



ALLIANCE FOR MICROBICIDE DEVELOPMENT

28 March 2008, Volume 9, Number 13

The Alliance for Microbicide Development *News Digest* is an **unedited** compilation of:

- Media coverage of microbicides;
- Abstracts of articles on microbicides and relevant science in peer-reviewed journals;
- Material on other reproductive health and HIV prevention technologies, including HIV vaccines; and
- Matters of policy and politics with importance for microbicide research, development, and advocacy.

Its purpose is to:

- Raise awareness around the range of opinions and information about microbicides disseminated in the press and scientific journals; and
- Provide a neutral, objective basis for decision-making and evidence-based advocacy.

The *News Digest* is produced in a web-based format. Readers can view complete issues of the Digest or search by keyword for individual articles at <http://www.microbicide.org/publications/>. If you would like to be removed from the *Digest* distribution list, please send an email to digest@microbicide.org. We welcome comments, questions, and ideas about other microbicide-relevant topics we might cover, services we might provide, and better ways of providing them!

Areas covered in this News Digest:

1. MEDIA COVERAGE OF MICROBICIDES

- [The snip that could save his life](#)

2. PUBLISHED RESEARCH: MICROBICIDE-SPECIFIC

- [A fusion inhibitor prevents dendritic cell \(DC\) spread of immunodeficiency viruses but not DC activation of virus-specific T cells](#)
- [A randomized six-day safety study of an antiretroviral microbicide candidate UC781, a non-nucleoside reverse transcriptase inhibitor](#)
- [Aqueous extracts from peppermint, sage and lemon balm leaves display potent anti-HIV-1 activity by increasing the virion density](#)
- [Deciphering human immunodeficiency virus type 1 transmission and early envelope diversification by single-genome amplification and sequencing](#)

- Sulfated K5 Escherichia coli polysaccharide derivatives as wide-range inhibitors of genital types of human papillomavirus

3. PUBLISHED RESEARCH: RELEVANT BASIC AND TRANSLATIONAL SCIENCE

- Circumcision and risk of sexually transmitted infections in a birth cohort
- Genital ulcers facilitate rapid viral entry and dissemination following intravaginal inoculation with cell-associated simian immunodeficiency virus SIVmac239
- Herpes simplex virus type 2 acquisition during recent HIV infection does not influence plasma HIV levels
- Increased levels of HIV-1-infected cells in endocervical secretions after the luteinizing hormone surge
- Mucosal irritation potential of personal lubricants relates to product osmolality as detected by the slug mucosal irritation assay

4. HIV/AIDS VACCINES

- AIDS vaccine testing at crossroads
- Vaccine failure is setback in AIDS fight

5. OTHER PREVENTION APPROACHES

- Religious leaders test for HIV/AIDS

6. NON-HIV STIS AND REPRODUCTIVE HEALTH

- An epidemic no one wants to talk about

7. POLITICS AND POLICY

- FDA denies it is risk-averse on drugs
- UK to force drugmakers to share info
- HIV/AIDS threatening democracy, governance in southern Africa, study says
- Adaptive clinical trials: more talk than action

8. HIV/AIDS FUNDING

- In search of new ideas for global health

9. ANNOUNCEMENTS

- AVAC Launches Px Wire

1. MEDIA COVERAGE OF MICROBICIDES

"The snip that could save his life"

Date: 27 March 2008

Source: *Globe and Mail (Canada)*

Author(s): Stephanie Nolen

<http://www.theglobeandmail.com/servlet/story/RTGAM.20080327.wcircumcision27/BNStory/specialScienceandHealth/?pageRequested=1>

Zandi Dlamini ran a practised eye over the anxious young men in the waiting area before summoning the first one into her small counselling room. Shongwe Bonginkosi, 34, told her he was interested in having a cleaner penis, more hygienic generally. Ms. Dlamini nodded. She'd heard it hundreds of times before.

"Nobody ever says 'HIV,' " she said later. "They talk about hygiene, and better sexual performance. Never HIV." Even here, where nearly one in two men has the virus that causes AIDS, no one wants to admit to being afraid of it.

With Mr. Bonginkosi before her, Ms. Dlamini quickly explained how, in a few minutes, a doctor would make an incision at the top and middle of his penis, cut all the way around it, and slide off the "sleeve" of his foreskin. He would have local anesthetic, she said. He would have to come back a week later to have his stitches checked. He would have to abstain from sex for six weeks. The young man, a government clerk who had taken the day off, nodded, shifting in his seat, clasping and unclasping his fingers. She took him through a door to the back of the clinic, handed him a maroon surgical gown, told him to take off his pants and underwear and wait.

With the operation minutes away, Mr. Bonginkosi admitted HIV was also one of his motivations. "You can still get it if you are faithful," he said. He doesn't know about his girlfriend's previous sex life. He can't know, really, whether she is having sex only with him. He had heard that circumcision could help to protect him, and that's what brought him to the tiny clinic of the Family Life Association of Swaziland.

Once primarily a family-planning organization, the agency these days does a booming business in circumcision and has a waiting list of hundreds for its lone doctor, who does about 10 of the operations a day.

Swaziland, which has the highest rate of HIV infection in the world, 42 per cent of young adults, is eager to see as many men circumcised as possible. The government would like to offer the procedure to an estimated 200,000 sexually active men over the next five years. The problem here is a shortage of doctors, fewer than 100 for a country of one million.

The Family Life Association has been offering "Circumcision Saturdays," assembly-line procedures in various clinics around the country, but one day last fall the crowd of would-be patients was so large at a rural clinic that it turned into a small riot.

