GEARING UP TO TEST ACTIVE AND PASSIVE IMMUNIZATION FOR HIV PREVENTION

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Encouraged by the results of the RV144 HIV vaccine trial conducted in Thailand, the USA-based HIV vaccine Trials Network (HVTN) has embarked on an ambitious program to determine whether this vaccine regimen can reduce HIV infection rates in southern Africa. While the 31% efficacy seen in RV144 was modest, the hope is that with modifications this vaccine will show sufficient efficacy to warrant licensure and general use. These newer vaccines have been tailored to target HIV subtype C viruses that circulate in southern Africa and are currently being tested in HVTN 100. This is a small Phase 1-2 trial of 252 individuals, with plans to conduct a large scale efficacy trial if the data look promising.

The vaccine regimen comprises two components that aim to stimulate both arms of the immune response. For the cellular arm, the relatively harmless canarypox virus (called ALVAC) has been engineered to carry small pieces of HIV which trick the body into thinking it is under attack thereby inducing an immune response to HIV. Soluble protein antigens derived from the HIV envelope gp120 glycoprotein are used to elicit an antibody response to HIV. An immune correlates analysis of RV144 showed that individuals who developed antibodies to the variable region 1 and 2 (V1V2) of the gp120 vaccine had a reduced risk of HIV infection. Results from RV144 are being used to set criteria for a crucial go/no-go decision in HVTN 100. More than 90% of individuals who receive the vaccine must have binding antibodies to HIV antigens with at least 56% having V1V2 binding antibodies for the vaccine to proceed. Furthermore, at least 60% of vaccinees must have HIV-specific CD4+ T-cell responses.

This go/no-go decision will be made in the first quarter of 2016. If the criteria are met, then 5400 individuals will be enrolled into the HVTN 702 efficacy trial across 13 clinical sites in southern Africa including 6 sites in South Africa (Cape Town, eThekwini, Isipingo, Klerksdorp, Soshanguve and Soweto). Half will receive the vaccine while the other half will receive a placebo which does not contain any HIV antigens. Neither the participants nor the study co-ordinators will know who received the vaccine or placebo. This is called a double-blinded randomized clinical trial, or RCT, and is the “gold standard” for assessing whether a product works. In the case of HVTN 702, participants will be followed for up to 3 years for evidence of HIV infection. If there are significantly fewer infections in those who received the vaccine, then the vaccine will be considered efficacious. A vaccine able to reduce infection rates even by 50% will have a major impact on the HIV epidemic.

In parallel, the HVTN 703 or antibody-mediated protection (AMP) trial will also be conducted in southern Africa. This trial aims to test a related but different concept (see figure below), namely whether or not a pre-formed monoclonal antibody called VRC01 can prevent HIV infection following passive transfer. Unlike the V1V2 binding antibodies induced by vaccination that are thought to function through antibody-dependent cellular cytotoxicity (ADCC), VRC01 is a broadly neutralizing antibody that directly blocks infection of cells by a range of diverse viruses. Since no vaccine is yet able to elicit broadly neutralizing antibodies, this trial aims to provide important proof-of-concept that broadly neutralizing antibodies can prevent HIV infection in humans. In addition, this trial will provide insight into the dose of an

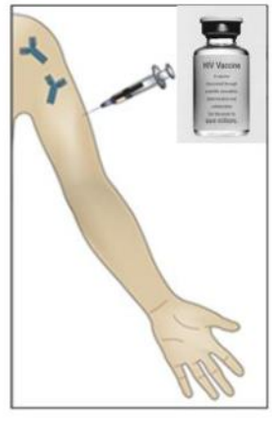
antibody that would be required for protection by vaccination.

The antibody VRC01 targets the CD4 binding site on the HIV envelope gp120 and is a highly conserved target. As such it shows excellent breadth, neutralizing more than 90% of global isolates including subtype C. It has previously been shown to be safe in humans and to prevent infection in monkeys. It has also been tested therapeutically in people infected with HIV and has been shown to reduce viral levels. However, the antibody was not effective in HIV-infected individuals whose virus was resistant to VRC01. This indicates that only viruses that are sensitive to VRC01 will be prevented from establishing HIV infection. Future trials may therefore need to consider the use of combinations of antibodies to cover the majority of HIV strains.

Participation in HVTN 703 will require that healthy HIV negative volunteers receive intravenous infusions every 2 months for 20 months (i.e. 10 infusions). A total of 1500 women at high risk of HIV infection will be enrolled into this study; 500 will receive VRC01 at the higher dose of 30 mg/kg body weight, 500 will receive 10 mg/kg and 500 will receive a placebo. This is also an RCT and vaccinees will be studied for over 2 years with HIV infection as an end-point. During the trial, volunteers will be counselled on safe sexual practises and provision of oral pre-exposure prophylaxis (PrEP) is under discussion. This trial is the first of its kind and is unprecedented in HIV prevention research.

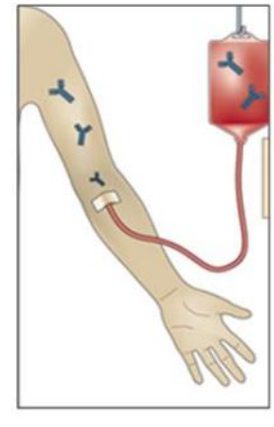
There is no doubt that the crisis caused by the HIV pandemic requires urgent and bold steps. While the roll-out of anti-retroviral therapy (ART) has greatly impacted the HIV epidemic, there are still 1.5 million deaths and 2 million new HIV infections around the world every year. In South Africa there are over 6 million people living with HIV of whom only 42% are being treated with ART. Issues of cost, access, toxicity and drug resistance make the use of ART to control the HIV epidemic unrealistic. The development of a vaccine or the use of passive immunization to prevent HIV infection remains our best hope for an AIDS-free future.

Active immunization



Vaccination to stimulate antibodies that correlate with a reduced risk of HIV infection. This is being tested in HVTN 702

Passive immunization



Pre-formed neutralizing antibody VRC01 is infused to provide protection against HIV infection. This is being tested in HVTN 703