



Alliance for Microbicide Development *News Alert*

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MEDIA COVERAGE OF MICROBICIDES 2008

This Alliance *News Alert* is a compendium of media coverage of the *Microbicides 2008* conference held 24-27 February 2008 in Delhi, India. It is not intended as a complete listing of *all* coverage of the conference but, rather, as a selection of coverage from different perspectives in a range of media outlets and regions. The articles are listed in reverse chronological order, that is, with the most recent items leading. Further conference coverage of particular interest will appear in forthcoming editions of the *Alliance News Digest*.

Contents

- Microbicides 2008: Third-generation microbicides might act as 'bacterial vaccine'
- Microbicides 2008: Will adherence issues affect all the first-generation trials?
- Microbicides 2008: Cellulose sulphate has unexpected tissue toxicity
- Microbicides 2008: Microbicides might benefit men more than women
- Cream to prevent transmission of AIDS virus
- Microbicides 2008: The second generation is on its way
- Microbicides in the bedroom
- Anti-HIV gel found safe for daily use as putative microbicide
- Anti-HIV gel well tolerated by women
- India developing neem based gel for women to counter AIDS
- Less silence, more science could make anal sex safer
- Vaginal anti-HIV gel 'safe for regular use'
- Anti-HIV gel proven safe, tolerable for women
- Experimental microbicide tenofovir safe for women to use daily, study finds
- Gels, creams to check spread of HIV
- HIV drug in microbicide gel safe for daily use
- Microbicides 2008: Accurate adherence reporting essential for microbicide trials
- Microbicides, new arsenals to battle AIDS
- New anti-HIV microbicide gel shows promise
- Tenofovir gel safe for daily use by women, new study suggests
- Zinc can prevent sexual transmission of HIV
- ARVs in microbicide research - keeping hope alive?
- Experimental anti-HIV gel safe, tolerable for women: study
- Microbicides conference begins
- Microbicide gel with AIDS drug marks vital success

- Microbicides 2008: First hint of efficacy in rectal microbicide trial, thanks to new biopsy assay
 - Tests of new AIDS gel show promise for women
 - HIV prevention gel passes safety trial at UAB
 - India to develop microbicides at earliest: Ramadoss
 - Ramadoss concerned over HIV infection
 - Microbicide gel passes safety test
 - Microbicides: why are they significant? (Part 1)
 - Microbicides: challenges to development and distribution (Part 2)
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“Microbicides 2008: Third-generation microbicides might act as ‘bacterial vaccine’”

Author(s): Gus Cairns

Date: 4 March 2008

Source: *Aidsmap.com News*

<http://www.aidsmap.com/en/news/B304319F-D6CC-495E-B225-1365F8AA6DDD.asp>

Studies are underway of genetically engineering naturally-occurring vaginal bacteria to produce microbicides against HIV, and in one case such a strategy has already proved effective in preventing HIV infection in monkeys, the Microbicides 2008 Conference heard last week in Delhi.

Qiang Xu of ‘bacterial therapeutics’ company Osel, Inc. of California reviewed the latest progress on getting naturally-occurring *Lactobacillus* bacteria to produce the microbicide Cyanovirin-N. Cyanovirin-N is a protein originally derived from algae that has shown promising efficacy as both a vaginal and a rectal microbicide. However it is a large molecule that might be prohibitively expensive to develop as a gel.

Dr Xu’s team inserted a gene into the genome of *Lactobacillus jensenii* 1153, a variety of the naturally-occurring bacteria that colonise the vagina. These already confer some protective effect by generating hydrogen peroxide, which has a microbicidal effect – see <http://www.aidsmap.com/en/news/C20869A7-FB55-4C87-A7B2-9E9A047E6466.asp> for a study of lactobacilli presented at CROI. The researchers were able to induce the modified bacteria to colonise the vaginas of female rhesus macaques (which naturally harbour lactobacilli) for over two months. In vitro experiments showed that the Cyanovirin-N produced inhibited CCR5-tropic HIV, with a 50% inhibitory concentration one one nanomolar, which is comparable to systemic antiretrovirals.

Studies are needed to establish whether the colonizing bacteria can produce enough Cyanovirin-N in situ to have a microbicidal effect, and also on fermentation techniques to produce bulk amounts of the bacteria. Asked about the possibility of escape of genetically-modified bacteria, Dr Xu said that they could be completely cleared with a short course of the antibiotic azithromycin and did not survive outside the body in water or air.

Another novel approach is to engineer altered versions of naturally-occurring CCR5 inhibitors which act, like maraviroc and vicriviroc, the ones developed as treatments, by blocking a co-receptor molecule needed by HIV to gain entry to CD4 cells. The natural ligand (molecule that naturally attaches to) the CCR5 co-receptor is the chemokine molecule RANTES, which acts as a means of mobilising immune-cell activity in cases of injury or infection. Because of RANTES’ immune activity and short half-life it cannot be used as an anti-HIV treatment or preventative in itself.

Dr Oliver Hartley of the University of Geneva in Switzerland has been developing an analogue or altered version called PSC-RANTES as an HIV treatment. This works by inducing CD4 cells to downregulate

their CCR5 receptors, in other words to pull the molecules inside the cell surface where they can no longer act as chemokine or viral receptors. In experiments in monkeys, PSC-RANTES was shown to protect against transmission in the macaque model – see <http://www.aidsmap.com/en/news/E31C54A1-F80E-4155-A2CB-0852AF6A04B6.asp> for progress up to the previous microbicide conference. However PSC-RANTES still acts as an immune-signalling chemical (it excites immune activity) and would also be impossible to produce in bulk cost-effectively.

Hartley generated a variety of other RANTES analogues and has found one called 5P12-RANTES that can be manufactured in bulk by fermentation methods. It acts as a CCR5 inhibitor but it neither induced CCR5 downregulation nor immune activation. It shows equivalent activity to PSC-RANTES and in the macaque model, when applied topically as one-micromolar solutions in saline, protected five out of five female macaques from vaginal SHIV infection.

Finally, in experiments combining both approaches, Luca Vangelista of the San Raffaele Scientific Institute in Italy has engineered the same lactobacilli as in the Xu study to produce human-type RANTES and is currently engineering another variant that will produce an analogue called C1C5-RANTES, and also small peptides – sections – derived from RANTES to see if these have anti-HIV activity.

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“Microbicides 2008: Will adherence issues affect all the first-generation trials?”

Author(s): Gus Cairns

Date: 3 March 2008

Source: *Aidsmap.com News*

<http://www.aidsmap.com/en/news/38A95881-B578-4DEC-8057-F39A599F1D8E.asp>

There are still two ongoing trials of the ‘first generation’ non-ARV-based microbicide candidates ongoing, and at the Microbicides 2008 Conference last week Sharon Hillier, Principal Investigator of the Microbicides Trial Network (MTN) gave delegates an update of data from these studies.

The data collected so far suggest quite high use of both condoms and the study gel. However at the same conference Elof Johannson, Vice President of Biomedical Research for the Population Council gave a post-mortem of the Carraguard trial which was recently closed – see <http://www.aidsmap.com/en/news/83D932E5-6D7B-4E45-AE95-17465D5FAAB8.asp> – and confirmed that the trial largely lost the power to determine whether Carraguard had any efficacy because of huge differences between claimed levels of gel use among trial participants and actual use.

The HPTN 035 study

HPTN 035 is four-arm, multi-centre Phase II/IIb randomised controlled trial that aims to determine the safety and effectiveness of two different candidate microbicides, BufferGel and 0.5% PRO 2000 gel for the prevention of HIV in women. It is supported by the US National Institutes of Health and is part of the MTN’s series of studies.

PRO 2000 is a sulphonated polymer similar to cellulose sulphate, but, as studies from the Conference found, less toxicity. It acts as an entry inhibitor. BufferGel works by lowering the pH of the vagina – in other words keeping the vaginal environment more acid, which has been shown to inhibit HIV transmission.

Participants are randomly assigned to one of four study groups: BufferGel, PRO 2000 gel, placebo gel, and no gel. Women assigned to the three gel groups apply gel up to one hour before sexual intercourse using pre-filled applicators.

The study design was much criticised at its inception for the incorporation of a ‘no-gel’ arm, Hillier noted. Critics had said it would be difficult to retain participants for the study arm that gave its participants no gel and just told them to use condoms, but Hillier said that retention had been as good in that arm as any other and that it was the only study that enabled researchers to detect any possible toxicity or efficacy of the placebo gel, hydroxyethylcellulose (HEC).

However the decision did have the effect of reducing the study’s power. As a result although the study was powered to detect an effect of either intervention against placebo if their joint efficacy was more than 43.6%, it was not powered to compare the interventions against each other.

The study enrolled its first participant in February 2005 and recruitment was completed in July 2007. At this time a total of 3,100 sexually active HIV-negative women had been enrolled at seven sites in Malawi, South Africa, Zambia, Zimbabwe, and Philadelphia in the United States. Each study participant is followed for at least one year.

The study is endpoint-driven, meaning that it will finish when it has reached 192 HIV infections amongst participants. At the current rate it is expected to be completed in July 2008, and results of the study available in early 2009.

The average age of participants was 27. Fifty-eight per cent of them were married and 64% living with a partner. The mean number of vaginal sex acts in a week was 2.7, and 65% of participants claimed condom use last time they had sex.

Self-reported adherence was high – though not as high as in the Carraguard trial, where 94% of participants claimed to use the gel. Condom use has remained at the same level in the study, and sex involving both condoms and gel has also remained at the same levels, with 83% of participants saying they used the gel when they used a condom.

However the percentage of women who used the gel when they did not use a condom increased as the trial went on.

Early on in the trial the percentage of unprotected sex acts that featured gel use was only 47% but as it has gone along that has increased to a cumulative average of gel use in 71% of unprotected sex acts. This may improve the possibility of a meaningful result, as early on in the trial there were concerns that too few women were relying on the gel for any statistical difference to be detected – see this report.

The MDP 301 study

This study, supported by the Microbicides Development Programme of the UK Medical Research Council was, when set up, intended to compare two doses of PRO 2000 – 2% and 0.5% - to placebo. A larger phase III study, with 9673 participants at six sites in South Africa, Zambia, Tanzania and Uganda, it will be fully recruited this month (March 2008) and is expected to report results in late 2009.

Last month it was announced that the 2% trial arm would be closed – see <http://www.aidsmap.com/en/news/B260FF22-293C-46F4-A947-307E0268BE02.asp> – because it had been decided that there was no possibility of the trial arm demonstrating an effect when compared to placebo. The reason the higher dose might demonstrate less effect is because, while PRO 2000 appears less toxic than some other candidates, a protective effect at this dose might be offset by a local irritant effect.

The 0.5% arm is continuing and Hillier commented: “We may still find that 0.5% PRO 2000 prevents HIV”.

Trial participants in MDP 301 were a little older than in the previous trial – mean age 30 – and reported condom use was lower, with 55% of sex acts protected. However the median number of vaginal sex acts a week was also lower, at 2.0. Retention was high, at 88% if withdrawal for reason of pregnancy was not counted at 84% if it was included. Women could rejoin the study after giving birth.

Claimed adherence to gel use was high, at 84%, though has declined during the study from 91%. The proportion of protected sex acts that also featured gel has increased, from 57% to 67%, but the proportion of unprotected sex acts that featured gel decreased, from 91% to 83%. However, unlike in the HPTN 035 study, gel use was more common in unprotected than in protected sex.

There was a huge range of condom usage between sites: a fact that may help generate meaningful data – ranging from 80% in South Africa to 17% in Zambia.

One interesting confounder may be anal sex. One per cent of women at the monthly visits said they’d had anal sex in the last month, and condom use was lower in anal sex, at 44%. Given that HIV is more efficiently transmitted anally and that participants were told that the gel was for vaginal use, anal sex could give rise to a number of infections.

Post-mortem on the Carraguard Trial

Elof Johansson of the Population Council reported on the Carraguard trial. Much of the data on the trial closure can be found in a previous report and we will only report what Johansson added here.

Johansson started by commenting: “We old guys who came from the contraceptive world have been humbled by the problems in microbicide studies.”

“In trials of contraceptives we had endpoints in phase II studies and could measure drug levels and efficacy. In microbicides phase III is the trial; all others are just safety trials.”

As previously reported, while participants claimed 94% usage of Carraguard, a technique that used a dye that reacted to vaginal mucus showed that only 61% of the returned applicators had actually been used and that Carraguard was only used in 43% of sex acts.

Furthermore, said Johansson, this test was not included in the protocol and was only introduced some way into study. In addition, when it was introduced participants would drop off applicators at the research centre reception, giving no chance to interact with staff. Halfway through the study they started leaving them with counsellors.

There was a huge range of gel use amongst participants, ranging from women who never used it to 10% of women who managed 100% use, and subgroup analyses of women who never used it, those who used it less than 35% of the time, less than 80% of the time and over 80% of the time are ongoing.

Low adherence was not the only reason the trial ended up having little power to generate a statistically meaningful result, said Johansson. Although the drop-out rate was only 13%, nine per cent were in addition lost to pregnancy, and pregnant women did not return to the study after giving birth.

One factor that may yet generate meaningful data is that trial participants at the three South African sites – at Cape Town, Pretoria and Durban – were very different. Durban participants has less sex – 1.3 acts per week compared with 2.2-2.3 at the other two sites. However HIV prevalence was much higher, at 43% of the adult population, compared with 24% at Pretoria and 18% at Cape Town. Circumcision rates in men were also very different, with 97% of men in the Cape Town area circumcised, 54% in Pretoria but only 24% in Durban.

This generated interestingly different results for efficacy in the Durban site. In that site there were actually more seroconversions amongst women using Carraguard than in the placebo arm – 48 (3.3% of participants) against 42 (2.8%).

In contrast there were more seroconversions in placebo users in the other two sites: 86 (1.9%) of Carraguard users and 103 (2.3%) of placebo users. This was still not significant but may indicate the protective effect of circumcision for women in the study.

As in MDP 301, there was a small but still significant minority of 2% of women who practised anal sex.

Lastly, Carraguard was popular: women said it improved sex and they liked the feel. Other studies at the conference reported similar findings, to the extent that participants at one site in the prematurely terminated cellulose sulphate trial refused to hand their gel back until they were given supplies of placebo.

Johansson said that with future trials close monitoring of adherence was essential. With this, it would be possible to do a ‘per protocol’ analysis only looking at efficacy amongst actual users rather than the ‘intention to treat’ analysis used.

Johansson commented that “using an intention-to-treat analysis in people who do not feel sick is very difficult”, and noted that trials of blood pressure drugs had run into the same problems. He said that in future trials he would also suggest a sub-study of the intervention in HIV-positive women.

