



SAAVI HIV vaccine trials – one small step for humankind

One small step for man, one giant leap for mankind

Neil Armstrong upon landing on the moon, 20 July 1969

Few South African medical professionals will not have experienced a patriotic moment with the recent announcement by the MRC of the start of phase I trials of two indigenously developed HIV vaccines in Johannesburg and Cape Town. The trials represent a triumphant milestone for the South African AIDS Vaccine Initiative (SAAVI), established in 1999 as an MRC unit 'to co-ordinate the development of an affordable, effective and locally relevant HIV vaccine for southern Africa'. The two vaccines – MVA-C and DNA-C2 – are also being tested in the USA.

The trials are a tribute to South Africa's intellectual prowess and research ingenuity, and to the resilience of our research community in the face of the oft-lamented brain drain, resource constraints and the prejudices associated with our location in the southern hemisphere. The MVA-C vaccine was conceptualised and designed at the University of Cape Town and constructed in the USA, whereas the DNA-C2 was constructed in South Africa using a plasmid (genetically engineered DNA) designed in the USA. SAAVI and its South African colleagues have forged international partnerships and collaborations and attracted national and international funding that have contributed to these historic developments.

Vaccination, the introduction into the body of an attenuated or killed form (or particle or toxin) of a disease-causing organism to elicit immunity against the disease, has arguably saved more lives globally than any other medical intervention since Edward Jenner conducted the world's first recorded medical trial using cowpox to immunise against smallpox in 1796, and reported his findings to the Royal Society in 1798. However, the idea of inoculation (variolation) with disease exudates or pox scabs as protection against future infection was already practised in China and India some 200 years before the Christian era, and is described in ancient Ayurvedic writings. In Jenner's time, an apparently effective form of inoculation called *ashi*, using exudates from lesions of mild cases of smallpox, had been common practice among the Ottoman Turks for at least 100 years, and the practice had spread to England via diplomatic contacts. Jenner's unique contribution was use of the milder cowpox (which he named 'vaccination' from the Latin *vacca* meaning cow) as a proxy for smallpox. Modern universal vaccination campaigns have since enabled the eradication of smallpox, the virtual elimination of polio, and the control and prevention of numerous other infectious diseases.

Not yet a giant leap

Since Jenner's experiment, the science of vaccines has become highly sophisticated and complex in step with the profound advances in immunology and genetics. But even as vaccine science has advanced, so has the HI virus seemingly contrived to evade and repel it, stubbornly staying a step ahead of the science. In a natural viral infection the immune system usually responds in two ways: by producing neutralising antibodies that prevent further viral replication in the body of intruding organisms, and by producing killer T lymphocytes that recognise and eliminate infected cells. Thus the invading virus is destroyed and prevented from multiplying, and immunological memory is developed that prevents future infection. A good vaccine works by mimicking these natural responses.

That said, finding an effective HIV vaccine faces huge and formidable obstacles. The immunology of HIV is complex and highly specialised. Broadly speaking, natural immune response to HIV invasion is weak, failing effectively to arrest replication (neutralising antibodies) or destroy infected cells (killer T-lymphocyte induction). Moreover, the window for this to happen is small, as the virus quickly merges itself into the host cell DNA within days or weeks of infection, attaining latency that renders it invisible to the immune system. Furthermore, the virus mutates with extraordinary rapidity, so that whatever neutralising antibodies there are, are constantly kept out of sync with the genetic make-up of the envelope protein that they target. Ingenious techniques are continuously being researched to fool and ensnare the HI virus. The South African trial vaccines utilise DNA derivatives (DNA-C) and the modified vaccinia Ankara virus (MVA-C2) to try to overcome these obstacles and elicit an effective HIV immune response.

Currently it appears more likely that the first HIV vaccine, if and when it is achieved, will be the kind that induces killer T lymphocytes that will ameliorate HIV disease by controlling virus levels and reducing the destruction of CD4+ T cells, but will not prevent infection. There are currently about a dozen HIV vaccine trials underway around the world, largely in phase I to test for safety. But we are at least a decade away from a proven HIV vaccine. Only then shall we have achieved a 'giant leap' for humankind.

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