Treatment for common STDs may not always reduce the spread of HIV

A major study in Uganda has contradicted previous findings about the impact of treatment for sexually transmitted diseases (STDs) on the spread of human immunodeficiency virus (HIV). The Rakai STD Control for AIDS Prevention Study, conducted by a large international team, found that mass treatment of common STDs such as syphilis and trichomoniasis made no difference to the incidence of HIV-1 infections over almost 2 years.

These findings, now published in full in the Lancet following an initial report at last year's International Conference on AIDS, held in Geneva, have come as a surprise to many. There is, as the authors of the Rakai study themselves point out, "substantial" evidence that HIV is more easily transmitted when individuals have other STDs. And, in 1995, a team based in Mwanza, United Republic of Tanzania, showed that the rate of new HIV infections fell by about 40% in the intervention group whose STDs were treated, compared with a control group.6

Yet the Rakai study reached different conclusions. Two groups each of about 6000 HIV-1 negative people were assigned at random to either antibiotic treatment at home for STDs or a placebo treatment consisting of an antimalarial, vitamins, and minerals. After 20 months' follow-up in the Ugandan study, the incidence of HIV infection was the same among those who received treatment for STDs as among those who did not, at 1.5 per 100 person-years. The prevalence of syphilis and trichomoniasis fell in the treated group.

One possible factor to explain the difference between Rakai and Mwanza, says Dr Ronald Gray, a member of the Rakai team from Johns Hopkins University, Baltimore, USA, is that the baseline prevalence of HIV is much higher in the Rakai population: 15%, compared with 4% in Mwanza. If an HIV epidemic is at a low level, or in its early stages, he says, then the presence of other STDs may be an important co-factor in the spread of the virus. If, however, the epidemic is well established and has spread beyond a core group of individuals at high risk, a significant proportion of the spread of HIV may be independent of such co-factors. In Rakai, the team estimated, about four out of every five HIV infections are independent of any association with STDs. In other words, if all STDs could be eliminated, the number of new HIV infections each year would be expected to fall by about one-fifth.

Dr Maria Wawer, another member of the team, from Columbia University, New York, points out that some STDs do not respond to treatment. For example, bacterial vaginosis and herpesvirus infections were extremely common in Rakai — 50% of women had bacterial vaginosis and a similar proportion, herpes infections. Among those cases of HIV infection that are associated with STDs, the latter may play a much more important role than previously recognized, she says.

The researchers stress that the findings should not be interpreted as a reason to abandon the intensive treatment of STDs in communities. That treatment is a vital public health intervention in its own right, they say. Gray adds that the study does not overturn the fact that, at the individual level, STDs are still associated with a greater risk of HIV infection. A key need, he says, is to find out more about those STDs, such as bacterial vaginosis and herpesvirus infections, that are essentially untreatable. "We need better research and better methods for treating these conditions." The Mwanza team and the Rakai team — whose members are from Makerere University, Uganda, the Uganda Virus Research Institute, and three US institutions — are now collaborating to try to find out why their studies produced such different results.

Malaria vaccine progress

The continuing search for an effective malaria vaccine has taken a significant step forward. Scientists in India, Kenya, and the USA have developed a recombinant gene candidate vaccine that stimulates immune responses against multiple stages of the malaria parasite's life cycle in animal experiments, and blocks infection of cells in the laboratory. The candidate vaccine is due to start more extensive studies in Anopheles monkeys this spring and, if these go well, a decision to start human trials could be reached by the end of the year.

The candidate vaccine, developed by a team led by Dr Altaf Lal at the Centers for Disease Control and Prevention in Atlanta, USA, is based on 21 separate epitopes from 9 different antigens from the principal malaria parasite, Plasmodium falciparum. The researchers used these epitopes because each of them is recognized by the immune systems of people who are clinically immune to malaria, suggesting that they may play a role in protection against the parasite.

One of the key difficulties with designing a malaria vaccine is that the parasite's complex life cycle allows it to evade simple vaccines directed against only one stage. An important advantage of this candidate is that it produces responses against four stages: sporozoite, liver, erythrocytic asexual and sexual. Studies in the laboratory suggest that the candidate vaccine is also recognized by human T cells and antibodies.

The team constructed a synthetic gene that codes for the 21 epitopes of P. falciparum antigens, expressed it in a baculovirus, and purified the resulting protein, termed CDC/NIAMID/1. When rabbits were immunized with the protein together with various adjuvants, they produced antibodies and T cells that recognized each stage. In the laboratory, the antibodies prevented sporozoites from invading liver cells, a key requirement for interrupting the parasite's life cycle.

Lal warns that the development of malaria vaccines is "a rocky road", but says he is optimistic. Dr Anthony Fauci, Director of the National Institute of Allergy and Infectious Diseases in Washington, DC, which partly funded the study, also voices cautious hope. "Although these results are preliminary and the candidate vaccine has yet to be tested in people, its effectiveness in
laboratory tests makes it an interesting candidate for further study," says Fauci. The results are reported in the Proceedings of the National Academy of Sciences of the United States of America.4

Shorter short-course treatment protects some infants from HIV

Pregnant women infected with human immunodeficiency virus (HIV) may now have a chance to protect their babies from becoming infected with the virus even where they have no access to medical care until the very end of pregnancy. Early results from a large clinical trial coordinated by the Joint United Nations Programme on HIV/AIDS (UNAIDS) and known as PETRA (Perrinatal Transmission) show that antiretroviral drugs given to mother and infant can reduce the risk of HIV infection in the infant by more than one-third even when treatment begins only in the last week of pregnancy and continues for the infant for a week after birth.