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“Microbicides 2008: Cellulose sulphate has unexpected tissue toxicity”

Author(s): Gus Cairns

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Source: *Aidsmap.com News*

<http://www.aidsmap.com/en/news/26B4DBEC-CF93-47B9-B1CC-4900B1957634.asp>

Investigations into the candidate microbicide cellulose sulphate (Ushercell) using the substance on vaginal tissue samples have revealed that it causes loss of tissue integrity by destroying proteins that bind cells together. This allows HIV to leak into the underlying tissues.

Trials of Ushercell were halted in 2007 after women who received the microbicide in one study became infected more frequently than those who received the inactive placebo gel.

A study presented at the Microbicides 2008 conference last week in Delhi found that this unexpected toxicity is also observed to a greater degree with the spermicide nonoxynol-9, and to a very limited degree with the microbicide PRO 2000, which is still involved in clinical trials, though in this case the tissue damage appears reversible.

This effect causes neither macroscopic tissue damage that can be seen by colposcopy nor a significant inflammatory immune response (though repeated application can cause inflammation), and would have been unobserved by standard ways of assessing microbicide toxicity.

The CONRAD trial of cellulose sulphate was stopped in January 2007. It involved 1428 high-risk women at four sites in Benin, South Africa, Uganda and India, and was stopped when it was noted that there were significantly more ($p < 0.1$) HIV infections in the microbicide arm than in the placebo arm at the Benin site.

The eventual total of infections for the whole study was 60 on cellulose sulphate (8.4% of participants) and 27 in placebo (3.8%), though this did not quite reach statistical significance. Another trial run by Family Health International in Nigeria was stopped at the same time.

The Microbicides 2008 conference heard more data from the Durban site (Govinden). At this site 606 women were enrolled before the trial was halted. There was an extremely high local HIV prevalence (49.7%) amongst women screened for the trial and only 46.6% reported regular condom use.

There were 28 new infections at the Durban site, 7.56% in cellulose sulphate recipients and 5.91% in placebo recipients. This 28% difference was not statistically significant. However there were significantly more infections in patients diagnosed with an STI – 18.31%.

There was a more than threefold greater risk of infection in patients diagnosed with chlamydia, bacterial vaginosis or trichomoniasis, and a more than fourfold higher risk of infection in participants who reported more than one new partner between the quarterly trial visits ($p = 0.01$).

There were however no seroconversions in married women and marriage conferred an estimated fourfold protective effect against infection.

Delegates were reminded why cellulose sulphate was considered as a microbicide by a report on an animal model trial using monkeys (Saifuddin). In this trial twelve rhesus macaques were randomised to receive either cellulose sulphate or placebo while being challenged with two viruses, one using the CCR5 receptor and one the CXCR4 receptor.

The former is the type most often transmitted, and over the course of 13 weeks and 13 challenges five out of the six placebo-receiving monkeys were infected (though only four produced antibodies to HIV, i.e. seroconverted) against zero on cellulose sulphate ($p = 0.005$). Only two monkeys became co-infected with CXCR4 virus.

However it was observed that there were transient viral 'blips' in two of the six cellulose sulphate-receiving animals (to 3,000 and 1,000 copies) and four out of the six showed signs of integrated proviral DNA in the lymphocytes in their blood, as did the two non-seroconverting placebo recipients. Four out of these six monkeys showed virus-specific immune activity in their CD4 cells.

Microbicides researcher Robin Shattock commented after this presentation that the presence of proviral DNA and transient viremia “was not indicative of a clean response” to the candidate microbicide.

The reason cellulose sulphate may have increased vulnerability to HIV was revealed by Pedro Mesquita of Albert Einstein College of Medicine at Yeshiva University, New York. His findings were also reported at the recent CROI Conference – see <http://www.retroconference.org/2008/Abstracts/33156.htm> for that abstract.

Mesquita incubated uterine epithelial cells and reconstituted vaginal tissue for 18 hours with one dose of nonoxynol-9 (N-9), cellulose sulphate, PRO 2000, and tenofovir gel, and also for repeated periods of two hours apiece. He measured tissue integrity by a technique called transepithelial electric resistance (TER), whereby resistance drops as cell architecture is damaged, and imaged the tissues using confocal microscopy, in which different proteins are stained with different fluorescent dyes.

In cells repeatedly incubated with N-9, TER dropped to zero after one day, and with cellulose sulphate after two days. PRO 2000 produced a 40% drop in TER by the time of microbicide removal, but levels recovered to normal after it was removed, unlike with the other two gels. Tenofovir gel produced no drop in TER.

Confocal microscopy showed that cellulose sulphate and N-9 selectively destroyed a protein called desmoglein, This is one of a group of hook-like proteins called cadherins that literally stitch cells together, and loss of these proteins causes tissues to become ‘leaky’. PRO 2000 and tenofovir gel did not have this effect.

This was shown to enhance HIV transmission by allowing diffusion of virus across the epithelium (the mucous membrane), as shown by measuring the HIV p24 protein. In cells treated with N-9, 25 nanograms per millilitre (billionths of a gram) of p24 diffused across cells and in cells with cellulose sulphate, ten nanograms. There was no viral translocation with the other two microbicides.

Prolonged incubation over 18 hours with cellulose sulphate also produced a previously-missed inflammatory response. Cells treated with cellulose sulphate developed threefold higher levels of the cell activation marker nuclear factor kappa B (NFkB), a molecule also associated with HIV proliferation. There was even a small degree of inflammation caused by PRO 2000, as indicated by other cellular markers, though not NFkB.

These changes would have been unlikely to be observed using the toxicity assays in safety trials prior to the current phase III trials, and Dr Mesquita recommended that his assays become standard practice in future.

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“Microbicides 2008: Microbicides might benefit men more than women”

Author(s): Gus Cairns

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Source: *Aidsmap.com News*

<http://www.aidsmap.com/en/news/2F884C59-5D1B-44FE-8FEF-0FFF3A451570.asp>

An antiretroviral-containing microbicide could have some very paradoxical effects, according to epidemiologist Sally Blower, speaking at the Microbicides 2008 conference last week in Delhi.

In particular, a moderately-effective ARV microbicide which had a high level of systemic absorption and produced sustained levels of ARVs in the blood could end up reducing HIV infections in men more than in women.

The potential for ARV-based microbicides to cause resistance is one of the biggest unanswered questions about this class. The conference featured several studies of pharmacokinetics and found that two of the candidate microbicide drugs, achieved measurable levels in the blood. Although these are far below the levels achieved by oral dosing, it is as yet an unanswered question as to whether someone using a microbicide containing one of these drugs who was HIV-positive and didn't know it, or who caught HIV despite using the microbicide, might develop drug resistance.

Blower gave preliminary figures from a mathematical model which calculated the risk of resistance and associated HIV incidence and mortality for a 'high risk' and 'low risk' microbicide, under various conditions of efficacy and use. (These figures are from a soon to-be-published paper and could change after peer review.)

The model showed that, because of drug resistance, a microbicide of 50% efficacy, which was used 50% of the time without condoms, and featured a high risk of producing HIV drug resistance, would end up reducing AIDS deaths more in men than in women. If women used this microbicide without condoms less than 30% of the time, it would have to have 90% efficacy if women were not to benefit less than men; and, as Blower commented, if a microbicide proved that efficacious in trials, there might well be pressure to license it even if there was significant systemic absorption.

Blower acknowledged that cases of HIV drug resistance in seroconverters in microbicide trials have so far proved to be extremely rare (about 0.3%); however this is because trial volunteers are screened for HIV and seroconverters are resistance-tested and get appropriate therapy if they do have primary resistance. Such conditions would not apply after licensing in many developing countries.

These paradoxical effects arise because men would only be vulnerable to resistant virus that they caught. Women, on the other hand, would develop it directly. In the UK at present, the risk of developing resistance on treatment is five times higher than the risk of being infected with resistant HIV.

Blower's model, assuming 50% use, predicted something similar; 22% of women would have resistant HIV whereas only 5% of men would develop resistance. Some of the resistance the men would develop would be due to their bodies absorbing the microbicide through the penis and urethra (another set of assumptions built into the model), but most drug-resistant HIV (3%) would be transmitted.

Because resistant virus is transmitted more rarely than wild-type, only 0.2% of women who did not use the microbicide would acquire primary HIV infections with resistance directly due to the microbicide. HIV incidence would decrease more in men than in women (by 14% compared with 11%), and whereas there would be more than six HIV infections prevented per case of resistant HIV infection in men, there would be two cases of resistant HIV infection per case prevented in women.

This is a model with a number of pessimistic assumptions built into it. Firstly, a strongly systemically-absorbed ‘high risk’ microbicide is unlikely to be licensed. However such risk might well apply should a single ARV be licensed for PrEP, especially in the absence of widespread testing. The other assumption is that the model assumed ARVs were only available as microbicides and did not factor in the effect of increasing treatment access for people with HIV.

The session also included another couple of models that produced predictions somewhat contrary to expectation. In one, microbicides with low and high degrees of protection against HIV and STIs were mathematically ‘tested’ against the real-life HIV and STI prevalences in Johannesburg, South Africa and Cotonou, Benin – which has less than 10% of South Africa’s HIV prevalence.

The results showed that microbicides are likely to have a much larger impact in low-prevalence, concentrated epidemics than they are in high-prevalence, generalised ones. A microbicide with 40% efficacy against HIV and 40% efficacy against STIs would reduce HIV infections by 48% in Cotonou but only 8% in Johannesburg – because the steepest part of the epidemic curve in South Africa has already happened.

Finally, a model that plotted the risks of HIV infection in serodiscordant couples who used a 50% effective microbicide and/or condoms found that switching from using condoms half the time to using the microbicide three-quarters of the time would result in an increased risk for the HIV-negative partner (using current estimates for HIV transmission rates, condom efficacy and typical sex frequency).

The full table of predicted effects looks like this:

Condom use	0	30%	0	50%	30%	50%
Microbicide use	0	0	75%	0	75%	75%
Annual HIV incidence, negative partner	23%	16%	13%	12.5%	12%	7%
Relative reduction in HIV risk	0	18%	40%	42%	48%	63%

Mathematical models are not predictions of how microbicides will work in the real world. But they can serve to forewarn public health workers of effects that might seem counterintuitive. And they do suggest that for any microbicide to have a good chance of reducing HIV infections, especially in the women using it, it must have had a high degree of efficacy under trial conditions, be used consistently, and not be likely to cause much, if any, drug resistance.

Reference

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“Cream to prevent transmission of AIDS virus”

Author(s): Priyanka Bhattacharya

Date: 28 February 2008

Source: *NDTV.com*

<http://www.ndtv.com/convergence/ndtv/story.aspx?id=NEWEN20080042581&ch=2/28/2008%2010:34:00%20AM>

It is being touted as the biggest hope against HIV/AIDS, a cream that if applied by a woman, could prevent the transmission of the deadly virus known as microbicides. It is critical for countries like India and Africa where women don't have the right or opportunity to refuse sex or demand a condom.

Globally there are about 39 million people living with HIV, almost 50 per cent of them are women. “Now, we have found it is safe so it is time for the study to move on to efficacy trials where we'll really know if this gel helps protect women from HIV,” Smita Joshi, Senior Science Officer, National AIDS Research Institute.

Around 10-15 years back, there was a germ of an idea within the medical community, just as women used contraceptives for birth control, would it be possible for women to use something like a cream or a pill. Something that could prevent them from getting infected by HIV, this idea soon gathered momentum and thus began the research on microbicides. Simply put, it is a vaginal gel or cream that could prevent the transmission of HIV.

Across the world, more than 50 products are in various stages of research, three are in the last phase of clinical trials. Though hailed as the biggest hope in the fight against Aids, microbicides have had their fair share of controversies. Last year, researchers suffered a setback when trials of a microbicide called Ushercell in Africa showed that it raised the risks of HIV rather than lowered it. But scientists did not give up. “It is a great hope and we need to put everything behind the development and introduction of these because this is the best and earliest hope we have. Women could use these independently without others interfering,” said Dr N K Ganguly, Former Director, Indian Council of Medical Research.

AIDS is one of the biggest challenges of the 21st century; so far it has baffled doctors and researchers and remains incurable. Now, scientists believe that microbicides can finally be the solution.

“Microbicides 2008: The second generation is on its way”

Author(s): Gus Cairns

Date: 28 February 2008

Source: *Aidsmap.com News*

<http://www.aidsmap.com/en/news/969360D8-96E6-4E85-873F-654BB7E652DA.asp>

The next generation of microbicides designed to protect women against HIV infection will rely on maintaining a high level of an antiretroviral drug in the genital fluids and tissue rather than using a barrier gel, Sharon Hillier, Principal Investigator of the Microbicides Trials Network, told the Microbicides 2008 conference this week in Delhi.

She described the second generation of microbicides about to start major trials, as ‘topical PrEP’ – pre-exposure prophylaxis with antiretroviral drugs in the vaginal tissues and fluids. Although this approach may be potent it could have drawbacks too – leakage of the drug into the bloodstream, with a potential risk of drug resistance if the user becomes infected, and toxicity.

She also reported preliminary findings from the two remaining studies of ‘first generation’ microbicides, the HPTN 035 study of 0.5% PRO-2000 or Buffergel, and the MDP 301 study of 0.5% PRO-2000, in

which the arm using 2% PRO-2000 was stopped recently because of futility (meaning it would produce no meaningful results). (These findings will be reported separately.)

The trial programmes

There are three major programmes of trials which will lead up to phase IIb/III efficacy trials of antiretroviral-containing microbicides for vaginal use:

- First to report - if all goes well - will be the CAPRISA 004 (Centre for the AIDS Programme of Research of South Africa) study of 1% tenofovir gel in 980 women at two sites in KwaZulu Natal, South Africa, a collaboration between CONRAD and Family Health International. This is the only study looking at 'coitally-dependent' use, in which women are told only to use the gel when they think they will have sex. CAPRISA 004 already has 566 women enrolled, and may report by April 2010.
- The Microbicides Trials Network (MTN) is co-ordinating studies leading up to the VOICE (Vaginal and Oral Interventions to Control the Epidemic) study, an inventive trial which, as its name suggests, will directly compare a tenofovir gel with oral tenofovir pre-exposure prophylaxis in 4,200 women at 10 sites in South Africa, Malawi, Uganda, Zambia and Zimbabwe. This is due to start in late 2008 and may report by 2011.
- The International Partnership for Microbicides (IPM) is co-ordinating a series of studies largely in Africa but also in the USA and Belgium, using the NNRTI dapivirine (TMC120) both as a gel and as drug infused into a silicone vaginal ring which can be left in place for a month: the phase III gel study (IPM 009) is at the planning stage, while the timing of the vaginal ring studies depends on preliminary safety and formulation studies. Study 009 may report by 2012/13.
- In addition to these vaginal studies, there is the U-19 programme using the NNRTI UC-781 as a rectal microbicide: see <http://www.aidsmap.com/en/news/357B9187-9B33-45D8-AA17-570A37781B29.asp> for more.

