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Lancet reports: Carraguard not effective in prevention of HIV

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According to recent UNAIDS estimates, in 2007 33 million people were living with HIV worldwide and nearly half of these were women (1). In sub-Saharan Africa women account for 55% of all infected adults (1). South Africa is the country with the greatest number of people living with HIV globally (1). The yearly HIV incidence (the proportion of new cases in the population per year) is highest in women aged 20 – 29 years (5.6%), which is a rate that is six times higher than that for men of the same age (0.9%) (2). Furthermore, in 15 – 24 year olds, 90% of new HIV infections occur in girls and women (2).

From ABC to M

Most women acquire HIV from sexual intercourse with their male partners. Traditional approaches to reducing the risk of HIV from sex – Abstinence, Being faithful, Condom Use - are often difficult for women to implement. And male circumcision, which has a protective effect in men, does not directly reduce risk in women. Among biology-based preventive interventions, the most important is a vaccine, but an effective one has not yet been found. Other strategies now being emphasized involve using antiretroviral drugs for prevention, as discussed in the article by Brian Williams et al in this issue. Microbicides, which are formulated as gels and creams, are designed to prevent the sexual transmission of HIV or other sexually transmitted infections when applied in the vagina. One of the most important rationales for developing a microbicide is to enable a woman to protect herself.

Carraguard trial

Previous studies of candidate microbicides have been unsuccessful; the use was associated with a (trend towards) increased risk of HIV infection. The Carraguard study began in March 2004 and ended in March 2007, enrolled 6,202 women and was conducted at three sites in South Africa: Isipingo (KwaZulu-Natal), Soshanguve (Gauteng) and Gugelethu (Western Cape). Aim of the study was to assess the efficacy of the candidate microbicide Carraguard, i.e. how effective is the product in a study setting, in preventing male-to-female transmission of HIV. In December 2008 the Lancet published an article on the study (3), although the Population Council previously released the main results to the press in February 2008.

In this study women were asked at different community venues (e.g. health clinics, shopping centres, taxi ranks, churches) whether they voluntary wanted to participate. They could participate in the study if they were sexually-active, HIV negative and aged 16 years and older. On the basis of chance (randomly) half of the women were given Carraguard plus condoms (as Carragard does not work as a contraceptive) and the other half received a placebo gel (i.e. without active ingredient) and condoms. As both gels looked the same neither researchers nor participants knew (they were blinded) who had been assigned to use which gel during the period of the study. Participants were told to use the gel plus condoms during each act of vaginal intercourse. The person allocating the women to the treatment was not otherwise involved in the trial, making the allocation concealed (secret).

Women returned to the study clinics after 1 and 3 months, and every 3 months thereafter for a minimum of 9 months and a maximum of 24 months. During these visits women were tested for HIV by two different rapid tests concurrently. Positive or discordant HIV rapid tests were confirmed by a third test. For all women suspected to have seroconverted (i.e. who were first HIV negative and later HIV positive), the laboratory data were then reviewed by an independent board, which consisted of three HIV diagnostic experts who did not know in which treatment group the women were, to verify the date of HIV detection. During the visits women were asked whether they had used the study gel during the last sex act (to assess adherence to the treatment). Furthermore, the applicators were tested whether they were vaginally inserted or not (using a blue staining fluid). The number of sex acts during which gel was used was estimated by dividing the average number of applicator insertions per week (on the basis of applicator testing) by the average number of sex acts every week (on the basis of the self-reports).

The most important outcome of the study was time to HIV seroconversion. Using a statistical test (log-rank test) it was tested whether the time to seroconversion was different for the Carraguard group and the placebo group or not. The midpoint between the date that a participant tested HIV positive for the first time and the date of the previous HIV negative test was taken as the seroconversion date. Time to seroconversion was calculated from the date of enrolment to the date of seroconversion. This analysis

was done in the participants for whom the effect of Carraguard could be assessed. So women who turned out to be HIV positive at enrolment, those that did not have any HIV tests after enrolment, and those who returned all applicators unopened to the clinic were not included.

Safe, but not effective

9564 women were screened for participation in the study of which 3362 did not participate, because they were HIV positive, pregnant (or both), not eligible for other reasons or did not want to participate. 3103 women were assigned to receive Carraguard and 3099 placebo. Data from 3011 participants in the Carraguard group and 2994 in the placebo group could actually be analyzed regarding the effect of treatment.

The next few years will be crucial for microbicide development. And although it is highly advisable to develop only those drugs that give the best preventive results, even a partially effective microbicide could have a serious impact on the dynamics of HIV transmission. The London School of Tropical Medicine calculated that a microbicide that reduces the risk of transmission by 40 percent, and used by only 30 percent of women in 73 developing countries over three years, could prevent 6 million infections in men, women and children (6).

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