# Clarifying the future of HIV vaccines and microbicides

*– Stacey Pene –*

**Several candidate vaccines and microbicides failed to demonstrate any benefit for the prevention and treatment of HIV infections in clinical trials that have been completed in the last 2 years. These results have necessitated reflection and reprioritisation in the area of HIV vaccine and microbicide research. A symposium at the XVII International AIDS Conference (AIDS 2008) [*Mexico City, Mexico; August 2008*] entitled *Vaccines and Microbicides: Where Do We go from Here?*, brought together senior scientists and advocacy leaders in the field of HIV vaccine and microbicide research. The session explored where the field is heading, reviewed the results of recent trials, and addressed key issues such as the scientific obstacles preventing rapid development of preventive vaccines and microbicides.**

The symposium was opened by Dr Tachi Yamada, Japan, who provided an overview of some of the challenges facing HIV vaccine and microbicide development. In the past 2 years, 5 million people have contracted HIV; of these, almost 2 million have begun treatment. One of the most important advances made in that time has been the discovery that circumcision is protective against the transmission of HIV. Dr Yamada, however, cautions that the recent failures with microbicides and HIV vaccines serve to highlight that the road to success is paved with failure. Making effective vaccines is an extremely difficult endeavour, with approximately 9 in 10 vaccines that enter human trials failing. Several technical difficulties inherent in clinical trials have hampered recent results. Firstly, patients in control groups receive the best tools available for counselling for the prevention of HIV transmission, with the net effect being that the control group has a lower rate of infection than that assumed when the clinical trial is initially planned. Secondly, patients in the intervention group are not always compliant with treatment, which attenuates the effect of the intervention. "**I think the most important lesson that we have learned is that vaccine science is still more of an art than a science**", contends Dr Yamada. "**We have very little predictive knowledge about when a vaccine will work and when it will not**".

## Where to next?

A safe, effective HIV vaccine is the most promising means of halting the spread of the AIDS pandemic, contends Dr Alan Bernstein, Canada. He argues that the world needs an integrated plan to defeat AIDS that includes short-, medium- and long-term strategies: short-term – expansion of currently accepted treatment modalities; medium-term – exploration of promising approaches, such as circumcision, microbicides and continued efforts in social intervention and education; long-term – development of a safe and effective vaccine.

In his presentation, Dr Bernstein identifies 6 key steps he believes are needed to develop an HIV vaccine:

- understand human immune response to HIV
- better exploit nonhuman primate models to inform and refine vaccine development
- shift from a licensure focus to a research focus
- develop upstream markers to monitor human immune responses to HIV
- bring post genomics revolution to HIV vaccine development
- attract the best young research minds to the problem.

"**I do not believe that any one country, any one scientist, any one team of scientists, will develop the vaccine. We need to be all pushing and pulling together to develop a safe and effective HIV vaccine**", concludes Dr Bernstein.

## Two STEPs forward, one STEP back

The STEP study was a pivotal trial in the HIV vaccine field. Dr Susan Buchbinder from the San Francisco Department of Public Health, presented data from, and highlighted several important lessons learned from, the STEP study.

STEP was design to evaluate the efficacy of the HIV vaccine MRKAd5 trivalent vaccine. In the initial study, 1500 high-risk HIV uninfected patients with Ad5 neutralising antibody (NAb) titre of ≤ 200 were randomised to receive MRKAd5 or placebo. When data from a phase I trial showed that the vaccine generated robust immune responses, even among individuals with a higher level of pre-existing Ad5 antibodies, an additional 1500 individuals with Ad5 NAb titre > 200 were enrolled and randomised to vaccine or placebo. Randomisation was stratified by Ad5 NAb titre: ≤ 18, 19-200, 201-1000, > 1000. In the first planned interim analysis among patients with Ad5 < 200, the vaccine was found to be ineffective for preventing HIV acquisition. Moreover, a futility analysis indicated that the probability of observing a positive result with continued follow up was less than 10%; within 24 hours all vaccinations within the trial were stopped.

Analysis of the entire cohort of data showed that, among participants with higher Ad5 titres, there was an increased risk of HIV infection among vaccine recipients than among placebo recipients. Further analysis of the data showed that, among male participants, being uncircumcised and Ad5 sero-positive was associated with a higher risk of infection [*see table*].

**Relative risk of HIV infection: STEP study***

| | Circumcised | | Uncircumcised | |
|---|---|---|---|---|
| | **Ad5 ≤ 18** | **Ad5 > 18** | **Ad5 ≤ 18** | **Ad5 > 18** |
| **Model:** | | | | |
| Univariate | 0.7 | 1.6 | 3.3 | 3.9 |
| **Multivariate** | | | | |
| Model 1 | 0.8 | 1.4 | 2.5 | 4.3 |
| Model 2 | 0.8 | 1.7 | 2.4 | 4.8 |
| Model 3 | 0.6 | 1.3 | 2.0 | 4.6 |
| Model 4 | 0.6 | 1.4 | 2.1 | 4.2 |

* vaccine:placebo

"**I think that the STEP study was a pivotal trial for the vaccine field. It brought us further forward than any single clinical trial has to date. We got a definitive result that this vaccine did not provide protection, just 33 months after the first participant was enrolled. This has made important contributions that I think could only have been learned through clinical**

**efficacy trials, and we are continuing to mine lessons from our trials data and specimens**", concludes Dr Buchbinder.

## Next gen microbicides cause for optimism

ARV-based Microbicides – Cause for Optimism was the title of the presentation by Dr Zeda Rosenberg. So far, 9.5 early generation efficacy trials have completed or been stopped, while two trials are ongoing. In her address, Dr Rosenberg outlines the reasons for continued optimism with regards to microbicides for the treatment of HIV infections. The next generation of microbicides are ARV-based, highly potent and HIV-specific. They have multiple mechanisms of action against HIV that can be developed as both single agents and in combination. The next generation of microbicides provide a longer duration of protection, so that 30 day vaginal rings or once-daily use gels may allow women to adapt them into the context of their lives more easily. There has also been increased support from pharma, scientific and advocacy communities, as well as from donors. Dr Rosenberg concluded with a quote from one of Africa's most distinguished proponents of health and human rights, Mrs Graca Machel: "**A microbicide could mean the difference between life and death for millions of women. Let us do everything in our power to accelerate its development**".

## Advocacy plays an important role

Manju Chatani, from the African Microbicides Advocacy Group, in a presentation entitled Microbicide Advocacy and Community Leadership in the South, highlighted several advocacy successes, including: increased field resources, improved standard of care in trials, ongoing access to care, community input into treatment protocols, working with media around trial results, and championing emerging issues. Chatani also pointed out the many challenges faced by advocacy groups in Africa, including: resources, an increased number of international players in Africa, dealing with confusion over recent trial closures and results, and giving voice to trial participants. Advocacy groups are responding to these challenges through innovative funding mechanisms, communication, proliferating accurate information, and continuing to build trust between groups.