Further into the future, IPM has now negotiated licensing agreements with drug companies to develop CCR5 inhibitors as microbicides: with Pfizer for its drug maraviroc, and – just announced at the Microbicides Conference - with Merck for a CCR5 inhibitor called MRK 167.

There were a number of preliminary results and presentations from the preparatory safety and drug-monitoring studies for these large trials at the Microbicides Conference.

Safety and acceptability: tenofovir gel

Sharon Hillier herself reported on safety and acceptability findings for a preliminary study on tenofovir gel in women that had both a coitally-dependent arm (as in the CAPRISA study) and a regularly-dosed arm (as envisaged in the VOICE study).

This, the HPTN 059 Study, gave tenofovir gel to 200 women aged 18 to 50, randomised to use tenofovir or placebo either daily, or only when sex was anticipated, for six months. The study results were widely reported in the Indian press, as one of the sites was at Pune in southern India (100 women), the others being at Birmingham, Alabama (52 women), and in New York City (48 women) in the USA. Safety and acceptability assessments were done at one, three and six months.

Retention of trial subjects was good, with 96% returning for their final visit at six months. There was only one pregnancy in the study. This was also good, as trial subjects have to drop out when pregnant and this has led to low numbers and meaningless results in certain African studies where pregnancy rates as high as 30 per cent have been recorded. Most future studies will provide women with contraception for this reason.

There were interesting differences between the Indian and the American women. They were about the same average age (33 and 31 respectively). However, in a country where marriage is the highest single risk factor for HIV in women), all but one of the Indian participants was married, compared to 28% of the US women. Sixty-three per cent of the US women had had over twelve years of education, whereas only 21% of the Indian women had had over ten years. And there was a stark reminder of economic inequality in that the average income of the US women was \$1503 a month, compared with \$55 a month in the Indian women.

There was one new case of herpes infection in the study and three of chlamydia, with no other STIs.

Self-reported adherence to the daily gel was good, and didn't vary much between sites, with 82% of the Pune women reporting use of the gel for at least six of the last seven days and 75% of the New York women (though see this report for the unreliability of self-reported adherence in microbicide trials). The most common reason for not using the gel daily was because the woman was having her period.

Adherence to the intercourse-dependent dosing was more variable, with the Pune women reporting use 88% of the time and the Birmingham women only 58% of the time.

There were 16 instances of cervical, vaginal or vulvar lesions seen in women using the daily dose of tenofovir gel compared with six (all cervical) using placebo, and ten in the sex-dependent arm, with none on placebo, indicating some marginal toxicity of the tenofovir-containing gel, although only one subject was withdrawn from the study due to adverse reaction to tenofovir gel.

What was encouraging was the acceptability data. Forty per cent of women said the gel was easy to use, and few found it difficult. No one said it made sex less pleasurable, and 12% said it made sex better. Two African studies also reported at the conference found that up to a third of participants said that using the gels made sex better. However six per cent of the sex-dependent users and 11% of the daily users said they'd had some opposition to the use of the gel from their partners.

Safety: dapivirine

Shanique Smyth of IPM presented data from a safety study of dapivirine gel. Dapivirine gel was packaged into pre-filled applicators delivering 2.5 millilitres of gel. Three concentrations were tested, ten micrograms per millilitre (mcg/ml), 20mcg/ml and 50 mcg/ml against a placebo gel (hydroxyethylcellulose or HEC, an inactive 'carrier' gel which is becoming the standard placebo in microbicide trials).

One hundred and eleven women in Rwanda, South Africa and Tanzania were instructed to use the dapivirine gel twice-daily for 42 days. There were 32 women in the 10mcg and 20mcg arms, 31 in the 50mcg arm and 16 in the placebo arm.

Safety was evaluated by adverse events (AEs), clinical laboratory tests, and colposcopy (examination of the cervix), with a follow-up visit at Day 56. No serious adverse events thought to be related to the drug were reported. Four women had lesions to the vulva, the vaginal lining (epithelium) or the cervix: two from the 10mcg group and one each from the 20mcg and placebo groups. Six women did develop neutropenia, a fall in white blood cells: two each in the 10mcg and 20mcg arms, and one each in the 50mcg and placebo groups. These were serious (grade 3 or 4), but thought unrelated to the drug and certainly didn't seem dose dependent.

Pharmacokinetics: dapivirine

Systemic absorption – leakage of the drug from the vagina into the bloodstream – is a crucial issue for ARV-containing microbicides, as the biggest safety concern surrounding these compounds is whether women using them who are HIV-positive but undiagnosed, or who catch HIV despite using them, could develop drug resistance.

In a study of dapivirine drug levels, IPM's Annalene Nel used the same three doses of dapivirine in 18 women, who used the gel for ten days. Dapivirine levels were measured in the blood after the first and last doses at six intervals during the day then daily from two to five days after the last dose.

Despite dapivirine being very insoluble, and chosen for microbicide use precisely because of its poor oral bioavailability, women did develop measurable levels of dapivirine in their blood. After the first dose peak levels were 60 picograms (trillionths of a gram) per millilitre (pg/ml) at the 20mcg dose and 80 pg/ml at the 50mcg dose. At day ten drug levels were higher, with a peak level of 500 pg/ml at the 50mcg dose twelve hours after application. Drug levels tailed off extremely slowly, with levels halving every 65-88 hours. "Increasing half-life at this level could indicate increasing accumulation of the drug in tissues," commented Annalene Nel.

Pharmacokinetics: tenofovir

Buildup in tissues could be good or bad depending on which tissues are affected, and whether cells containing HIV are active in them. Jill Schwartz of CONRAD reported on a similar pharmacokinetic study of tenofovir gel as part of the studies leading up to the VOICE trial.

Twenty-one women used a single dose of four grams of tenofovir gel. Drug levels were taken seven times in the 24 hours after the dose. Drug levels were also measured in vaginal fluid and inter- and intracellular levels in vaginal tissues were measured by biopsy. Once this was done the women then took a single oral dose of tenofovir to compare levels.

Most tenofovir concentrations in the blood were below five nanograms (billionths of a gram) per millilitre (ng/ml), though peak values of up to 19.5 ng/ml were measured in some women.

This is way below the dose seen when tenofovir is taken orally, and indeed the study then gave an oral dose to the women to compare levels, and blood levels 100 times greater were seen, at 296 ng/ml, after the oral dose.

Vaginal fluid levels were, as one would expect, a million times higher than blood levels, at 1.5 to five milligrams per millilitre at eight hours, and 0.045 to 0.47 milligrams per millilitre at 24 hours.

Levels also built up in the tissues lining the vagina, to levels a thousand times those seen in the blood, with levels at one hour after dose of 0.45 milligrams per gram of tissue and 0.015 milligrams per gram at 24 hours. The tenofovir was mainly concentrated into the gaps between cells but low but detectable levels were seen inside the cells of three-quarters of the women. As long as this is localised to vaginal tissues, this is a good thing as it should mean that tenofovir is being absorbed to a sufficient depth to defend the immune cells vulnerable to HIV against infection.

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“Microbicides in the bedroom”

Date: 28 February 2008

Source: *Plus News*

<http://www.plusnews.org/Report.aspx?ReportId=77025>

Bedroom politics were in the spotlight this week at the fourth international conference on microbicides in New Delhi, India, as researchers explored the power dynamics in sexual relationships, and their implications for microbicides.

The idea behind microbicides has always been to finally give women the power to protect themselves from HIV infection. But how would this work in the real world, where the power still largely rests with men?

According to Ravi Varma, a researcher exploring male sexuality in India, sexuality is a tool of control and power, and men would find it hard to accept something that could change this. Varma presented findings of a survey that sought to gauge the reaction of Indian men to condom and microbicide use. The study found that more than half the men interviewed would be “outraged” if their wife suggested they use condoms; an even larger percentage viewed women who carried condoms as “loose”. He said men held wives to different standards from other partners, who would be permitted to use a microbicide, while their wives would not be allowed to use this potential prevention method.

Although HIV is transmitted mainly through heterosexual sex in much of Africa and Asia, there is no widely available female-controlled HIV prevention method. The female condom, the only female-controlled HIV prevention method, is still beyond the reach of many women who need it. An effective microbicide would be important for women whose partners refused to use condoms because, in theory at least, it could be used secretly, without the male partner's knowledge.

But studies of women participating in microbicide trials have revealed that covert and autonomous use of the gel may not be feasible. Most sex is spontaneous, so inserting the gel secretly would be difficult; the desire for intimacy and sharing in established relationships could also make it problematic to keep the gel hidden.

Oliver Mweemba, a social scientist researcher at the University of Zambia, said trial participants reported that they had informed their partners they were using the gel, as they were scared their partner might feel the difference during sex because the vagina was “too wet”. He noted that some men responded positively, even going so far as to help their partners insert the gel, and reminding them to use it, while others discouraged the women from using it.

In Zimbabwe, women expressed fears that they would be accused of promiscuity if they used the gel, and also that their partners would see this as an incentive to become unfaithful. “The man might think there is something that she is doing somewhere else; where would she get that idea [to use the gel]?” one participant was quoted as saying.

“While microbicides are designed to be woman-initiated, the dynamics within sexual relationships can't be ignored ... they may impact gel acceptability and use,” warned Jessica Phillips, of South Africa's

Medical Research Council (MRC). She said an MRC study found that women who told their partners they were using the gel while participating in trials were able to use the gel most of the time they had sex. Women with supportive partners were more likely to use the gel consistently and follow trial procedures correctly.

Manju Chatani, coordinator of the African Microbicides Advocacy Group, agreed that use of the gel would ideally involve a discussion between the woman and her partner, but said this might not always be possible. "There are women who are in situations where they cannot talk about those issues; there are situations where women don't have permission to talk about [how] to protect themselves, and we always have to keep in mind that even those women should be in a position to have options," she told IRIN/PlusNews. "Of course we will be encouraging discussion, but when it cannot be discussed, we will still be encouraging use."

While microbicides could offer women more control over how they choose to protect themselves against HIV, inherent gender imbalances in the bedroom, and beyond, will persist. "What we really need is a structural response, where we look at gender equality issues; where women are empowered, where women can protect themselves, where men are using more male condoms, and women can use female condoms," Chatani added. "Microbicides could be part of that package."

"Anti-HIV gel found safe for daily use as putative microbicide"

Author(s): John Gever

Date: 27 February 2008

Source: *MedPage Today*

<http://www.medpagetoday.com/HIVAIDS/HIVAIDS/tb/8518>

Women may safely use a vaginal gel containing an anti-HIV drug on a daily basis, researchers here said, but the microbicide's efficacy against the virus has not been tested.

The tenofovir (Viread) gel caused no more adverse effects than placebo in a six-month, randomized phase II study, and was acceptable to most participants, reported Craig Hoesley, M.D., of the University of Alabama at Birmingham, and colleagues at Microbicide 2008, a biennial conference held this week. It's the most advanced study to date with a topical microbicide gel specific for HIV, Dr. Hoesley said in an interview. He characterized it as potentially "a terrific option" for sexually active women, he said. The study did not include any efficacy evaluation, Dr. Hoesley said. On the basis of the favorable safety results, effectiveness trials are now being planned, he said.

Earlier this month, the New York-based Population Council announced at a press conference that an anti-HIV microbicide gel called Carraguard had been found in clinical trials to be safe for up to two years of vaginal application. This study also did not involve an efficacy evaluation.

Previous microbicides have not only failed to work but appeared to increase the risk of HIV infection. The New York gel is now being combined with antiretroviral drugs for phase I studies (See: <http://www.medpagetoday.com/HIVAIDS/HIVAIDS/tb/8417>).

In the current double-blind trial, organized by the Microbicide Trials Network in Pittsburgh, 200 women at three sites were assigned to four treatment arms: regular daily application of tenofovir or placebo gel, or tenofovir or placebo gel applied only before sex. Half the participants were enrolled in Pune, India. The rest were in New York and Birmingham, Ala. Participants were instructed to have their partners wear condoms. The women also received HIV risk-reduction counseling and testing and treatment for sexually transmitted diseases.

Dr. Hoesley said there were no significant differences, or even notable trends, between placebo and the active treatment in any safety parameter studied. These included liver, kidney and blood function tests as well as clinical adverse effects such as itching or burning. Only one participant dropped out of the study, a woman who became pregnant. No one acquired HIV during the trial.

Participants underwent structured interviews about their compliance with the protocol. Among those in the daily-use arms, 83% reported using it during the previous week. In the before-sex application groups, 80% said they had followed the protocol. The most common reasons given for noncompliance were menstruation (41%) and forgetting (23%).

The women were also asked about ease of use and problems they had with the gel. About 39% said it was easy to use. The most common objections were that it was messy and that application was time-consuming, Dr. Hoesley said. Some 12% said it made sex more pleasurable. Perhaps most importantly, when asked if they would use the gel if it were found to help prevent people from getting HIV, 90% of participants who used the gel at the time of sex and 96% of the daily-use group said yes.

Dr. Hoesley said there were no differences in safety or acceptability results between the study sites. "Women are definitely willing to use a gel to protect against sexual transmission of HIV," said the study's principal investigator, Sharon L. Hillier, M.D., of the University of Pittsburgh. "That's very encouraging."

"Finding that daily use is both safe and feasible is important because we believe a daily approach may provide more sustainable protection against the virus in women who can't always predict when they will have sex," she added. "Based on what we have learned we can proceed with greater confidence on a path that will answer whether tenofovir gel and other gels with HIV-specific compounds will be able to prevent sexual transmission of HIV in women when other approaches have failed to do so. It is a critical time for all of us engaged in HIV prevention, and I truly believe we are turning a corner."

Additional data from the study on tenofovir absorption into blood and effects on vaginal flora are still being evaluated.

Dr. Hoesley said future clinical studies would take place largely outside the United States, because that is where the product is expected to be used.

Tenofovir was originally developed by Gilead Pharmaceuticals, which markets it in oral form for treating HIV infection. In 2006, the company assigned rights to use it in topical microbicides to two non-profit groups: the International Partnership for Microbicides and CONRAD. Gilead is not involved with the studies of the tenofovir gel, Dr. Hoesley said.

Besides efficacy studies, another safety trial with tenofovir gel will be conducted in pregnant women.

