

Universal testing and treatment is only likely to be cost-effective in settings where HIV is hyper-endemic and where AIDS seriously threatens long-term stability and growth. Further cost-effectiveness analysis will be needed. The WHO analysis looks at the relative costs of pursuing the universal approach or treating people when their CD4 count falls below 350 cells/mm<sup>3</sup>. The universal approach demands substantially greater expenditure during the first two decades, but begins to become cheaper than the default treatment approach by 2030. This balance and time-scale may differ in other countries in the southern Africa region.

However, such large expenditure is likely to raise concerns about distortion of health system priorities. A universal approach to HIV treatment in settings where prevalence exceeds 15% is only likely to avoid health system distortion if it is situated within a wider package of essential health care delivered through the primary care system.

**Universal testing and treatment would provide a major opportunity to promote and strengthen primary health care services** and the integration of maternal/child health, TB and HIV care.

## References

- Granich R et al. *Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model*. The Lancet ([online publication, November 26 2008](#)): doi:10.1016/S0140-6736(08)61697-9
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- Unfortunately the full text versions of these articles are only available to subscribers.