TENOFOVIR GEL – THE NEW HIV PREVENTION 'BANKER'?

Lead investigators of the Durban tenofovir microbicide gel trials, Professors Salim and Quarraisha Abdool Karim with UNAIDS chief scientific advisor Catherine Hankins (centre).
Picture: Chris Bateman

Most of South Africa and the world's top HIV/AIDS scientists are 'excited and hopeful' about the first-ever trial of a vaginal microbicide gel containing the highly effective ARV agent tenofovir, launched in Durban last month.

The test product, even if partially successful, has profound self-protection implications for millions of HIV-vulnerable sub-Saharan women, with the potential to directly impact the dynamics of HIV transmission.

With highly enhanced adherence potential (it needs application within 12 hours before and after coitus) and a sophisticated 'chain terminator' cell mechanism, tenofovir gel has already proved an effective barrier to HIV infection in monkeys.

Until now microbicide gels had to be applied within, at most, an hour of coitus.

Tenofovir is one of the most effective new-generation antiretrovirals (until now in oral form) because of its minimal side-effects, high genetic barrier for resistance and long half-life.

Different to controversial predecessors

Unlike the controversial two failed microbicides (Ushercell cellulose sulphate-based vaginal gel and nonoxynol-9), where trial participants sero-converted, the tenofovir gel does not act in the vaginal lumen to kill the virus. Instead, the drug is rapidly absorbed into the tissue and blood cells where it prevents the virus from growing.

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With a formulation of just 1% tenofovir in the gel, the researchers are aiming at further reducing the chances of resistance developing. One of the most exciting 'bonus' prospects is that even if a participant becomes infected, the drug may have a major impact in slowing the progression of the disease.

Says Henry Gabelnick, director of CONRAD, the international reproductive health foundation backing the project, 'we've been trying to get a microbicide going since 1998 and we're very enthusiastic about tenofovir'.

Adds Doug Taylor, Associate Director of BioStatistics for Family Health International, the other major international co-sponsor, 'this product has a very good chance of success and the investigators are best suited to make that happen'.

While the final data on what went wrong with the Ushercell trial remained outstanding at the time of writing, researchers believe nonoxynol-9 harmed participants by causing lesions in the vagina.

Results on the recently completed Carraguard microbicide study (done at Medunsa, Durban and Cape Town) are expected in the next 4 months (Carraguard prevents the virus from attaching to cells in the vagina).

Momentum 'vital' argues Karim

Lead investigator and Director of the Centre for the AIDS Programme of Research in South Africa (Caprisa), Professor Salim Abdool Karim, said 3 microbicide trials had so far been stopped for futility and 2 for harm.

'In reality we've had a series of disappointments, but to retain perspective you must remember that there've been even fewer trials for an HIV vaccine – and you don't see them giving up! We have to keep a clear focus on our goal to find a woman-controlled HIV prevention method – I think that's the challenge,' he added.

The tenofovir trial is being conducted among 1 000 HIV-negative women attending the Ethekwini Clinical Research Site in Durban and the rural Mafakathini clinic at Vulindlela, 90 km

away. The cohort includes outpatients at the Ethekwini Clinic and Durban sex workers, among whom general HIV prevalence stands at 55%.

Karim said this identical figure in both groups 'just illustrates the diffuse nature of the pandemic'.

Should the results of this (phase 2b) study suggest a partially protective effect against HIV, then a full-scale phase 3 trial may be needed to produce definitive results.

After 4 years of preparing their research teams, Karim and his wife Quarraisha (Associate Scientific Director, Caprisa) took selected health journalists on a comprehensive tour of the facilities and outlined the trial on 29 May this year.

'This is the litmus test. This is where the rubber hits the road,' said Quarraisha Abdool Karim. The Durban duo is considered to be among the world's top AIDS researchers and have over 2 decades of experience in the field.

Home-grown research and development

The tenofovir trial is the first ever microbicide partnership led by a developing country institution. It is also the first to secure upfront public sector pricing for South African Development Community countries plus a voluntary licence for local manufacture (if cheaper).

Significantly, the study is backed by Lifelab, a biotechnology innovation vehicle set up by the Department of Science and Technology. Lifelab's CEO, Blessed Okole, said his company was already conducting negotiations with local manufacturers to provide generic tenofovir, should the trials succeed.

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Most major drug companies were self-evidently more interested in the far greater payoff of developing a curative rather than a preventive product. Gilead, the manufacturers and suppliers of tenofovir, have pledged full co-operation with Caprisa to ensure affordable access, especially where needs were greatest, should the trial hit the jackpot.

Caprisa's leader of 'targeted AIDS interventions' for the rural area of the study (Mafakathini near Bulwer), Ms Gethwana Makhaye, said HIV prevalence among local women there aged under 20 had leapt from 15% to 27% between 2001 and 2004.

For women between 20 and 29, this had rose from 39% to 66% over the same period.

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The first government clinic onto which the comprehensive Caprisa health care facility has been added, was only built in 1998.

Extensive consultation with the *amakhosi*, *indunas*, women's groups, community leaders plus *imbizos* at churches, schools and NGO sites had led to the formation of community research groups that now met regularly to discuss the impending study.

Makhaye quoted one local chief who, when first asked how he felt about the research, replied tellingly, 'what kind of a leader would I be if I had nobody left to lead?'

'i-Five-rands'

Salim Abdool Karim revealed, to general laughter, that when news of a sister AIDS treatment project first began spreading in the area, it soon became known as the 'i-Five-rands' after the mispronounciation of efavirenz, an antiretroviral drug widely referred to in community AIDS treatment education programmes. The trial is being integrated into the same facilities which provide a comprehensive Caprisa HIV/AIDS VCT, prevention, ART and care programme.

Quarraisha Abdool Karim explained that, by necessity, they had to embrace large cohorts to identify women who had not used condoms or face turning it into an exercise in futility. The study would however take into account any additional benefit of the gel when used by participants in coital acts that involved condoms.

She said the gel had no contraceptive function and did not act against other STDs.

'We need to prove that we have a product that can prevent HIV infection – further down the line there will be more stratification to determine if it has any benefit on STDs and pregnancy,' she added.

Asked what happened if a participant fell pregnant, she said they would be advised to stop using the gel, referred to an antenatal clinic and then, depending on the outcome of the pregnancy, allowed to rejoin the trial.

The wellbeing of all participants was 'paramount', with condoms and frequent prevention counselling provided to all participants. Those who had unprotected sex with an infected partner during the study, or anyone who sero-converted during the follow-up period, had several choices. These included taking part in one of Caprisa's long-term acute infection cohort studies that had excellent care, ARV and support systems or being referred to their preferred AIDS care provider.

'People must always come first,' she emphasised, adding that the study had rigorous scientific and ethical oversight and approval.

Cate Hankins, chief scientific advisor to UNAIDS, told *Izindaba* that, if successful, an ARV microbicide gel would dramatically increase the prevention/treatment options available to clinicians. Any efficacy would be highly significant, 'especially in a situation where most women cannot negotiate the use of a condom and female condoms are too expensive'.

Chris Bateman