"Anti-HIV gel well tolerated by women"

Date: 27 February 2008

Source: *United Press International*

http://www.upi.com/NewsTrack/Health/2008/02/27/anti-hiv_gel_well_tolerated_by_women/6743/

A U.S. study of women with the human immunodeficiency virus found an experimental gel, which keeps HIV from replicating, is safe for daily use. "The gel -- tenofovir -- is safe to use, and well tolerated by HIV-negative women. That's a key message in our findings," study author Dr. Craig Hoesley, of the University of Alabama at Birmingham said in a statement. "This sets the stage for larger studies to see if tenofovir can prevent HIV infection."

Hoesley and colleagues at the University of Pittsburgh School of Medicine study included 200 sexually active HIV-negative women -- ages 19 to 50 -- 64 percent of whom were married. The active ingredient in tenofovir gel is a class of anti-retroviral drugs called nucleotide reverse transcriptase inhibitors, which act against HIV by blocking the virus' ability to replicate and grow inside the body, Hoesley said. The study findings were presented at an international microbicides meeting this week in New Delhi.

“India developing neem based gel for women to counter AIDS”

Author(s): Prashant K. Nanda

Date: 27 February 2008

Source: IANS

http://www.thaindian.com/newsportal/sci-tech/india-developing-neem-based-gel-for-women-to-counter-aids_10021662.html

India has successfully completed phase two trials of a neem based microbicide gel for women that promises to help prevent transmission of HIV/AIDS. “It will be a gel-based microbicide to be used in the vagina to stop new HIV/AIDS infections,” said Nomita Chandhok, deputy director general of the Indian Council of Medical Research (ICMR). “It’s purely an indigenous product. We have found success in phase two of the trials at the National AIDS Research Institute (NARI) in Pune. Fifty high risk but HIV negative women used it regularly for six months and we are happy at the outcome,” Chandhok told IANS.

Microbicides are a compound with the ability to protect against sexually transmitted diseases.

She said the microbicide named Praneem is a herbal composition and researchers are optimistic about its future. “During animal trials we tested the microbicide on rats and rabbits among others. The gel was put inside their vagina and researchers recorded the toxicological effect of the compound,” she said. “The third phase of the trials will begin very soon and its result can be expected in 18 months.”

After animal trials, the first phase of human trials check the toxicological effect of the drug, like itching and swelling. The sample size could be as small as 10 people. Phase two of the clinical trial takes into account more individuals than the previous phase and monitors side effects of the product. In phase three, the trials are generally conducted in multiple sites and amongst multiple risk groups. A favourable result leads to its application for licensing and mass production. According to Chandhok, the ideal sample size in the last stage should not be less than 2,000.

India is home to 2.5 million HIV/AIDS patients and nearly 40 percent are women. “Women are more vulnerable to AIDS but we don’t have anything specific for them to counter the disease. Staying away from sex and change in behavioural changes are good but we need something that can prevent fresh infections,” Chandhok said.

Indian experts said the world’s first microbicide gel for women with an AIDS drug has successfully crossed phase two trials in three places, including in India, but that was entirely a US project. “Though India was one of the sites to conduct clinical trials yet the project was entirely of the United State’s National Institute of Health (NIH). Praneem is entirely an Indian effort and the brainchild of a scientist named G.P. Talwar,” she added. Talwar is a Delhi-based scientist working in close collaboration with ICMR.

“Less silence, more science could make anal sex safer”

Date: 27 February 2008

Source: *PlusNews*

<http://www.plusnews.org/Report.aspx?ReportId=77003>

The silence and taboo surrounding anal sex is putting millions of men and women at risk of HIV, delegates attending the fourth international microbicides conference in New Delhi, India, heard this week.

Often thought of as strictly a “gay thing”, studies are showing that anal intercourse is also part of heterosexual coupling, and is largely unprotected, said Jim Pickett, chair of International Rectal Microbicide Advocates (IRMA), which released a report on the subject at the conference. The report, *Less Silence, More Science* warned that researchers could no longer afford to ignore anal sex - one of the biggest drivers of the epidemic - and called for more research into the development of a rectal microbicide. “We must consider the possibility that unprotected anal intercourse, even when practiced rarely, may in fact be a significant source of HIV transmission in many contexts,” the report said. Women were also likely to engage in anal sex in cultures and regions where virginity was especially prized and contraception was not easily available.

The danger of unprotected anal sex is that the lining of the rectum is more fragile and contains more susceptible cells than the lining of the vagina and part of the cervix, making it easier to transmit HIV. “This is a highly vulnerable region for infection ... It’s a very easy portal for HIV infection,” Dr Ian McGowan, from the Microbicide Trials Network, told delegates.

Although progress has been made in the race towards an effective vaginal microbicide, studies looking at rectal microbicides lag behind. “Within 10 minutes of a vaginal microbicide going on the shelves, it will be going up someone’s butt,” said Pickett.

Potential microbicides include a range of products - such as gels, films and sponges - that could help prevent the transmission of HIV and other sexually transmitted infections. No microbicide has yet been shown to be effective.

Rectal microbicides could offer both primary protection in the absence of condoms and back-up protection if a condom broke or slipped off during anal intercourse. The only rectal microbicide safety trial so far is currently underway, and two more Phase 1 trials are in the planning stages, the report said. Phase 1 trials are where researchers test a new drug for human safety to determine a safe dosage range and identify side effects.

Pickett attributed the slow pace of research in this field to the scientific challenges in testing products rectally, as well as widespread stigma and homophobia, besides a lack of funding. The fragile nature of the rectum - which is just a single cell-layer thick - could mean that it could be damaged by some of the study-related actions and tests, making it difficult to measure the safety of the product.

Stigma, homophobia major barriers

In Jamaica, a country where homophobia is “deeply embedded” and popular musicians sing about shooting men who have sex with men (MSM) in the head, Jamaican researcher Dr Nesha Haniff has been working with members of a local non-governmental organisation (NGO), Jamaica AIDS Support for Life, to advocate for new prevention approaches to protect MSM.

HIV prevalence in the Caribbean country is 2 percent at present, but an estimated 25 percent of the country's MSM are estimated to be living with the virus. Haniff acknowledged that part of the dilemma in calling for rectal microbicides was the act of anal intercourse.

The practice is illegal in many countries, and the strong taboo and homophobia associated with anal sex makes it difficult for both MSM and heterosexual couples to find out about how they can protect themselves from HIV infection.

“Vaginal anti-HIV gel ‘safe for regular use’”

Author(s): T.V. Padma

Date: 27 February 2008

Source: *SciDev.net*

<http://www.scidev.net/gateways/index.cfm?fuseaction=readitem&rgwid=3&item=News&itemid=4263&language=1>

A vaginal gel containing the anti-HIV drug tenofovir is safe for daily use by women, a study shows. The research was presented at Microbicides 2008, an international microbicides conference, in Delhi, India, this week (February 25).

Tenofovir is one of the primary antiretroviral drugs. It targets HIV by blocking the action of a key enzyme needed for the virus to replicate.

The Microbicides Trials Network (MTN) — sponsored by the US National Institutes of Health — conducted phase II trials on tenofovir gel in India and the United States in 2007, to test whether it is safe for women to use the gel daily instead of before having sex, and whether women complied with the procedure correctly and willingly. The six-month study compared tenofovir with a placebo in 200 sexually active, uninfected women. It found the gel was safe — with no effects liver, blood or kidney function — both when it was used daily for a period of six months and before each act of sex.

The study also found high levels of compliance — over 80 per cent — Sharon Hillier, director at the Department of Obstetrics, Gynaecology and Reproductive Sciences at the University of Pittsburgh, and principal investigator of Microbicides MTN, said at the conference. Over 90 per cent of the women involved said they would use such a gel if it were found to be effective against HIV.

A series of trials in Africa and the United States over the next two years will study if the drug is absorbed into the foetus during pregnancy, dose absorption in women and whether the drug is more effective as an oral pill or vaginal gel. “The oral route versus topical application (of an anti-HIV drug) is the key scientific question,” Hillier told SciDev.Net.

Between 70 and 90 per cent of HIV infections in women are due to heterosexual intercourse. Women are biologically more vulnerable to HIV infection as the cells in the lining of the female genital tract rupture more easily, making it easier for the virus to enter.

The tenofovir results will be encouraging to the microbicide research community who have faced a series of setbacks in recent years, including the early closure of trials for cellulose sulphate microbicide (see <http://www.scidev.net/News/index.cfm?fuseaction=readnews&itemid=3393&language=1>) and the announcement this month that a microbicide gel based on a seaweed extract, Carraguard, failed to prevent HIV transmission (see <http://www.scidev.net/News/index.cfm?fuseaction=readnews&itemid=4260&language=1>).

“Anti-HIV gel proven safe, tolerable for women”

Date: 26 February 2008

Source: Xinhua News Agency

http://news.xinhuanet.com/english/2008-02/27/content_7676644.htm

A gel using anti-HIV drug tenofovir to shield women from AIDS has been proven safe for daily use and acceptable to women, study findings showed Tuesday. The study, conducted by researchers at the University of Alabama at Birmingham (UAB) and the University of Pittsburgh to test the gel's safety, involved 200 sexually active HIV-negative women aging from 19 to 50, of whom 64 percent were married. “The gel is safe to use, and well tolerated by HIV-negative women. That’s a key message in our findings,” said Craig Hoesley, one of the authors of the Phase II trial report. “This sets the stage for larger studies to see if tenofovir can prevent HIV infection.”

Tenofovir, the active ingredient in the gel, is an antiviral drug called nucleotide reverse transcriptase inhibitor, which acts against HIV by blocking the virus’ ability to replicate and grow inside the body.

Women showed great tolerance to the gel, which is a significant boost to HIV and AIDS prevention efforts focusing on next-generation microbicides to reduce infection rates, researchers said.

Eighty percent of the women instructed to use the gel within two hours before sex said they followed instructions, and 83 percent instructed to use the gel daily said they had done so in the week prior. If the gel were proven helpful to prevent HIV infection, more than 90 percent of participants said they would seriously consider using it to protect their sexual health.

Women, who are physically more at risk from AIDS infection than men, currently protect themselves mainly by relying on male consent to wear a condom.

“Experimental microbicide tenofovir safe for women to use daily, study finds”

Date: 26 February 2008

Source: Kaiser Daily HIV/AIDS Report

http://www.kaisernetwork.org/daily_reports/rep_index.cfm?DR_ID=50597

The experimental microbicide tenofovir is safe for women to use daily, according to results from clinical trials funded by NIH and conducted in three locations in the U.S. and India, though it is too early to tell if it actually prevents HIV infection, *Reuters* reports (Fox, *Reuters*, 2/25). Microbicides include a range of products – such as gels, films and sponges – that could help prevent the sexual transmission of HIV and other infections (*Kaiser Daily HIV/AIDS Report*, 2/6). A study released last week showed that the microbicide candidate Carraguard, though safe, was ineffective in preventing HIV transmission. Other candidates, including nonoxynol-9 and Ushercell, have been found to increase women's risk of HIV infection, according to *Reuters* (*Reuters*, 2/25).

The study -- presented at Microbicides 2008, the biannual international conference that began on Sunday in New Delhi, India -- was conducted from August 2006 to September 2007 at the National AIDS Research Institute in Pune, India; the Bronx-Lebanon Hospital Center; and at the University of Alabama-Birmingham, the *Times of India* reports. Tenofovir gel is a HIV-specific microbicide that is designed to prevent HIV from replicating when it comes in contact with uninfected T-cells (Sinha, *Times of India*, 2/23). The study involved 200 HIV-negative women of reproductive age who were asked to apply the gel either daily or before sexual intercourse for about six months. The women were asked to use condoms as well as the gel, *AFP/Yahoo! News* reports.

The study found no disruption of blood, liver or kidney function and found that women were willing to follow the treatment guidelines. According to the study, more than 90% of the participants said they would consider using the gel to prevent HIV transmission if it were approved. More than 80% of the participants followed the experimental regimen, the study found.

Sharon Hillier, lead investigator and director of reproductive infectious diseases at the University of Pittsburgh School of Medicine, said, "Based on what we have learned, we can proceed with greater confidence on a path that will answer whether tenofovir gel and other gels with HIV-specific compounds will be able to prevent sexual transmission of HIV in women when other approaches have failed to do so" (*AFP/Yahoo! News*, 2/25). Craig Hoesley of UAB said a "key message" of the results is that the "gel is safe to use and well-tolerated by HIV-negative women," adding, "This sets the stage for larger studies to see if tenofovir can prevent HIV infection" (*Reuters*, 2/25). According to the *Times of India*, a Phase II trial is under way among 1,000 women in South Africa to test the microbicide's effectiveness at preventing HIV transmission (*Times of India*, 2/23).

Development of Microbicides Top Priority for India, Health Minister Says

In related news, India's Health Minister Anbumani Ramadoss at the conference said the development of microbicides is a priority for India, the *Press Trust of India* reports. "At the moment, 50 experimental substances as possible vaginal microbicides are being examined and about a quarter of these agents are at various stages of human testing and four of these are in advanced states of clinical trials," Ramadoss said. He added that "women need a product that they can control and even use without their partners' consent or knowledge." Effective microbicides would offer an alternative method of protection for women, Ramadoss said (*Press Trust of India*, 2/24).

"Gels, creams to check spread of HIV"

Date: 26 February 2008

Source: *The Statesman*

Gels and creams will be in the market in about 5 years to check the spread of HIV. These products which are under clinical trial could be used shortly to take on the HIV virus.

The 2008 International Conference which is being organized in collaboration with Indian Council of Medical Research (ICMR) on striving ways towards HIV prevention primary focus on the use and awareness about microbicides. The conference is focusing about the risk of women who suffer the most with such contagious disease because of their partner's sexual activity outside the home.

Microbicides are products made to kill HIV virus and other germs that cause sexually transmitted infections (STIs). It is not yet in the market for sale and research is being done to find the safest and the most effective to prove its worth. It is expected to be in the market within the next five years.

A special online course is being introduced in August 2008 under the global campaign to educate more and more people about microbicides.

The Population Council is actively involved in research work to understand the individual social and economic circumstances that causes HIV. It is focusing on HIV and AIDS prevention treatment and care activities all over the world. The special programmes are being conducted by the Population Council in South Africa and Sub-Saharan countries. The other UN-based agencies, International and National Funding Agencies also participated in the conference actively.

“HIV drug in microbicide gel safe for daily use”

Date: 26 February 2008

Source: *HealthDay News*

<http://www.washingtonpost.com/wp-dyn/content/article/2008/02/26/AR2008022601771.html>

A vaginal microbicide gel that contains the antiretroviral drug tenofovir is safe for HIV-negative women to use every day, according to a six-month study of 200 women in India and the United States.

