

HIV research for prevention – huge potential but no ‘magic bullet’



HIV research for prevention has so far produced a mixed bag with no magic bullet, but results for an antiretroviral (ARV)-infused vaginal ring that stays in place for 30 days, potentially offering women up to 50% (or more) protection against HIV and theoretically saving millions of lives over time, will be reported in 2016.

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There are two parallel, almost identical major microbicide ring trials currently underway, the ASPIRE trial and the Ring trial. The results of the former are due in early 2016 – and if positive with high efficacy, the device will almost certainly be licensed for use. This potentially major leap forward in adherence to interventions for women, in addition to the HIV prevention armament of circumcision, male and female condoms, prevention of mother-to-child transmission and oral ARVs (among others), is generating the most excitement among the South African (SA)-led global community of HIV researchers, because of how far advanced its twinned international studies are. The research focus on female-initiated methods of HIV prevention makes solid sense on taking a quick glance at the statistics: of more than 35.3 million people living with HIV, over half are women. In sub-Saharan Africa, where unprotected heterosexual sex is the primary HIV driver, women account for nearly 60% of adults with HIV. Young women are especially vulnerable, those aged 15 - 24 being twice as likely as young men to be infected with HIV. Efforts to promote abstinence, monogamy and the use of male condoms have either not done enough to stop the HIV epidemic or are not realistic in many settings. Women lack practical and discreet tools they can use to protect themselves from HIV infection. Many women are unable to negotiate successfully with their male partners to use condoms or to be faithful. Abstinence

is simply not realistic for women who are married, who want children or who are at risk of violence.

ARV gel well ahead in the efficacy stakes

Findings of a confirmatory trial of the far earlier Durban-based CAPRISA 004 trial led by Prof. Salim Karim that showed an ARV-based microbicide gel to be 39% effective, which are being confirmed through the FACTS 001 trial by Prof. Helen Rees of the Wits Reproductive Health and HIV Institute and Prof. Glenda Gray, now Medical Research Council (MRC) CEO, will be released at the Conference on Retroviruses and Opportunistic Infections (CROI) in Seattle, USA, in late February next year. One of the major challenges with pre-exposure prophylaxis, including vaginal gel, is its low adherence threshold (the gel needs to be applied 12 hours before and 12 hours after coitus). However, the CAPRISA 004 trial is the only ‘proof of concept’ trial of a vaginal microbicide so far, and an improved efficacy result through the FACTS 001 trial would increase options for those women who have a preference for gel as an HIV prevention method. The CAPRISA 004 trial also showed efficacy of 50% protection against herpes simplex virus 2.

Other scientific advances are novel formulation of pre-exposure prophylaxis in the form of long-acting injectables. It is hoped that a decade from now we will have injectable ARVs offering prevention and treatment for HIV-negative and HIV-positive people, respectively. The concept has gone through preclinical and animal studies and is currently being tested in early-phase human trials. Based on safety and pharmacokinetic and pharmacodynamic data, the products are slated to move to phase 2/2b trials.



HIV vaccine candidate.

Vaccines to prevent HIV are much-needed options to add to the current toolbox of HIV prevention options. Prof. Gita Ramjee, Director of the HIV Prevention Research Unit at the MRC, speaking at the HIV Research for Prevention Conference in Cape Town (the first global conference to feature all forms of biomedical HIV intervention), said that the most exciting news on the vaccine front would be adapting the partially successful Thai HIV vaccine trial to a local HIV sub-type C virus. New local trials are planned, building on the moderate success of the Thai RV144 trial.

Nobody expects the vaccine to offer complete protection from the virus, but even 30 - 40% protection will significantly reduce the rate of new infections. Gray said that should this kind of efficacy be shown, in 2019 researchers will apply for approval by the Medicines Control Council for use and sale. Should the local vaccine enhancement boost efficacy to 50%, the vaccine would be ‘a global game changer’.

Adapted, longer-acting HIV vaccine would be a ‘global game changer’

Gray told the conference that after 30 years of trying to find a vaccine for HIV, scientists in Thailand announced this success in 2009. The vaccine offered people who received it almost 60% protection from the virus, for the first year. After 3 years, recipients were 31% less likely to contract the virus. Researchers in SA have managed to show two things so far: that it is safe to use on South Africans, and that it (i.e. the Thai clade) provokes an immune response. A new trial will start in January with the Thai vaccine modified to fight against the African strain of the virus, and strengthened to offer protection from HIV for a longer period than the Thai

vaccine does. Participants will receive a booster vaccination after a year. No one expects the vaccine to offer complete protection from the virus, but even 30 - 40% protection will significantly reduce the rate of new infections. Gray said that should this kind of efficacy be shown, in 2019 researchers will apply for approval by the Medicines Control Council (MCC) for use and sale. Should the local vaccine enhancement boost efficacy to 50%, the vaccine would be 'a global game changer'.

For now, all eyes on microbicide ring study results

Ramjee, an MRC veteran of two decades, said that her institution was the biggest contributor to the twinned microbicide ring studies, with six sites in Durban. Other sites include CAPRISA, Cape Town, Johannesburg, Malawi, Uganda and Zimbabwe. Underpinned by the International Microbicides Partnership and the US National Institutes of Health-funded Microbicide Trials Network, the 'sister studies' involve 4 500 women and are being run concurrently to keep the timeline to potential approval and product access as short as possible. (Two efficacy trials are usually needed for a product to be considered for regulatory approval.) When the datasets are merged and the



Prof. Gita Ramjee, Director of the HIV Prevention Research Unit at the MRC.

MCC takes a decision on the efficacy threshold (Ramjee speculates that the MCC will go for safety and efficacy, with an upper bound of 60% and lower bound of 50%), the product can be licensed. 'We've completed enrolment with follow-up by June next year. Then we begin the process of data cleaning, and we're hoping for results by December 2015 or early in 2016.' Asked how she felt, given that

she's been involved in all the large-scale microbicide trials so far, Ramjee said she was 'a bit confident that this may show something, given that we are alleviating some of the daily adherence issues'. Emphasising that the other products may have been 'perfectly good', she said that adherence was historically the single biggest issue. Products for HIV prevention and treatment would only work if they were taken or used as required.

Ramjee said that another exciting product was a similar flexible ring that delivered both an ARV drug and a contraceptive drug for 3 months (currently in the early testing phase). This multipurpose technology is being developed to protect women from HIV and unintended pregnancies. The rings are being developed by various groups using ARV agents such as dapivirine and tenofovir. She said that given the high incidence of HIV among women in Africa, it was 'imperative' that women's needs for HIV prevention were met. This included providing choices of various formulations and dosages for prevention of both HIV and unintended pregnancies.

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