

# NEW AGENTS AND VACCINES

In this regular feature we want to keep you up to date with exciting new information about the development of new therapeutic and preventive interventions. In this issue of *IATEC Update* we will discuss the recent developments in the field of vaginal microbicides.

## Vaginal microbicides containing non-nucleoside reverse transcriptase inhibitors

Microbicide development began over fifteen years ago, when optimism about the swift development of an HIV vaccine began to wane, and it was recognized that significant progress in HIV prevention could not be expected with the currently available HIV-prevention tools. Microbicides are being developed as products to be applied topically inside the vagina or rectum to prevent infection with HIV and potentially other sexually transmitted infections (STIs). They could be formulated as gels, creams, suppositories, or vaginal rings; they could be contraceptive or not; and they could be used alone or in combination with a physical barrier. Remarkable progress has been made in the microbicides field in recent years. According to the Alliance for Microbicide Development, 29 candidate products are in the pipeline. The majority of these are in pre-clinical stages of development, approximately ten are in Phase I and II safety trials, and five are in Phase IIb/III effectiveness trials.<sup>1</sup> Funding for the field has increased significantly, and the global movement for microbicides continues to grow. The field even established its own biennial international confer-

ence in 2000, with attendance steadily growing with each subsequent meeting.

Candidate microbicides are usually categorized based on their mechanism of action. The first generation includes compounds that directly kill or inactivate infectious pathogens (such as detergents), enhance naturally occurring vaginal defense mechanisms (such as bioengineered *lactobacilli* and acid buffers), or nonspecifically block pathogen attachment to receptors on target cells (such as anionic polymers). Detergents (particularly nonoxynol-9) have been shown to damage the cervicovaginal epithelium and cause acute inflammatory tissue responses, thereby potentially enhancing the sexual transmission of HIV.<sup>2,3</sup> Several anionic polymers (Carraguard, 0.5% and 2% PRO-2000, and cellulose sulfate), a *lactobacilli*-based product, and an acid buffer (BufferGel) did not show undesirable side effects and are currently in advanced stages of clinical testing.<sup>1</sup> However, some microbicide researchers worry that these products may not be sufficiently effective due to a lack of specific activity against HIV. The newer generation candidate microbicides include products containing antiretroviral compounds that specifically block entry of HIV in target cells, inhibit post-fusion events essential for infectivity, or inhibit intracellular replication. Five of such products are currently in clinical development: four products containing tight-binding non-nucleoside reverse transcriptase inhibitors (NNRTIs: TMC120 vaginal gel and ring, UC781 gel, and PC815 gel containing MIV150) and one containing a nucleotide-analogue reverse transcriptase inhibitor (NRTI: tenofovir gel).<sup>1,4</sup> Furthermore, pre-clinical work on

candidate microbicides containing entry inhibitors is ongoing.

The advantages of tight-binding NNRTIs are that they – unlike NRTIs – do not require metabolic activation to achieve antiviral activity. They are active against cell-free as well as cell-associated HIV-1, and against both R5 and X4 strains, in semen and in the vaginal environment. TMC120 is 50- to 100-fold, and UC781 5- to 10-fold more potent than conventional NNRTIs: in *in vitro*, *in vivo* and *ex vivo* studies, TMC120 prevented infection at nanomolar and UC781 at micromolar concentrations.<sup>4,6</sup> However, unlike UC781, TMC120 showed significant degradation and binding to serum albumin. The disadvantages of tight-binding NNRTIs are that they are capable of inducing drug resistance, and that they may not be able to prevent infection with HIV-1 isolates containing pre-existing resistance to NNRTIs. While TMC120 can adapt to changes in the NNRTI-binding pocket, *in vitro* data suggest that, over time, some degree of resistance against TMC120 does occur in HIV with the L100I and K103N mutations.<sup>4</sup> Studies have shown that UC781 induced drug resistance more easily than TMC120. The NNRTIs selected for use in candidate microbicides are generally not easily absorbed systemically to minimize drug resistance and systemic side effects. However, clinical studies have shown that some systemic absorption does occur (in the picogram per milliliter range, which is several orders of magnitude lower than absorption after oral administration).<sup>4</sup> It is currently unknown what the consequences are of such low levels of systemic absorption over long periods of time. Results of a Phase I clinical trial with TMC120

gel in Belgium have not given rise to any other safety concerns.<sup>7</sup> Additional safety trials with TMC120, and a trial with UC781, are currently ongoing.

An expert meeting, organized by the World Health Organization, the International Partnership for Microbicides, and the US Centers for Disease Control and Prevention in September 2004, concluded that trials of NNRTI-containing microbicides should proceed as quickly as possible, but that emergence of drug resistance in such trials should be closely monitored. Meeting participants thought that parallel studies in HIV-infected women (to study genital shedding and development of drug resistance) should also be considered. They agreed that study sponsors should ensure that study participants have access to effective antiretroviral therapy, even if they need an antiretroviral regimen that is not available in the national program (for example, due to emergence of drug resistance while participating in a study).

HIV is capable of establishing infection through multiple pathways involving a variety of target cells and co-receptors. It is not yet clear what the relative importance is of the various pathways. For this reason, and to minimize selection for resistant HIV strains, it is likely that combination products will be developed in the longer term. Combination products should ideally have broad-spectrum activity (protection against HIV, other STIs, and/or pregnancy), provide sequential blocking of events that take place before systemic HIV infection is established to maximize efficacy, minimize potential for resistance and ensure cross-clade activity. For example, one could combine an anionic

polymer gel with an entry inhibitor and an NNRTI. It may in the future also be possible to combine vaccination approaches that elicit a mucosal immune response in the genital tract with traditional vaginal microbicide approaches. Unfortunately, much work remains to be done before such combination products will reach human trials. However, some potential ingredients of combination pro-

ducts are already in (advanced) clinical development. The first results of Phase III effectiveness trials with anionic polymers are expected in 2007.