This study, by researchers at the U.S. National Institutes of Health-funded Microbicide Trials Network, looked at whether women were able to adhere to a regimen of either daily or sex-dependent use of the gel. Both regimens proved equally safe, and women's adherence to each regimen was similar. Notably, none of the women who used the new gel got HIV during the study period. There were no differences in liver, blood and kidney function between women who used the gel and those who used a placebo, nor were there any differences in rates of genital symptoms such as itching and burning. The compliance rate was 83 percent among women in the daily use group, and 80 percent among women instructed to use the gel within two hours of having sex.

The results are an advance in efforts to use microbicides to prevent HIV infection in women, the researchers said. Worldwide, almost half of people with HIV/AIDS are women, and 70 percent to 90 percent of all HIV infections in women are due to heterosexual intercourse. In many areas of the world, even married women and those with steady partners are at risk for HIV infection. Correct and consistent use of male condoms prevents HIV infection, but it's often difficult for some women to convince men to use condoms. “Finding that daily use is both safe and feasible is important, because we believe a daily approach may provide more sustainable protection against the virus in women who can't always predict when they will have sex,” study leader Sharon L. Hillier, said in a prepared statement. “Based on what we have learned, we can proceed with greater confidence on a path that will answer whether tenofovir gel and other gels with HIV-specific compounds will be able to prevent sexual transmission of HIV in women when other approaches have failed to do so. It is a critical time for all of us engaged in HIV prevention, and I truly believe we are turning a corner,” said Hillier, director of reproductive sciences at the University of Pittsburgh School of Medicine.

Microbicides designed to prevent HIV infection are applied on the inside of the vagina or rectum.

The study was presented this week at Microbicides 2008, an international meeting in New Delhi, India.

“Microbicides 2008: Accurate adherence reporting essential for microbicide trials”

Author(s): Gus Cairns

Date: 26 February 2008

Source: *Aidsmap.com News*

<http://www.aidsmap.com/en/news/033267ED-1E91-438D-A085-3EC86CB287D0.asp>

Researchers need much better ways of determining adherence to candidate microbicides in trials, and also of ways of determining sexual behaviour, the 2008 Microbicides Conference heard today in Delhi, India.

Barbara Mensch of the Population Council told the Conference: “The inability to prove effectiveness leaves the question of product efficacy unanswered.”

Several trials of new prevention technologies have failed recently despite excellent adherence to the intervention reported by participants. In the recent Carraguard trial (run by the Population Council), 96 per cent of women claimed to be using gel correctly. However when applicators were tested to see if they

had actually been used, only 44 per cent had. Similarly the figures for women who claimed always to use condoms only, condoms plus gel, or gel only, added up to more than 100 per cent.

Similar problems may have plagued the recent HPTN 039 trial of acyclovir for herpes prophylaxis, in which the reduction in genital ulcers was suspiciously low despite reported 94% adherence amongst participants and pill counts.

Low adherence in itself may not jeopardise a trial as long as sufficient participants are high adherers and as long as we know which is which, Mensch said. “Poor adherence means that results of an intention-to-treat analysis will be very different from a per-protocol one,” she said, “but inability to measure poor adherence biases effects towards the null.” In other words, the inability to even compare intention-to-treat analysis, in which results are viewed as if all participants adhered to the trial medication, with per-protocol analysis, in which only participants that took it as prescribed are counted, is likely to lead to negative results even when the microbicide is highly effective in those who use it.

What are researchers doing to try and establish true adherence and behavioural data? One way is to use Automated Computer-Assisted Self-Interviewing (ACASI) with participants instead of face-to-face interviews live researchers. This technique worked well in a substudy of the Carraguard study. This was a simulated three-month microbicide study in which 848 women were given placebo gel but assessed as if they were taking a trial compound. As well as using ACASI to assess adherence, researchers visited the women to count off used applicators. The trial also used a PCR test to detect sperm in vaginal fluids to assess the true levels of sexual activity.

Establishing the latter is also extremely important; microbicide researchers are just beginning to understand the degree to which trial participants give unreliable reports of their own sexual activity. For instance, in the MIRA trial, which looked at the possibility of using the female diaphragm in HIV prevention, the pregnancy rate was actually higher in women who reported contraceptive use than in women who did not. In the MTN 035 phase IIb trial of the microbicides Buffergel or 0.5% PRO-2000, at one site participants reported more sex acts protected by a condom than the total number of sex acts reported to investigators at that site. In the simulated trial, 19% of women who reported no sex in the last 48 hours tested positive for semen in the vagina.

Sex may be misreported for a variety of reasons, not all of them due to deception; women may differ in their definitions of what ‘sex’ is, may fail to report non-consensual experiences, or may simply tell the researcher what they want them to hear: very few of us accurately report our sex lives, even to ourselves.

The ACASI technique proved particularly useful in assessing non-adherence to the product. Face-to-face interviewing (FTFI) consistently produced lower figures for non-adherence than the ACASI technique, as in the following table:

Reason for non-use	FTFI	ACASI
“It might cause harm”	3%	13%
“I ran out of gel”	5%	14%
“I had no privacy”	4%	15%
“There was no time/sex was unplanned”	18%	39%

Researchers also had to take lessons from demographers and opinion pollsters in how they phrased questions, Mensch added, for instance, asking “Were you able to use the gel last time you had sex?”

instead of the more direct “Did you use the gel last time you had sex?” Better still might be to ask about non-use rather than use: “In how many sex acts were you not able to use the gel?”

Interviewers should be trained to use supplementary questions to establish how participants arrived at answers (“When I just asked you how many sex partners you’d had, how did you count them up?”) and what their understanding of terms was (“What counts as a sex partner for you?”).

Mensch asked a list of questions microbicide trials had failed so far to ask, or have answered. Are the highest-risk participants the most or least adherent? Does adherence and sexual behaviour change over the trial? Under what circumstances are microbicides most and least likely to be used? What influence do partners and family have on women? Are trial populations really representative of the target population and if not, does it matter?

Future trials will try and answer some of these questions with more sophisticated monitoring. The MTN 035 trial site in Malawi, for instance, has started using an ACASI system asking questions of participants in writing, in voice and with graphics.

The CAPRISA 004 tenofovir-gel study, which has recently started in South Africa, is considering issuing participants with modified Blackberry terminals in which to record their gel use and behavioural data and transmit them to the centre. And the International Partnership for Microbicides is considering how to do the most direct-possible observation of women’s gel use in its series of studies of dapivirine (TMC120) without endangering or stigmatising participants.

In conclusion: the recent failure of the Carraguard trial to produce a positive result has not dampened researchers’ and advocates’ enthusiasm or belief in the concept of microbicides. It has instead highlighted the extreme complexity of these large trials and the numerous social and behavioural influences that need to be considered if researchers are to generate a meaningful result for the millions of dollars spent on them.

Reference

- Mensch B. Approaches to integration of behavioral research into regulatory phase I II, and III studies of microbicides. Plenary presentation, microbicides Conference, Delhi. 2008.

“Microbicides, new arsenals to battle AIDS”

Author(s): Sanchita Sharma

Date: 26 February 2008

Source: *Hindustan Times*

<http://www.hindustantimes.com/StoryPage/StoryPage.aspx?id=d626ed34-cb55-46dd-b3ee-58091f8aedd0&&Headline=Microbicides%2c+new+arsenals+to+battle+AIDS>

Microbicide gels that use anti-retroviral medicines to prevent HIV infection are the newest arsenals in the global battle against AIDS. One such candidate is a gel called tenofovir, which has been found safe for daily use by women in simultaneous trials conducted in India and the US, announced researchers at the International Microbicides Conference being held in New Delhi.

Human trials at Pune’s National AIDS Research Institute (NARI), the University of Alabama at Birmingham (UAB) and the University of Pittsburgh School of Medicine showed that the gel was safe for use. The active ingredient in tenofovir gel is a class of anti-retroviral drugs called nucleotide reverse transcriptase inhibitors, which act against HIV by blocking the virus’ ability to replicate and grow inside the body.

“Microbicides are one of the top 10 technologies identified to have a positive impact on the health needs of people living in developing countries. There is an urgent need for more methods to prevent HIV infection, especially those that put women in control,” says Dr N. K. Ganguly, distinguished biotechnology fellow and former director general, ICMR, which is hosting the New Delhi conference.

The findings are significant because of the failure of the first-generation microbicide gel Carraguard, which was safe but did not protect from HIV infection. One arm of another microbicide, PRO 2000, was dropped earlier this month.

Microbicides are synthetic or natural substances – manufactured in the form of a gel, cream, suppository or film – that can neutralise or kill the HIV virus. Unlike condoms, an HIV microbicide could be used without the cooperation or knowledge of one’s partner, offering protection to women at risk of unprotected sex with a person who may be HIV-positive.

“The Phase II trial in Pune and the US evaluated if tenofovir was safe to use every day for six months, or safe to use prior to each act of sex. The next step is to determine whether tenofovir gel and other gels with HIV-specific compounds prevent sexual transmission of HIV in women when other approaches have failed to do so,” said Sharon L. Hillier, director of reproductive infectious disease research at the University of Pittsburgh School of Medicine and principal investigator on the Phase II study.

The study included 200 sexually active HIV-negative women at NARI, UAB and the Bronx-Lebanon Hospital Centre in New York. The participants were all HIV-negative and aged between 19 and 50. Of them, 64 per cent were married. There was no disruption of liver, blood or kidney function in each group of women using a different gel regimen, including those given a placebo gel that looked and felt identical to the tenofovir gel. The women study participants said if tenofovir gel is approved for the prevention of HIV infection, they would be willing to apply the gel to themselves daily or before sex, whichever is determined the best use.

“New anti-HIV microbicide gel shows promise”

Author(s): Sonal Singh Wadhwa

Date: 26 February 2008

Source: *Desicritics.org*

<http://desicritics.org/2008/02/26/130026.php>

Experts said on Monday that they were closer to developing a vaginal gel that will give control over sexual health and against HIV/AIDS to women. The study, released at the international conference on microbicide currently being held in New Delhi, was welcomed by those working in the HIV/AIDS field.

Microbicides are products such as gels, creams, suppositories or a long lasting vaginal ring can be applied vaginally or anally to prevent the spread of sexually transmitted diseases, and especially HIV/AIDS. At present, there is no cure or vaccine against HIV/AIDS, and prevention of sexual transmission of the disease depends largely on the use of condoms or abstinence.

This kind of vaginal gel will allow women to protect themselves from HIV and other diseases without having to rely on their partner’s decision to wear or not wear a condom. “There is a need for products besides and in addition to condoms that will prevent HIV/AIDS,” said Dr. Sharon Hillier, Professor of Obstetrics, Gynecology, and Reproductive Sciences at the University of Pittsburgh School of Medicine.

A number of different gels are currently being tested around the world but none have been proven to be effective to preventing the transmission of HIV. “There have been disappointments in the field of

microbicide,” Dr. Hillier said. “But now there are encouraging studies.” This latest attempt by researchers in the United States and India is still in the early stages.

Researchers asked 200 sexually-active, HIV-negative women in New York and Pune, India to apply the Tenofovir gel either daily or before intercourse for a period of six months. They were also asked to use condoms in addition to the gel.

Tenofovir, a drug approved by the U.S. Food & Drug Administration, is marketed by Gilead Sciences under the name Viread, an anti-retroviral drug which blocks enzymes that are crucial to the viral production in HIV infected people.

It was found that over 80% of the women in the recently concluded study actually did use the Tenofovir gel as directed.

In 2004-2005, the Cambodian government had ordered researchers to stop a clinical trial to test Tenofovir after protests by commercial sex workers who opposed the trial due to the lack of information of the side effects and provision of health insurance to treat those side effects post the completion of the study.

In the current study, researchers found no disruption of liver, blood or kidney function and found a significant willingness among the women to follow the treatment guidelines. Dr. Hillier said that 100% of the women in the clinical trial said they would seriously consider using the gel if it were approved to help prevent HIV infection.

The UNAIDS estimates that there are 33.2 million people living with HIV/AIDS across the world, of which 46% are women. In high-risk areas such as sub-Saharan Africa, over 60% of those infected are women. According to the Indian government and UNAIDS, nearly 2.5 million people are infected with HIV/AIDS in India and similar to global trends, 40% of those infected are women. HIV/AIDS is believed to be transmitted via sexual contact in 85% of the cases in India.

At the same conference, Dr. Salim Karim from the University of KwaZulu-Natal in South Africa said that if approved, anti-retroviral gels can be used up to 12 hours prior to sex as a protection mechanism against HIV/AIDS.

“Tenofovir gel safe for daily use by women, new study suggests”

Date: 26 February 2008

Source: *Science Daily*

<http://www.sciencedaily.com/releases/2008/02/080225090821.htm>

A vaginal microbicide that incorporates an antiretroviral (ARV) drug normally used to treat people with HIV is safe for sexually active HIV-negative women to use every day over an extended period, suggest results of a clinical trial of tenofovir topical gel. Moreover, most of the women who participated in the study conducted in India and the United States adhered to a regimen involving either daily or sex-dependent use of the gel, report researchers from the U.S. National Institutes of Health-funded Microbicide Trials Network (MTN) at Microbicides 2008, an international meeting taking place Feb. 24-26 at the Hotel Ashok in New Delhi.

The findings are a significant boost to HIV prevention efforts focused on the potential of "next-generation" microbicides to curb infection rates in women. Globally, nearly half of those living with HIV/AIDS are women, and between 70 and 90 percent of all HIV infections in women are due to heterosexual intercourse. In India and many other parts of the world, even married women and women with steady partners are at risk.

In this Phase II study, called HPTN 059, researchers wanted to understand if tenofovir was safe to use every day for six months compared to its use prior to each act of sex, and if women were able to adhere, or follow, each regimen. Researchers found both approaches equally safe and women's adherence to product use similar. Interestingly, most participants also said they would be willing to apply gel, including daily, if one were found effective to prevent against getting HIV from their sexual partners.

Microbicides are products designed to prevent the sexual transmission of HIV when applied topically on the inside of the vagina or rectum. Tenofovir gel is among a newer class of candidate microbicides that differ from early types because they have specific action against HIV. In addition, because tenofovir gel and similar products are longer acting, their use may not be required before each act of sex, which is not always practical or desirable for some women.

