'BREAKTHROUGH' THAI HIV VACCINE TRIAL CONTROVERSY

Professor Salim Abdool Karim, Director of the Centre for the AIDS Programme of Research of South Africa (CAPRISA).

Picture: Chris Bateman

'For the first time ever we know that an HIV vaccine is possible.'

That's what several excited top South Africa HIV/AIDS researchers thought following the surprise findings in September's 16 000-person trial in Thailand (the much-maligned RV 144 trial), which claimed a 31% reduction in infection risk among participants.

Professor Glenda Gray, head of the perinatal HIV Research Unit at Witwatersrand University, said the efficacy of the combination prime-boost vaccine paved the way for future designs – 'it's exciting because it means that a vaccine is attainable'.

She and fellow researchers like Professor Salim Abdool Karim, Director of the Centre for the AIDS Programme of Research of South Africa (CAPRISA), saw the initial results as a boost for sagging morale after so many failed trials. Confessed a rejuvenated Gray: 'I've devoted my life to HIV vaccines since the early to mid 2000s – I was starting to wonder if I'd made the right choice'.

Karim said that after the scepticism that followed the failed Merck vaccine trials, 'this is big scientific news', while Gray affirmed that 'this is huge'. 'Researchers were becoming despondent about ever making a vaccine and were starting to become disinterested. Basically this means that a vaccine is possible in our lifetime.'

Then the storm broke around the alleged selective leaking of only part of the results by the US Military HIV Research Program. They, together with the Thai government, managed and conducted the trial, originally aimed at 50% efficacy for impact in the relatively low HIV incidence country.

An *Izindaba* search that included *Science Magazine*, *The Wall Street Journal*, *The New York Times* and the United Press International press agency, reveals that the excitement around the selective 24 September data release was based on a

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'modified intent to treat analysis' (which prevents bias from the selective exclusion of trial participants from the analysis), and excluded the secondary 'per protocol' analysis.

The former includes everyone who enrolled in the study, regardless of whether they ended up getting the full course of the vaccine while the latter adheres strictly to how the trial was designed by only including those study participants who got the full regimen of the vaccine shots at the right time. The 'per protocol' analysis, usually used as a supportive analysis to corroborate to the more stringent 'intent to treat' analysis, showed that the supposed effectiveness was only 26.2% – and thus not statistically significant.

This news, breaking several weeks after the two South African scientists were approached for comment by *Izindaba*, ignited a volcanic stream of scientific calls for laying out all possible data at the conclusion of trials to enable differences to be properly analysed.

Dr Anthony S Fauci, Director of the National Institute of Health which financed the trial, agreed that different analyses of the data could show a weaker effect but insisted that the one released on 24 September was 'the gold standard'. He said putting several biostatistical analyses in a news release 'would have confused everybody', while suggesting that researchers were engaging in a cover-up was 'absurd'.

'They couldn't be that stupid; they were already planning to give confidential briefings to experts and publish everything in a journal before heading to Paris, where the results would be presented to the world,' he said.

However, Fauci admitted that the army's decision to brief other players in the field before the 20 October Paris conference backfired. Statistical calculations around the 'intent to treat' analysis reportedly showed there was a 3.9% probability of the study results being a fluke – but for the 'per protocol' analysis this leapt to 16%. In drug and vaccine trials, anything above a 5% probability of a chance result is deemed statistically unacceptable.

Sleuths closing in on protection mechanism

Karim, whose best HIV microbicide gel trial results so far (PRO2000) fell just short of being statistically significant, believes the important thing – if moderate efficacy of the Thai vaccine is proven – would be that it may be possible to identify what led to protection.

'It's not about getting this vaccine in a clinic anytime soon – we'd need to better understand what cellular and humoral responses were engendered. In other words, did those in the vaccine arm who became infected have poorer responses to the vaccine than those who didn't become infected? That will give us clues as to what might have been responsible for the protection. If we can find that, it will be a major step forward in the field.'

Gray doubts that the Thai vaccine results will be taken forward in that country, where HIV incidence stands at around 1%, in stark contrast to South Africa, where HIV incidence is closer to 6%.