The PETRA trial is continuing in South Africa, Uganda, and United Republic of Tanzania. Previous studies had shown that a course of antiretroviral treatment begun in the 36th week of pregnancy halves the risk of mother-to-child transmission of the virus. Although the efficacy of the shorter treatment, based on combined zidovudine and lamivudine, is lower, at 37%, it may offer an alternative option for women living in different real-life situations," says Dr Awa Coll-Seck, Director of Policy, Strategy and Research for UNAIDS. Dr Peter Pirot, the programme's Executive Director, says: "Now we may be able to help women protect their babies, even if they do not come to a hospital or clinic until very late in pregnancy."

Among populations where breastfeeding is the norm, the risk that an HIV-positive woman will infect her infant ranges from 25% to 35%, of which about one-third is attributed to breastfeeding. When the announcement of the PETRA results was made, at the Sixth Annual Conference on Retroviruses and Opportunistic Infections in Chicago, USA, in February, the babies had been followed up for only 6 weeks after birth.

There is a continued risk of infection with HIV for as many months or years as breastfeeding continues, and, in the PETRA trial, most of the participants are breast-feeding. However, preliminary results from a trial conducted by the French national research council, l'Agence Nationale de Recherches sur l'SIDA (ANRS), suggest that the protective effect of short-course treatment persists for the first 6 months of breastfed infants' lives. Full details of this trial are expected to be published soon. The follow-up in the PETRA trial will continue for 18 months.

USA gets to grips with priority-setting for health research

How should public funds for health research be divided up? This question is central to an intense ongoing debate over priority-setting in the US Congress and at the world's biggest publicly funded health research organization, the US National Institutes of Health (NIH). The fallout from the debate is already reaching beyond the USA to influence other national and international agencies whose research resources are more modest.

The latest move comes this spring, when NIH is due to name the members of a 20-strong Council of Public Representatives to increase communication between the NIH director, Dr Harold Varmus, and the public, which funds its $15.6 billion budget. The council has been created following a review last year of NIH's priority-setting process by the Institute of Medicine (IOM). The review was ordered by the US Congress amid mounting controversy over how health research money is spent.

Increasingly through the 1980's and 1990's, Congress, as a result of lobbying, had been tending to set aside research funds for specific diseases, particularly AIDS and breast cancer. Advocates of other conditions such as Parkinson and Alzheimer disease have also secured specific budget increases. For example, in 1997 the lobby for Parkinson disease won qualified approval for an additional $100 million for NIH-sponsored research into the disease, while research into prostate cancer receives a $50 million boost in the current year's budget. The result has been a chorus of increasingly angry objections that some diseases fare much better than others when research dollars are measured per death — a process referred to by some sceptics as 'body-count budgeting'.

One assessment found, for example, that AIDS research received US$ 110 per death compared with US$ 10 per death for cancer and US$ 3 for heart disease.4 Some advocacy groups have claimed that their views are being ignored. Congress has grown increasingly uncomfortable with earmarking funds, and called on the IOM to help.

NIH currently uses five criteria to guide decisions on how to allocate its funds: public health needs; scientific quality of the research; potential for scientific progress; portfolio diversification along the broad and expanding frontiers of scientific knowledge; and adequate support of the people, equipment, instrumentation and facilities needed for research. These criteria are generally sound, concluded the report, and NIH should continue to use them in a balanced way. But the report also concluded that NIH must make aspects of the process more transparent and formal, and must increase public awareness of how the criteria are implemented; it must, for example, be able to show that it has systematically compared data on the burdens of various diseases, and the costs of treating them, against the resources devoted to them. Thus, the Council of Public Representatives should not set the priorities itself, but should help to increase public awareness of the process. In addition, the IOM committee recommended that each institute of NIH that as yet has no public liaison office should set one up.

Provided these improvements were made, Congress should be able to leave the process of priority-setting to NIH and intervene only if it failed, said the report. It also called upon Congress to give the NIH the resources to improve its analytical capacity so that it could follow these recommendations.

NIH has stressed its willingness to consult the public, pointing out that it already has numerous public liaison panels and committees. Varmus told a meeting of the Advisory Committee to the Director that "Of all the government institutions I know, NIH has the most extraordinarily rich interactions with the public". At the meeting,


5 Scientific opportunities and public needs: improving priority setting and public input at NIH. Washington, DC, Institute of Medicine, National Academy Press, 1998 (for Executive Summary see www.nap.edu/readinrom/books/nihSummec.htm).


7 Setting research priorities at the National Institutes of Health. Washington, DC, National Institutes of Health, 1997 (NIH booklet, currently under revision).
he is also reported to have questioned whether the IOM panel fully appreciates how seriously the NIH takes the issue of assessing disease burden and the cost of disease when it allocates research funds. "There seem to be two extremes of conception about NIH priority-setting," Varmus told a meeting of the NIH's advisory committee to the director. "There's the 'King and His Counting House' model, where I push piles of money in certain directions, and the Tolstoyan model, where there are many soldiers and many trenches, each ignorant of the other's battle." Varmus reportedly argued that neither extreme does credit to the actual effort that NIH makes.  

Dr Anne Thomas, NIH Associate Director for Communications, says that the establishment of the council is well under way and offices of public liaison are in place in each institute. The council's members will represent a wide range of interests including patients, health workers, academics, lawyers and media representatives. All members are expected to leave any personal interest in a particular disease behind when they join. "There are many aspects to priority setting and I don't think the council will sit there and do this," she told the Bulletin.  

Criteria for priority-setting in health research are being sought by an increasing range of funding bodies. In 1996 the WHO Ad Hoc Committee on Health Research Relating to Future Intervention Options outlined criteria for assessing the relative claims of different global health problems on limited research resources. Others have set down criteria for specific research areas such as vaccines. But with around one-quarter of the world's health research spending, public and private, within the hands of NIH, the current scrutiny of its own process is a global concern. ■

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