“Finding that daily use is both safe and feasible is important because we believe a daily approach may provide more sustainable protection against the virus in women who can't always predict when they will have sex. Based on what we have learned we can proceed with greater confidence on a path that will answer whether tenofovir gel and other gels with HIV-specific compounds will be able to prevent sexual transmission of HIV in women when other approaches have failed to do so. It is a critical time for all of us engaged in HIV prevention, and I truly believe we are turning a corner,” said Sharon L. Hillier, Ph.D., professor and vice chair for faculty affairs, and director of reproductive infectious disease research in the department of obstetrics, gynecology and reproductive sciences at the University of Pittsburgh School of Medicine, who is MTN principal investigator and led the study.

According to UNAIDS, women represent nearly half, or 46 percent, of the 33.2 million people living with HIV/AIDS worldwide, and they are more than twice as likely as men to acquire HIV through sexual intercourse, due to both biological and cultural factors. Although correct and consistent use of male condoms has been shown to prevent HIV infection, women often cannot successfully negotiate condom use with their male partners.

HPTN 059 involved 200 sexually active HIV-negative women: 52 were enrolled at the University of Alabama at Birmingham (UAB) in Birmingham, Alabama; 48 at Bronx-Lebanon Hospital Center, Bronx, New York; and 100 women entered the study at the National AIDS Research Institute in Pune, India. The mean age was 32 and 64 percent of the women were married. All but one of the women at the Indian site were married compared to 28 percent of the women at the two U.S. sites.

Once enrolled, women were randomly assigned to one of four groups: tenofovir gel applied daily; tenofovir gel applied up to two hours before sex; placebo gel (without an active drug) used every day; or placebo gel applied prior to sex. Because the tenofovir and placebo gels look the same, neither researchers nor participants knew who had been assigned to use which gel during the six-month study period. Women were assessed at one month, three months and six months. Throughout the study, participants received free condoms and HIV risk-reduction counseling as well as routine testing and treatment for sexually transmitted infections.

The study found no differences in liver, blood and kidney function between the groups of women using either regimen of tenofovir gel and the groups assigned to use placebo, nor were there differences in these safety measures between groups using daily gel and groups using gel with sex. Likewise, researchers report no statistical differences in the development of genital symptoms such as itching and burning, which are considered minor. One woman became pregnant and stopped gel use. No participants acquired HIV during the study.

Adherence to treatment was also similar. According to structured interviews, 80 percent of the women instructed to use gel within two hours of having sex said they complied with the regimen. Of the women in the daily-use groups, an average of 83 percent reported study gel use in the past week. The two most cited reasons women gave for not using gel was menstruation (41 percent) and forgetting (23 percent).

Overall, 41 percent of the women indicated there was nothing they disliked about using the gel and 39 percent said it was easy to use. Other attributes of the gel women identified included its potential for protecting against HIV (19 percent), its smell and appearance (14 percent) and that it made sex more pleasurable (12 percent). Thirty-two percent didn't like that the gel was messy, but none of the women said sex was made less pleasurable because of the gel.

Importantly, when asked if they would use the gel if it were found to help prevent people from getting HIV, 90 percent of the women who had been assigned to use the gel at the time of sex and 96 percent of the women who had been asked to use gel daily said yes. "Women are definitely willing to use a gel to protect against sexual transmission of HIV. That's very encouraging," Dr. Hillier commented.

HPTN 059 also evaluated how the active ingredient in the gel was absorbed from the vagina into the blood and vaginal tissue; and looked at the effects of prolonged use on vaginal flora, the vagina's naturally protective population of microorganisms; and whether the activity of certain immune system molecules called cytokines could serve as a useful measure, or marker, for assessing the safety of microbicides. Results of these evaluations are not yet available.

HPTN 059 was conducted by the Microbicide Trials Network (MTN), a clinical trials network established in 2006 by the National Institute of Allergy and Infectious Diseases (NIAID) with co-funding from the National Institute of Child Health and Human Development and the National Institute of Mental Health, all components of the U.S. National Institutes of Health (NIH). Prior to the establishment of the MTN, HPTN 059 study was led by the NIAID-funded HIV Prevention Trials Network (HPTN), from which the study gets its name.

At the site level, HPTN 059 was led by Smita Joshi, MBBS, in Pune, India; Jessica Justman, M.D., at Bronx-Lebanon Hospital; and Craig Hoesley, M.D., UAB.

In its pill form, tenofovir is a mainstay of one of the most widely used regimens for treating HIV. The active ingredient in tenofovir gel belongs to a class of anti-retroviral drugs called nucleotide reverse transcriptase inhibitors, which act against HIV by targeting a key enzyme the virus needs to copy itself before taking over a host cell. The topical gel form of tenofovir was not developed as treatment for HIV but as an approach to prevent the sexual transmission of HIV. Both oral and topical formulations were developed by Gilead Sciences, Inc., of Foster City, California, which assigned a royalty-free license for the topical gel to the International Partnership for Microbicides of Silver Spring, Maryland, and CONRAD, of Arlington, Virginia, in December 2006.

MTN will launch a series of other trials that will further evaluate the safety and adherence of tenofovir gel as well as look at its effectiveness for preventing HIV. Researchers will soon begin enrolling participants into MTN-002, the first trial of a candidate microbicide in pregnant women that seeks to understand the extent of drug absorption during pregnancy and the degree to which the active ingredient in tenofovir gel can be transferred to the fetus. Another trial, MTN-001, will be the first direct comparison of oral and vaginal gel preparations of tenofovir -- looking at differences in drug absorption (systemically and locally) and adherence and acceptability of each approach separately and in combination.

Finally, the VOICE Study (Vaginal and Oral Interventions to Control the Epidemic) will be the first effectiveness trial of a microbicide that women use every day instead of at the time of sexual intercourse.

Moreover, VOICE will be the only trial evaluating two promising HIV prevention approaches in the same study: tenofovir gel and pre-exposure prophylaxis, or PrEP, an HIV prevention approach that involves daily use of oral anti-retrovirals.

Currently, tenofovir gel is being evaluated in a Phase IIb study being conducted at the Centre for the AIDS Programme of Research in South Africa (CAPRISA) in Durban. The study, known as CAPRISA 004, will enroll 980 women. Unlike VOICE, researchers are evaluating a dosing strategy timed around sexual intercourse.

Other microbicide products have been or are currently being tested in clinical trials, although none is yet approved or available for use by women.

In addition to Drs. Hillier, Justman, Joshi and Hoelsley, other authors of the HPTN 059 study presented at Microbicides 2008 are Elena Cyrus-Cameron, M.P.H., Family Health International, Research Triangle Park, North Carolina; Benoît Mâsse, Ph.D., Statistical Center for HIV/AIDS Research & Prevention at the Fred Hutchinson Cancer Research Center, University of Washington, Seattle; and Craig Hendrix, M.D., Johns Hopkins University, Baltimore, Maryland.

“Zinc can prevent sexual transmission of HIV”

Author(s): Abhishek Shuklain

Date: 26 February 2008

Source: *Mail Today*

<http://mailtoday.in/>

Zinc can help prevent transmission of human immunodeficiency virus (HIV), scientists have said. The metallic chemical element is currently being harnessed to develop microbicides. Microbicides are products which in the form of creams or gels can stop the transmission of HIV and other sexually transmitted diseases. But, even though scientists are working on several different products, they haven't succeeded in developing one. Applied to the female genitalia before intercourse, it can safeguard the woman from being infected by HIV.

Population Council, an NGO, is working on a new product based on zinc, MIV150 and their previous microbicide Carraguard. MIV150 is a drug used for the treatment of HIV infection whereas Carraguard is a first generation microbicide that did not deliver expected results. The new product has been named PC815. “It will be harsh to say that Carraguard failed. The product was found safe but results were not statistically encouraging. Women who underwent trials said the product was very good. They even said that they would prefer this gel before going for intercourse. It may have been stimulating,” said Melissa May from Population Council.

The findings of Population Council scientists show Carraguard with zinc slightly increases the microbicides activity against HIV-1. PC815 will undergo first level trials later this year. The new product has already shown significantly increased activity against herpes simplex virus type 2 which causes genital herpes. Latest findings also show that the formulation is useful in the case of unprotected sex. The new combination even shows increased activity against trichomoniasis — a sexually transmitted disease that may cause infertility. “We discovered that MIV150 was not getting absorbed in the body. Such a product can be excellent when in gel or cream form. Thus we are trying to develop a product which is based on it,” said May. If the drug is absorbed it can interact adversely with other medications the person is taking and cause unwanted side-effects. But, says May: “Extensive toxicology studies have shown that MIV150 is safe and well tolerated.”

Of five major products that underwent trials in the first phase in 2000, only two are still being tested. The rests of the products were dumped because the trials were not encouraging. Scientists are now concentrating on a new set of products derived from anti-retroviral drugs —used as a treatment for HIV.

“ARVs in microbicide research - keeping hope alive?”

Date: 25 February 2008

Source: *Plus News*

<http://www.irinnews.org/Report.aspx?ReportId=76940>

After a string of depressing trial results, the fourth international microbicides conference in New Delhi, India, kicked off this week with a ray of hope that new research could deliver a new generation of HIV prevention approaches for women.

It has been a disappointing year for scientists and activists. First, there was the early closure of clinical trials using a cellulose sulphate-based microbicide, after preliminary findings indicated higher HIV infections among the trial group. Then came last week’s announcement from the US-based reproductive health organisation, Population Council, that Carraguard - the first microbicide to complete the advanced stage of clinical testing - had failed to prevent HIV infection.

Pamela Mthembu, of South Africa’s Medical Research Council, has found all this gloom hard to take. She has been working to educate communities in KwaZulu-Natal about microbicides - the province hardest hit by the HIV/AIDS epidemic - and told IRIN/PlusNews that “delivering bad news” was the hardest part of her job.

The Carraguard setback had been particularly disappointing because there was “so much hope” pinned to the product, said Dr Salim Abdool-Karim, director of the Centre for the AIDS Programme of Research in South Africa (CAPRISA).

Microbicides are usually creams or gels applied inside the vagina or rectum to prevent sexually transmitted infections (STIs), including HIV; they have generated a high level of interest because they give women control over protection decisions.

But the latest reverse has raised the fear that donor and government support for microbicides could fade. However, Dr Sharon Hillier, a principal investigator with the US-based Microbicides Trials Network (MTN), warned that “it would be really naïve” to expect all the microbicide products tested so far to have been successful. “We’re not there yet. Only three ... [substances] have gone through [for testing: cellulose sulphate, Nonoxyl9 and Carraguard]. That’s it ... we don’t need to beat ourselves up so much,” she told microbicide advocates at a workshop ahead of the conference. “Our failures should only renew our interest because we’re in a place of great hope in HIV prevention research.”

Are ARV-based microbicides the solution?

A new buzz has now been generated by the concept of microbicides based on antiretroviral (ARV) drugs, with researchers trying to discover whether ARVs - which prolong the lives of people who are HIV positive - might also prevent HIV infection if they are used as externally applied microbicides.

In the same way that the ARV drug, nevirapine, has been used as a prophylactic in mother-to-child transmission of the virus, researchers are hoping that adding an ARV compound to a cream or gel could create a microbicide that would prevent a woman exposed to HIV during sex from becoming infected.

On Monday, 25 February, MTN released the results of a phase-two study on the safety of a vaginal microbicide containing the ARV drug, tenofovir, which found that sexually active HIV-negative women

could use the gel safely every day for an extended period of time. The women's adherence to the product was also high. "Finding that daily use is both safe and feasible is important, because we believe a daily approach may provide more sustainable protection against the virus in women who can't always predict when they will have sex," said the MTN's Hillier.

Researchers from the CAPRISA centre in Durban, South Africa, are now investigating whether the tenofovir gel can protect women from HIV infection. In October 2008, MTN will embark on a larger study of tenofovir gel, involving over 4,000 women in Africa. They will also test whether taking ARV pills orally is an effective form of HIV prevention.

MTN's John Mellors acknowledged that using the same drugs to prevent HIV as are used to treat HIV was "not an optimal situation", but was the "most likely route to success". One of the biggest concerns is drug resistance. CAPRISA's Abdool-Karim told IRIN/PlusNews that if a woman stayed negative while using an ARV-based microbicide, drug resistance was not an issue; but women who became positive while using the microbicide could develop resistance to treatment. "It's a concern we take very, very seriously and it's going to require a huge effort in monitoring and measuring resistance, and other concerns," said Karim.

"Experimental anti-HIV gel safe, tolerable for women: study"

Date: 25 February 2008

Source: *Agence France Presse*

http://news.yahoo.com/s/afp/20080226/hl_afp/healthusindiaaids_080226022057

The quest to develop a vaginal gel to prevent HIV infection took a step forward Monday when researchers announced that one such gel is safe for women to use on a daily basis. The announcement comes a week after researchers announced that the first prototype to complete advanced clinical trials was ineffective in preventing infection.

Microbicides are one of the most eagerly-sought avenues in the war on AIDS, where at present there is neither a cure nor a vaccine and prevention depends on the condom or abstinence. Scientists are grappling for a means by which women, who are physically more at risk from AIDS infection than men, can protect themselves without having to rely on male consent to wear a condom. A number of different gels are currently being tested around the world but none have been proven to be effective and some have even increased the risk of contracting HIV. This latest attempt by researchers in the United States and India is still in the early stages.

Researchers asked 200 sexually-active, HIV-negative women in New York and Pune, India to apply the gel either daily or before intercourse for a period of six months. They were also asked to use condoms in addition to the gel. The researchers found no disruption of liver, blood or kidney function and found a significant willingness among the women to follow the treatment guidelines. More than 90 percent of the women said they would seriously consider using the gel if it were approved to help prevent HIV infection and more than 80 percent had followed the experimental regime. "Based on what we have learned we can proceed with greater confidence on a path that will answer whether tenofovir gel and other gels with HIV-specific compounds will be able to prevent sexual transmission of HIV in women when other approaches have failed to do so," said lead investigator Sharon Hillier, director of reproductive infectious diseases at the University of Pittsburgh School of Medicine.

The findings were presented Monday at an international microbicides meeting in New Delhi.

An estimated 33.2 million people, in a range from 30.6 to 36.1 million, are living with AIDS or the human immunodeficiency virus (HIV) that causes it, the specialised UN agency UNAIDS says.

“Microbicides conference begins”

Date: 25 February 2008

Source: *The Tribune News Service*

<http://www.tribuneindia.com/2008/20080226/delhi.htm#6>

The four-day International Microbicides Conference to identify safe, effective and accessible microbicide began in the Capital yesterday. It is for the first time that such a meeting is being held in the Asian region. Indian Council for Medical Research (ICMR) had organised the meet. Union health minister Anbumani Ramadoss inaugurated the conference. Over 1100 delegates would attend the four-day meet.