'Thirty-one per cent doesn't give it much value there, but in heavily burdened countries like ours you'd have to vaccinate far fewer people to get the benefit, so it would do a lot of good,' Gray explained. More than five million South Africans are HIV positive.

Both experts cautioned that the vaccine was 'no panacea', adding that doubts existed about whether the vaccine will be used for anything more than further study, about how much was still left, and about who will be actively producing it at present.

Gray believes that 'because we've come a long way from the old canary pox vaccine (which the Thai used), the question is should we use this or the new generation of pox vectors (upon which the best South African Vaccine Initiative trials are based)?'

Huge boost for SA pox vector research

The dramatic and at first seemingly serendipitous Thai findings would have thrown the pox vector research field (in which South Africa is a global leader), wide open.

The Vaxgen boost (monomeric gp 120) and the Aventis Pasteur (live replicating canary pox vector) in the Thai vaccine was rubbished by a prominent group of researchers in *Science Journal* in January 2004.[1] They argued that Vaxgen had already been tested and showed no protection whatsoever while Alvac was tested and found to be 'not very immunogenic'.

Writing in the 'Policy Forum' section of the respected journal, they doubted whether 'these immunogens have any prospect of stimulating immune responses anywhere near adequate', pointing to the cancellation of a similar phase III trial in 2003. The cancelled trial was to have been conducted in the USA by

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the HIV Vaccine Trials Network (HVTN), the world's largest consortium of AIDS vaccine scientists and clinicians.

Questioning the scale and cost of the Thai trial (more than R650 million), they said the overall approval process lacked input from independent immunologists and virologists who could have judged whether it was scientifically 'meritorious'.

They argued that with two large phase III trials of immunogens that 'all too predictably' had already failed to generate protective immunity, the price of repetitive failure could be 'crucial erosion of confidence by the public and politicians in scientific capability of developing an effective AIDS vaccine collectively'.

Stumbling around the edge of making history

Said Karim: 'One of the things about vaccines (generally) that we seem to forget is that with most of those we have, we actually don't know how they work. Many were developed when we couldn't even grow those organisms or had no idea what immunity was required to be protective. Many were developed on serendipity, like the smallpox vaccine or the hepatitis B vaccine…we only understood them much later.'

He added: 'So the one lesson in all this is that in vaccines, what we don't know is a lot more than what we know.'

With circumcision trials for HIV prevention showing similar efficacy in South Africa, the Thai finding held the potential to become incrementally and collectively highly significant to containing the pandemic locally.

South Africa's Medical Research Council president, Anthony Mbewu, recently said the eventual development of an HIV vaccine would rank among the 'greatest achievements of mankind in the 21st century'.

Elise Levendal, chairperson of the South African AIDS Vaccine Initiative (SAAVI), emphasised that without Thailand's excellent community involvement, the trial would not have been possible. 'It meant a massive and dedicated community involvement strategy by the Thai people, NGOs and the sponsors. The staff of 47 health centres and eight clinical trial sites engaged their communities in a strategy that resulted in tremendous building of trust and respect…that we can learn from.'

He added: 'So the one lesson in all this is that in vaccines, what we don't know is a lot more than what we know.'

While initially 'elated' at the results, she said they were no replacement for other prevention methods and that a vaccine would 'always be part of a comprehensive approach'. Karim said one surprise factor of the results was that those developing the trial strategy thought they had a higher likelihood of reducing viral load than preventing HIV – and the exact opposite seemed to have happened.

He believes much of the controversy surrounding the Thai trial was being driven by those who previously attacked the trial, 'finding weaknesses and exploiting them'. It was 'important to remember' that the secondary 'per protocol' analysis was not statistically significant because its sample size was smaller.

Like the discovery of penicillin, many of history's scientific breakthroughs have come when researchers, tinkering on the edge of what is known, stumbled fortuitously into brand-new territory.

Chris Bateman

1. Burton D, Desrosiers R, Doms R, Feinberg M, *et al*. *Science* 2004; 303: 316.