**JANNEKE VAN DE WIJGERT,  
IATEC FOUNDATION AND  
AMC CENTER FOR POVERTY-  
RELATED COMMUNICABLE  
DISEASES**

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# MENGO HOSPITAL MICROFINANCE PROJECT FOR HIV-INFECTED INDIVIDUALS

AIDED BY THE INTERNATIONAL SCHOOL HILVERSUM, THE NETHERLANDS, AND IATEC BV, AMSTERDAM, THE NETHERLANDS

In December 2004 a musical event at the 'International School Hilversum' in the Netherlands raised funds to support a number of African projects. A student of this school, Iris Nieuwenhuis, approached IATEC BV for assistance in choosing a program that could benefit directly from this initiative. Because of the existing collaboration between IATEC and Mengo Hospital in Kampala, Uganda, and the involvement of IATEC in international HIV clinical trials, the most appropriate start of the program was a project at Mengo Hospital for the benefit of HIV-infected individuals.

Mengo Hospital is one of the largest private hospitals in Uganda and is located in its capital, Kampala. It was founded in 1897 by Sir Albert Cook and Catherine Cook, members of the Church Missionary Society. Since the start as a 12-bed inpatient and outpatient clinic, operating from mud huts and focusing on malaria, sleeping sickness, gonorrhoea and tropical ulcers, the present hospital has developed into a modern multi-discipline complex. The hospital's vision is to offer health care to especially the poor population. It has 300 beds for inpatient care and offers a complete package of clinical services. Besides patient care, the hospital is involved in the training of medical doctors, nurses and midwives. The hospital also has a specialized Counseling and Home Care department. This department was set up in 1989 in order to provide better services to HIV/AIDS patients who were growing in number every day. The services offered are pre-test, post-test and ongoing counseling, a home visitation program for bed-ridden PLWA (People Living With AIDS), a good Samaritan clinic for opportunistic infections, a chest clinic that targets tuberculosis, and a children's club for infected and affected children. Mengo Hospital has also implemented an extensive community program offering outreach services. The hospital has started a department for antiretroviral therapy for HIV-infected clients, where at present  $\pm 100$  adults receive treatment at no cost. Instead of a 'one-time-only' donation a project was developed that would be continuous and self-sustainable with minimal initial investment.

The idea of the microfinance project was to start a small shop at the hospital compound selling utilities and commodities, snacks and drinks as needed by in- and outpatients and their visitors. The shop is to be run by a low-income HIV-infected individual for a period of four months after which period a new person will be assigned. During this period the shopkeeper will be reimbursed for transport and lunch on a weekly basis. The money needed for this reimbursement is deducted from the weekly profits made from selling products. After four months the shopkeeper receives a

significant share of the overall profits, which allows this person to start his/her own business. In this way the shop will gather its own stock renewal and expansion; the remaining profits will give at least four people per year a chance to build on their future and to generate their own income.

After agreement on the project with the donor a total of 500 Euros was granted to Uganda. Dr George Bukenya, the deputy medical director of Mengo Hospital, kindly contributed to this project by allowing the use of an existing 20-ft. container and allocating a convenient location on the hospital compound between the Maternity and Children's ward.

Approximately 250 Euros were spent on these activities. In January 2006 the remaining 250 Euros were used for buying the initial stock of the shop. On January 30, 2006 the shop opened its doors to customers. After the first week it became clear that in order to make this project successful an extra



Deputy Director Dr George Bukenya (Mengo Hospital), Dr Nadine Pakker (IATEC) and Mrs. Hanipha Kakooza (IATEC) agreeing on the microfinance project

investment was needed to buy a fridge and water cooker to accommodate for cold and hot drinks. Ever since the acquisition of these items by private sponsoring the weekly sales have been increasing.

Besides the money that is kept aside for the weekly reimbursement and end-of-period start-up capital of the shopkeeper, enough profit is currently being made to allow for a continuous expansion of stock according to the demands of the customers. The shop sells a wide variety of merchandise, such as hygienic products (soap, tooth paste, washing powder, lotions etc), plastic items (cups, saucers, basins, baths etc), cutlery, snacks, sweets and drinks (juice, sodas, tea, coffee). Some products, such as second-hand baby clothes and toys, were donated by friends and are sold at low prices.

After having been operational for 2.5 months it can be concluded that this microfinance project is a success. A net profit of  $\pm 300$  Euros has been made in nine weeks. Not only will this project provide an opportunity for the persons selected to run the shop, it will inspire positive living and have a beneficial spin-off to the extended families of the shopkeepers.

Special thanks to: Ms Joyce, current shopkeeper, Mrs. Hanipha Kakooza (IATEC), project assistant, inspiration and initiation of the project, Dr George Bukenya (Mengo Hospital), deputy director, support of hospital management, Mrs. Olivia Sendagalaa (Mengo Hospital), community worker, project supervisor, Mrs. Margaret Emudu (Mengo Hospital), community worker, project supervisor, Mrs. Catherine Mukasa (Mengo Hospital), community worker, project supervisor, Mr. Wilbert Sserwaniko (Mengo Hospital), community worker, project supervisor, and all who donated items to this project.

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