Microbicides refer to a range of different products that share one common characteristic — the ability to prevent sexual transmission of HIV and other sexually transmitted infections when applied topically. A variety of microbicides are being researched which could be delivered in forms like — gel, cream, suppositories, films, sponge or ring. Microbicides are currently under research & development.

The delegates comprising researchers, public health workers, communities and advocacy organisations debilitated over the research and development of an effective microbicide. The biannual International Microbicides Conference has become one of the most important scientific and networking conferences in the fight against HIV/AIDS.

Maintaining global commitment to this effort requires continued pressure from scientists and advocates who are working on microbicides. The conference allows critical research field to be continuously profiled and developed. It provides updates on recent microbicides research, creates a forum for discussion of developments in microbicides research and presents opportunities for knowledge sharing between microbicides researchers, public health workers, advocates, communities and civil society organisations.

Despite the knowledge of successful HIV prevention strategy, HIV continues to spread at an alarming rate, especially among women in developing countries. Specifically, there are about 2.5 million cases of HIV in India. The prevalence rate of HIV among 15-49 years age group is 0.9 per cent and a mere 0.1 per cent increase in the HIV prevalence would result in addition of 0.5 millions new cases. The use of current HIV controlled methods such as abstinence, monogamy and condoms – males/females are not always feasible. Therefore, there is an urgent need to have other HIV prevention technologies, which are women initiated.

“Microbicide gel with AIDS drug marks vital success”

Date: 25 February 2008

Source: *IANS*

<http://in.news.yahoo.com/indiaabroad/20080225/r t ians hl/thl-microbicide-gel-with-aids-drug-marks-b9640bb.html>

The world’s first microbicide gel for women with an AIDS drug has successfully crossed Phase II trials in three places including India, holding out promise of an effective method to prevent transmission of the deadly health condition. “The microbicide with Tenofovir has crossed the wider safety test during the Phase II trials. It’s really a very good development and brings with it hope for millions of women across the globe,” Nomita Chandhok, deputy director general of the Indian Council of Medical Research (ICMR), told IANS.

There are nearly 20 million HIV/AIDS women patients worldwide.

Microbicides are a compound with the ability to protect against sexually transmitted disease. With a combination of an anti-retroviral drug (AIDS drug), it will help protect the women from contracting HIV/AIDS. The microbicide is in a gel form to be applied inside the vagina.

“The Phase III trials will be conducted among volunteers across the globe and the final results are expected in around a year-and-a-half,” Chandhok said. During the Phase II trials, scientists at the National AIDS Research Institute (NARI), Pune, an ICMR regulated institute, conducted the tests on 100 non-HIV women. “The women are in the reproductive age group and had used the gel regularly, both before and after sex. The gel passed the wide safety tests very well. The safety profile among these volunteers was good and it seems to be a widely acceptable gel,” Chandhok said. N.C. Jain, another ICMR scientist, said: “Though we don’t have a ready-to-use product now but the future looks bright.”

Nearly 1,000 researchers and scientists from several countries, including around 300 from the US, are in the capital to participate in a microbicide conference. With first-generation microbicides like Carraguard and Ushercell having failed during clinical trials, scientists are now keeping their fingers crossed for achieving a breakthrough with Tenofovir.

The clinical trials of the microbicide with Tenofovir were carried out in Pune and two other places in the US. The third phase is likely to be carried out on 5,000 women. The Phase-II (B) trial was also carried out on 1,000 women, mainly from South Africa, the most AIDS endemic country in the world. Experts said that over 85 percent of those who volunteered for the study were happy with it and only 11 percent were not. At least 40 percent said it was easy to use. “Overall we can say the response was good,” said another scientist.

“Microbicides 2008: First hint of efficacy in rectal microbicide trial, thanks to new biopsy assay”

Author(s): Gus Cairns

Date: 25 February 2008

Source: *Aidsmap.com News*

<http://www.aidsmap.com/en/news/357B9187-9B33-45D8-AA17-570A37781B29.asp>

Preliminary, still blinded data presented to the 2008 Microbicides Conference in Delhi today offered a strong hint that a rectal microbicide gel containing a non-nucleoside HIV drug may prove to be effective at stopping infection in humans.

The same preliminary analysis also seems to indicate that the drug may be safe, at least if volunteer reports, and the results of a battery of tests of inflammation marker chemicals, are reliable indicators of likely harm.

The trial

Peter Anton of the ‘U19’ rectal microbicide programme was presenting data from the first 19 of 28 subjects enrolled into a phase I safety study of two doses of a microbicide gel containing the NNRTI drug UC-781. This programme, funded by the US National Institutes of Health, is the first series of studies to trial rectal microbicides in human subjects. It involves a series of double-blinded trials, currently comparing two doses of UC-781 (1% and 2.5%) with placebo; as the programme progresses this may be narrowed down to one dose.

This initial study is primarily designed as an acceptability study. However the use of some innovative inflammation markers and assays allows early educated guesses to be made about toxicity and even eventual efficacy.

In this study 36 male and female volunteers were screened at the beginning of the trial for exclusion criteria such as HIV and STI infection. Those enrolled inserted a measured dose of the UC-781 gel with a rectal applicator at two separate timepoints. At baseline and both times after gel application, biopsies – small sections of rectal tissue – were taken for the safety and drug efficacy assays – of which more below. At the same time samples of rectal fluid/mucus were taken for evaluation of soluble proteins.

On the second week of the study volunteers applied a single dose of UC-781 gel or placebo under supervised conditions, and biopsies were taken immediately afterwards (within 30 minutes).

After a rest period, volunteers were then issued with a week's worth of gel doses, again in applicators, which they used every day at home on the sixth week of the study. At the end of this week they returned to the research centre for more biopsies to be taken. Anton emphasised that each biopsy, of which typically 15 were taken from each subject at distances of 10cm and 30cm into the rectum, were small and painless procedures.

Adverse events and toxicity

Anton was presenting data from the 19 out of 28 subjects who have completed all visits. Importantly, all the data he was presenting was blinded: so we cannot be sure whether results are due to the microbicide, the placebo, the participants, or chance. However they do describe general changes within the trial population over time.

In terms of safety there were no serious adverse events (grade 3 or 4). There were seven minor events reported from four participants, but four of these (diarrhoea, bloating and abdominal discomfort) were reported by a single participant at the single-dose visit – and were probably due to his previous meal.

There were also preliminary, blinded safety data available in terms of laboratory markers of toxicity. The U-19 programme will use a whole battery of tests to try and find any indication of cellular toxicity or inflammation in gel recipients. Conscious that the rectum has been largely 'unknown territory' in terms of what constitutes a 'normal' immune picture, this had to involve a lot of preliminary studies to assess benchmarks – see this report.

The early data also showed no difference between the trial groups in terms of macroscopic or microscopic cell damage, nor any signal of an inflammatory response in terms of the levels of a large number of different cytokines and chemokines (soluble inflammatory proteins produced in response to injury).

A hint of efficacy, and a way of estimating it

The really innovative aspect of this trial is the way the biopsies are being used as 'surrogate markers' for HIV seroconversion.

Microbicide studies have suffered from the huge disadvantage that up till now there has been no early way of estimating their likely protective effect in humans. Animal models can give unreliable results and there have been no 'correlates of protection' such as the immunogenicity markers that have been used in vaccine trials to select promising candidates (though those are currently being called into question). The only way up until now has been to put on a huge and expensive efficacy trial on the basis of results in a handful of monkeys, or even in vitro data, and hope the candidate proves to be effective.

The U19 Programme is getting round this by using an 'in vivo-ex vivo' HIV infection model. In this, volunteers use the microbicide or placebo gel as instructed, and biopsies are taken. These are then cultivated as cellular explants – small pieces of tissue kept alive on gel rafts in a nutrient medium. Two hours after being set up, the explants are then incubated with HIV. The proportion that get infected with HIV is then determined by measuring the amount of the HIV p24 protein in the culture medium over the

next month (which typically grows exponentially in cases of infection). In this study, explants were infected with two different doses of HIV, one containing 100 times more virus than the other. The stronger of the two doses should in theory infect 100% of biopsies containing cells expressing the CCR5 HIV co-receptor.

Ninety-six per cent of volunteers' biopsies taken at baseline, before any gel application, were infected with HIV (i.e. 18 out of 19 subjects – one person's biopsies stubbornly resisted HIV infection throughout, despite his having CCR5-expressing cells).

At the three-week visit, one-third of the explants grown from biopsies taken immediately after gel application (six subjects) resisted infection with the higher dose of virus, while another third showed reduced p24 expression. The final third were infected just as easily.

This pattern was not observed at week seven. This is probably, Anton commented, because biopsies were taken the morning after the last day of gel use, in other words anything between ten and 24 hours after the last possible exposure to UC-781. "It would be convenient to anticipate from this blinded data," said Anton, "that the high drug dose group will turn out to be the ones whose cells showed no response." And, he might have added, the lower dose group those with a blunted response.

However, this being blinded data, with full unblinded results not available until the end of this year, anything could turn out to be the case, ranging from complete concordance with microbicide use to a worst-case perverse response in which the lower rate of infections turn out to be in those who received placebo. At the moment all we can say is that the 33/33/33 split in cellular response is suggestive.

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“Tests of new AIDS gel show promise for women”

Author(s): Maggie Fox

Date: 25 February 2008

Source: *Reuters*

<http://www.reuters.com/article/healthNews/idUSN2417051220080225?feedType=RSS&feedName=healthNews>

A gel that uses a popular HIV drug to protect women from the AIDS virus is safe and acceptable to women, although it is too early to know if it actually prevents infection, researchers reported on Monday.

The gel uses the drug tenofovir, sold under the name Viread by Gilead Sciences Inc. The study, released at a meeting of AIDS researchers in India, is a welcome piece of good news for the struggling field of microbicides. It involved 200 sexually active HIV-negative women in the United States and India.

“The gel is safe to use, and well tolerated by HIV-negative women. That’s a key message in our findings,” said Dr. Craig Hoesley of the University of Alabama at Birmingham. “This sets the stage for larger studies to see if tenofovir can prevent HIV infection.”

Microbicides are products, such as gels or creams, that can be applied vaginally or anally to prevent transmission of the human immunodeficiency virus that causes AIDS. Just last week a study showed one candidate, called Carraguard, did not protect women from infection. Two other potential microbicides have made women more likely to become infected – a spermicide called nonoxynol-9 and a product called Ushercell, made by Toronto, Canada-based Polydex Pharmaceuticals.

The tenofovir product appears to be safe, said the research team, funded by the National Institutes of Health, found. It is the first potential microbicide to use a licensed AIDS drug. It was a phase II clinical trial designed to show safety, not that it was effective. “It is a critical time for all of us engaged in HIV prevention, and I truly believe we are turning a corner,” said Sharon Hillier of the University of Pittsburgh School of Medicine, who led the study.

Women make up 46 percent of the 33.2 million people infected with the AIDS virus, according to the United Nations Agency UNAIDS.

Hillier said it is not clear how long tenofovir stays in a woman's vagina. “Currently, there are very encouraging studies suggesting that even when tenofovir is gone from the vagina the drug itself is there in the vaginal tissue,” Hillier said in an e-mail. “The important thing we learned is that covert use, or secret use, is not an important parameter for women, and that in fact we found that 12 percent of the women who used to the gel said it made sex more pleasurable and none of the women said that the gel made sex less pleasurable.” Eighty percent of the women told to use gel within two hours of having sex said they had done so. “We asked women ‘How acceptable is this as a prevention option, is it too messy, is it a nuisance, and will you use it?’ Our study showed they will use it and they’re not bothered by the gel,” Hoesley said.

“HIV prevention gel passes safety trial at UAB”

Author(s): Dave Parks

Date: 25 February 2008

Source: *The Birmingham News*

<http://www.al.com/birminghamnews/stories/index.ssf?/base/living/120393093586860.xml&coll=2>

An experimental gel formulated to prevent the transmission of HIV has passed an important human safety trial, indicating that it could be used by women daily, according to an announcement scheduled today by researchers from UAB and the University of Pittsburgh School of Medicine.

The vaginal gel, called tenofovir, contains a class of anti-retroviral drugs that block the ability of HIV to replicate, and public health authorities hope that the self-applied gel could help stem the AIDS pandemic. Tenofovir was developed by Gilead Sciences of Foster City, Calif., and is being tested through the Microbicide Trials Network, which includes the University of Alabama at Birmingham and Pittsburgh School of Medicine.

The researchers were at an international conference in India today and planned to announce that the gel was successfully tested for safety by 200 women. “The gel is safe to use, and well tolerated by HIV-negative women,” Dr. Craig J. Hoesley of UAB's Division of Infectious Diseases said in a prepared release. “This sets the stage for larger studies to see if tenofovir can prevent HIV infection.”

Women in the safety study were from Alabama, New York, Pennsylvania and India. Hoesley reported that 90 percent of the study participants said they would consider using the gel to protect themselves from HIV, and they didn't find the gel too messy or inconvenient.

“India to develop microbicides at earliest: Ramadoss”

Date: 24 February 2008

Source: *Press Trust of India*

http://economictimes.indiatimes.com/News/News_By_Industry/Healthcare_Biotech/Biotech/India_to_develop_microbicides_at_earliest_Ramadoss/articleshow/2810383.cms

India today said developing microbicides was on the top of its priority list and they will be developed in the earliest possible time to prevent transmission of STDs and HIV/AIDS to women. “Microbicides are still in research process. We are expecting vaccines (to prevent HIV/AIDS) to come out early but it will take some more time. Experts say that microbicides will come early,” Union Health Minister Anbumani Ramadoss said here today on the sidelines of Microbicides 2008 conference.

“At the moment 50 experimental substances as possible. Vaginal microbicides are being examined and about quarter of these agents are at various stages of human testing and four of these are in advanced stages of clinical trials,” he said.

Microbicides are the products that can be used as creams, gels and other products to stop the transmission of HIV and sexually transmitted diseases (STDs) from one person to another.

Women can apply these products in their genitals to prevent infection being transferred to them. Although scientists are working on several different products but they have not succeeded in developing one.

“Women are biologically more susceptible than men to many STDs including HIV. HIV infection in women is increasing faster than in men,” Ramadoss said, adding “Hence women need a product that they can control and even use without their partners’ consent or knowledge.” Effective microbicides would offer an alternative method of protection to them, the health minister said.

The global figures up to 2006 show that estimated HIV/AIDS cases are 39.5 million, out of which 48 per cent are women. In India, estimated HIV/AIDS cases are 2.5 million, out of which 39 per cent are women.

“Ramadoss concerned over HIV infection”

Date: 24 February 2008

Source: *The Statesman*

The Union minister for health and family, Dr Anbumani Ramadoss, inaugurated the international conference on microbicides, 2008, to contain the fast growing HIV infection. Dr Ramadoss voiced his concern about gender equality, the empowerment of women and the improvement of maternal health. He expressed concern about the fast growing problem of HIV infection among women and suggested safe steps for sex, including the use of condoms which provided more effective protection against sexually transmitted diseases (STDs) like HIV.

For couples who didn't use condoms consistently and correctly, safe and effective microbicides would offer an alternative method of protection. “Many men are unwilling to use condoms all the time, if at all,” said Mr Lori Heise of the Center for Health and Gender Equity (CHANGE).

Speaking to media persons, the Union minister said, “The new technology of invisible HIV condoms will go a long way in this direction. Microbicides become natural companion products,” said Dr Ramadoss.

The Union minister emphasized on regular campaigning to create awareness among the people, which could save their lives. Dr Ramadoss also stressed the need of increasing the tax on liquor and chewing pan masala. He also criticized the promotion of cigarette smoking by Shah Ruhk Kahn and said “creativity should be used to save life, not to take life.”

He evinced interest for introducing a policy, which would link contraception with safe sex. He also stressed the need to empower women by introducing injectable contraceptives and safe birth practices and other modes through the training of anaesthetic agents.

“Microbicide gel passes safety test”

Author(s): Kounteya Sinha

Date: 23 February 2008

Source: *The Times of India*

http://timesofindia.indiatimes.com/Microbicide_gel_passes_safety_test/articleshow/2806265.cms

The world’s first microbicide gel, that has an anti-retroviral (ARV) drug as its active ingredient, has passed the safety test. Scientists at National Aids Research Institute, Pune, who have been conducting phase-II trials of Tenofovir gel to look at its safety and acceptability, told TOI that “the overall safety profile of the vaginal gel is good”.

According to Smita Joshi from NARI, 100 women in their reproductive age, who used the gel daily or two hours after sex for 24 weeks, reported no side-effects. Joshi and Dr Sharon Hillier, principal investigator for the Microbicide Trials Network, plan to make this announcement at Microbicides 2008 - the biannual international conference to discuss the latest development in microbicides, that begins on Delhi on Sunday. According to Joshi, the study involved 200 HIV- negative women at three sites - NARI, Bronx-Lebanon Hospital Center and University of Alabama at Birmingham. The study started in August 2006 and was completed by September 2007.

Tenofovir gel is an advanced second-generation HIV-specific microbicide that does not try to kill the AIDS virus or block HIV from entering the body as its predecessors tried to do. Instead, it is designed to prevent the HIV virus from replicating when the virus comes in contact with an uninfected T-cell. The virus will therefore fail to survive long enough to cause systemic infection.

Tenofovir gel has another significant advantage - it has a long intracellular half-life. The Phase-II B trial presently being undertaken on nearly 1,000 women in South Africa is trying to see whether women who apply the gel up to 12 hours before having sex and within 12 hours of having sex, are protected or not.

Microbicides are products, such as gels or creams, that could be applied vaginally to prevent HIV transmission. With two of the most promising first-generation microbicides - Carraguard and Ushercell - failing to protect women against HIV infection, the world’s top HIV/AIDS scientists now have their hopes pinned on second-generation microbicides.

Namita Chandhiok, deputy director-general of ICMR’s division of reproductive health and nutrition, said, “The first-generation microbicides were non-specific and were developed to protect against HIV and other sexually transmitted diseases. The second-generation candidates, which are under trial, are specifically created to combat HIV as they contain ARVs. Tenofovir is characterised by its ability to enter and inhibit viral replication, where it may form protective reservoirs of active drug. We hope they prove effective.”

Kamini Walia from ICMR's epidemiology and communicable diseases division, however, added, "STDs causing genital ulcerations makes people more vulnerable to HIV infection. Microbicides therefore should be able to protect women against HIV and STDs."

Tenofovir is the active ingredient in Gilead's popular oral ARV drug Viread. Animal studies demonstrated the potential of Tenofovir to prevent transmission by 100 per cent.

WHO estimates that half of the 39 million people infected with HIV today are women.

"Microbicides: why are they significant? (Part 1)"

Date: 20 February 2008

Source: UNAIDS

http://www.unaids.org/en/KnowledgeCentre/Resources/FeatureStories/archive/2008/20080218_Microbicides_why_are_they_significant_Part1.asp

Ahead of next week's biannual international microbicides conference Microbicides 2008 running 24 - 27 February in New Delhi we take an in-depth look at microbicides. In part 1 of this 2-part series we look at why they are considered significant in the response to HIV. In part 2 the challenges to the development of this biomedical prevention technology will be explored.

With 2.5 million people newly infected with HIV in 2007 there is global consensus on the need for new HIV prevention technologies to complement existing strategies. While the search for a HIV vaccine looks set to continue for some years, many believe that with similar investment a successful microbicide could be developed much sooner. An effective microbicide would offer significant protection to women who currently comprise about half of all people living with HIV worldwide.

UNAIDS works with number of microbicide networks to highlight the critical need for female-controlled prevention options. Along with other global advocates, UNAIDS continues to emphasize the importance of a concerted effort to develop microbicides and make them accessible to the people that need them. Addressing women's needs for HIV prevention is vital for curbing the epidemic.

Why do women need specific HIV protection?

It is an uncomfortable reality that many women across the globe do not have power over what happens to their own bodies. Deep-seated social and cultural norms and the effects of gender inequality mean many women and girls live with violence or the threat of violence and are unable to successfully negotiate fidelity or condom use. Women who sell sexual services are often unable to negotiate the wearing of condoms with their clients. Even women abstained from intercourse before marriage and have only one sexual partner can be vulnerable to sexually transmitted infections from partners if that partner engages in unprotected sex with other women or men.

Due to biological differences, in unprotected heterosexual intercourse women are at least twice as likely as men to acquire HIV from an infected partner. HIV data reflects this, for example among young people (15-24 years) in sub-Saharan Africa an estimated three young women are HIV-positive for every young man.

Experts believe if women have the option of using a microbicide to protect themselves from HIV it could make all the difference to their lives. "A man may refuse to wear a condom and his partner may be powerless to insist. Access to safe and effective microbicides will offer women more choices and help them take charge of their sexual health and their future," said Director of the Global Coalition on Women

and AIDS, Kristan Schoultz. “Microbicides will be a key tool in empowering women, and in halting the alarming spread of HIV infection among women,” she added.

What is a microbicide?

A microbicide is a compound whose purpose is to reduce the infectivity of viruses or bacteria. The term has come to refer to a potential product which would prevent the transmission of HIV and other sexually transmitted infections (STIs) inside a woman’s vagina. A rectal microbicide would act similarly to protect men who have sex with men and women during anal intercourse.

There are different candidate microbicide products currently under research and development; many are in the form of a gel or cream to be applied to the surface of the vagina. Scientists are also exploring other ways of drug delivery such as by a vaginal ring which would be inserted into the vagina and provide controlled release of an effective microbicide.

Mechanisms of action

A successful topical microbicide - applied to the vagina surface - would probably act in a combination of ways. Scientists are researching different products which would:

1. Kill pathogens without damaging the healthy cells of the vagina
2. Strengthen the body’s natural defence system by increasing the natural acidity of vagina inactivating pathogenic viruses and bacteria
3. Inhibit the virus getting into the white blood cells - the target cells of HIV
4. Inhibit viral replication by using derivatives from anti-retroviral drugs

For some women, it is important that the action of the microbicide not impair their ability to conceive a baby. Both contraceptive and non-contraceptive microbicides are currently under development, as well as rectal microbicides for heterosexual women and men who have sex with men.

No silver bullet

Some advocates believe that the successful development of a microbicide would bring significant emancipation for women who due to cultural, economic and social drivers are disempowered and unable to protect themselves from HIV.

With the stakes so high, microbicides seem like a very attractive solution. However experts are realistic about the complexity of the research task and drug efficacy and urge caution over raising unrealistic expectations.

Successful microbicides products will be partially protective. Although they may be up to 80% effective in preventing the transmission of HIV during sexual intercourse, they would need to be complimented by other prevention tools in a combination prevention strategy.

A comprehensive HIV prevention package includes, but is not limited to, delaying sexual debut, mutual fidelity, reduction of the number of sexual partners, avoidance of penetration, safer sex including correct and consistent male and female condom use, and early and effective treatment for sexually transmitted infections.

In part 2 we look at the challenges in current microbicide research and development and explore why there is a large funding gap between what is needed to bring clinical trials to completion and lay groundwork for effective distribution and what is currently available. We also look at the ethical considerations of clinical trials.

“Microbicides: challenges to development and distribution (Part 2)”

Source: UNAIDS

http://www.unaids.org/en/KnowledgeCentre/Resources/FeatureStories/archive/2008/20080222-microbicides_Part_2.asp

The biannual international microbicides conference "Microbicides 2008" will run 24 - 27 February in New Delhi under the theme "Striving towards HIV Prevention". The gathering will enable knowledge-sharing between microbicide researchers, public health workers and advocacy organizations and will provide a forum for the discussion of new developments in microbicide research including basic science, clinical trials and social science issues as well as discussion on behaviour, community engagement and advocacy. In the second of a two part series looking at microbicides, we will be exploring some of these topics.

For several years, UNAIDS has insisted that the development of an effective microbicide is a public health priority and has emphasized the importance of access and affordability. However due to a lack of significant investment, the research and development pipeline has been slow and inefficient. UNAIDS Executive Director, Dr Peter Piot said, "The international community, including the private sector, must continue to invest in effective HIV prevention technologies that can be used by women."

"Ensuring access to safe and effective microbicides will be of critical importance to all our prevention efforts and to our goal of stopping and reversing the epidemic."

The cost of saving lives

The total global funding for microbicide research and development in 2006 done by the non-commercial sectors was \$217 million. The pharmaceutical sector chooses to invest into the search for new antiretroviral drugs, attracted by a potentially large return-on-investment. If there was comparable investment into microbicide research, it is thought that a safe and effective product would be on the market much sooner than a vaccine. However, as any microbicide would have to be affordable to consumers to whom it would make most difference - women living in low- and middle-income countries - the profit margins would be low. This economic reality makes microbicide research a less attractive investment. As a consequence virtually all microbicide research is conducted by small biotech companies funded by the public sector.

Research and development pipeline

Research and development is continuing in spite of the large funding gap. More investment will be needed to bring clinical trials to completion and lay groundwork for distribution of an effective product. As with any new drug, candidate microbicides must pass a series of rigorous laboratory tests and then a series of human clinical trials.

What are the different phases of a clinical trial?

Phase I clinical trials are the first stage of testing in humans and are designed to evaluate safety. Normally the trials are conducted in an inpatient clinic, where volunteers can be monitored closely. A group of 20-80 healthy volunteers will use the product for 1-2 weeks.

Once the initial safety of the study drug has been confirmed in Phase I trials, Phase II trials are performed on larger groups of 20-300 and are designed to assess how well the product works, as well as to continue safety and tolerability assessments in a larger group of volunteers over 6-18 months.

When the development process for a new drug fails, this usually occurs during Phase II trials when the drug is discovered to show no evidence of potential effect, or found to have toxic effects.

Phase III studies are randomized controlled multi-centre trials on large groups (300-3,000 or more) and are aimed at being the definitive assessment of how effective and safe the drug is. Because of their large size and duration (1-2 years), Phase III trials are the most expensive, time-consuming and difficult trials to design and run.

A range of contraceptive and non-contraceptive microbicide products are currently in different phases of development and trial including over 30 candidates in clinical trials. More than 30 others are in pre-clinical testing. However, results to date have been disappointing.

The microbicide search had an unexpected setback in February 2007 when an advanced Phase III study of a candidate microbicide Cellulose Sulfate was stopped early because women who used the gel were suspected to have a higher risk of HIV infection compared with women in the placebo group.

Earlier this week it was announced that Carraguard, a candidate microbicide that had completed large-scale Phase III trials, was unable to prevent HIV transmission. Encouragingly the product was found to be safe for long-term vaginal use making it the first microbicide Phase III trial to be completed without safety concerns. Researchers are hopeful this is a finding which will be built on.

“The next generation of antiretroviral-based microbicide products holds much promise. We do need to develop better safety biomarkers and improve measurements of adherence and we can learn much more from trials which have not resulted in an effective product,” said UNAIDS Chief Scientific Adviser, Dr Catherine Hankins.

Timing of microbicide availability

The Global Campaign for Microbicides estimated that if one of the products in advanced clinical trials proves to be effective, a microbicide could be ready for distribution in a small number of countries by the end of 2010. However, if the current sets of products do not prove effective, the timeline will be longer.

Ethical considerations

Advocates and civil society work hard to ensure that as the science proceeds, the rights and interests of trial participants and their communities are protected. In microbicide trials all women are provided with a comprehensive HIV prevention package including counselling on condom use and safe sex, supplies of free, high quality condoms and regular screening for HIV and other sexually transmitted infections.

Well-run trials are vital to women’s positive perception of trial participation - participants have expressed the importance of having access to information, being treated with respect, having an opportunity to be listened to, access to HIV testing and counselling and access to condoms. It is also vital that trial designs take into account local social and community perceptions of HIV, health and sex and that participants who become HIV-positive during or after the trials have access to care and support services.

UNAIDS and AVAC have published “Good participatory practice guidelines for biomedical HIV prevention trials” which sets out ten principles for community engagement throughout the research life cycle.

International consensus has been reached and detailed in 19 guidance points on a range of topics including confidentiality, informed consent, control groups and potential harms, in the recently published UNAIDS/WHO guidance document “Ethical considerations in biomedical HIV prevention trials”.

Next steps

Next week’s Microbicide conference will be an important forum for the discussion of the challenging issues of research, financing, clinical trials and ethical considerations.

Experts will gather to hear updates on current and emerging candidate product trials and will debate a range of topics. UNAIDS Chief Scientific Adviser Dr Catherine Hankins will make presentations on the implications of the results of male circumcision trials for microbicide research and present findings from the December 2007 consultation “Making HIV trials work for women and adolescent girls”.

UNAIDS Executive Director Dr Peter Piot will address the conference closing ceremony which will be attended by politicians, policy-makers, scientists, community activists and other AIDS experts.

The London School of Hygiene and Tropical Medicine estimated by mathematical modelling that the introduction of even a 60% effective microbicide into the world's 73 lowest-income countries which would be used by only 20% of women already in contact with health services could avert up to 2.5 million infections in three years.

With many observers confident that a successful microbicide could make a significant impact in HIV prevention around the globe, the wait is all the more frustrating, the set-backs all the more disappointing.