In the past few months, a piece of information long muted in the medical world has suddenly seeped into public consciousness in this tiny southern African country, and many of the other nations worst hit by AIDS: Circumcision helps to protect men from contracting HIV from infected female sexual partners. It's cheap, about \$82 an operation at this clinic, although the U.S. AIDS program is helping the Swazi government to offer it free. It's relatively easy. (A wincing Mr. Bonginkosi, when his anesthetic had worn off, was quick to point out that it is, however, initially very painful.)

It isn't just Swaziland: In most countries in east and southern Africa, private urologists are reporting an upsurge in demand from educated men who have heard about the research and can afford to have it done privately. And several countries are moving ahead with national plans to increase rates of circumcision.

In the perennially bleak work of the fight against AIDS, the hope offered by male circumcision is a rare piece of good news.

Research has shown that a circumcised man is 65 per cent less likely to contract HIV from a woman who has the virus than is a man whose penis still has a foreskin.

Circumcision appears to offer protection from heterosexual transmission of HIV in a number of different ways. First, the fragile inside of the foreskin is rich in a kind of white blood cell, called the Langerhans cell, which are favoured targets of HIV, which hooks itself on to them to gain entry to a new body. Remove the foreskin, and remove a key entry point.

Also, a circumcised penis develops a toughened layer of skin that is much harder for the virus to penetrate. And finally, circumcised men are less likely to contract herpes, syphilis, genital ulcers and other infections, all of which increase the likelihood of contracting the virus.

Research has not shown that a woman having sex with an HIV-infected circumcised male would be less likely to get the virus than one whose HIV-positive partner was not circumcised, but women do benefit from a larger "herd immunity" effect, in that if more men are circumcised, women are less likely to encounter an HIV-positive partner.

AIDS researchers often note that although hundreds of millions of dollars have been spent on research into vaccines and **microbicides** trying to figure out how to stop the virus, the condom remains the only successful piece of technology for blocking its spread. Meanwhile, behaviour-change campaigns pushing abstinence, fidelity or condom use have limited impact. In Africa, home to 70 per cent of the world's HIV-AIDS cases, where nearly half of men are not circumcised, the procedure could prevent millions of infections.

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EDITOR'S NOTE: *The full text of this article is available for public access at the above website.*

[Return to Table of Contents](#)

2. PUBLISHED RESEARCH: MICROBICIDE-SPECIFIC

"A fusion inhibitor prevents dendritic cell (DC) spread of immunodeficiency viruses but not DC activation of virus-specific T cells"

Author(s): Frank I, Stossel H, Getti A, et al

Reference: N/A Epub ahead of print.

<http://jvi.asm.org/cgi/content/abstract/JVI.01987-07v1?maxtoshow=&HITS=3&hits=3&RESULTFORMAT=&andorexacttitle=and&andorexacttitleabs=and&fulltext=microbicide%2C+microbicides&andorexactfulltext=or&searchid=1&usestrictdates=yes&resourcetype=HWCIT&ct>

Published Abstract: Dendritic cells (DCs) play a key role in innate immune responses, and their interactions with T cells are critical for the induction of adaptive immunity. However, immunodeficiency viruses are efficiently captured by DCs and can be transmitted to and amplified in CD4+ T cells, with potentially deleterious effects on the induction of immune responses. In DC-T cell co-cultures, contact with CD4+, not CD8+, T cells preferentially facilitated virus

movement to and release at immature and mature DC-T cell contact sites. This occurred within 5 minutes of DC-T cell contact. While the fusion inhibitor T-1249 did not prevent virus capture by DCs nor the release of viruses at the DC-T cell contact points, it readily blocked virus transfer to and amplification in CD4+ T cells. Higher doses of T-1249 were needed to block the more robust replication driven by mature DCs. Virus accumulated in DCs within T-1249-treated co-cultures but they were actually less infectious than DCs isolated from untreated co-cultures. Importantly, T-1249 did not interfere with the stimulation of virus-specific CD4+ and CD8+ T cell responses when present during virus-loading of DCs or for the time of the DC-T cell co-culture. These results provide clues to identifying strategies to prevent DC-driven virus amplification in CD4+ T cells, whilst maintaining virus-specific immunity, an objective critical in the development of **microbicides** and therapeutic vaccines.

"A randomized six-day safety study of an antiretroviral microbicide candidate UC781, a non-nucleoside reverse transcriptase inhibitor"

Author(s): Schwartz JL, Kovalevsky G, Lai JJ, et al

Reference: N/A 35(4):414-19.

<http://www.stdjournal.com/pt/re/std/abstract.00007435-200804000-00020.htm;jsessionid=HpLNQpwDkbFlhp8vxfJI6J0KX3hpxvBg0syQHKx5YvHx1c26pJqJ!923867264!181195629!8091!-1>

Published Abstract: *Goal:* This study evaluated the effect of a single dose and 5 additional consecutive daily doses of UC781 gel at concentrations of 0.1%, 0.25%, 1.0%, and 0% on urogenital irritation. *Study Design:* Forty-eight healthy sexually abstinent women were randomly assigned to 1 of 4 groups. *Methods:* Urogenital irritation was assessed by pelvic examination, colposcopy, and reports of genital symptoms at baseline and after 1 and 6 doses. Vaginal health was assessed by wet mount and systemic safety by laboratory evaluation after 1 and 6 doses, and UC781 levels were assessed at baseline and after 6 doses. *Results:* Some evidence of urogenital irritation was common in all treatment groups and was most often transient and mild. Colposcopic findings were infrequent in the placebo group (8%) and more common in the 3 treatment groups (24%-42%). Edema, which may indicate underlying inflammation, was observed in the vaginal fornix of 2 women exposed to UC781. There was no apparent increase in vaginal infection or clinically significant changes in laboratory values. Two of 12 participants randomized to 1% UC781 gel had detectable plasma levels that were less than the lower level of quantification. *Conclusions:* UC781 was well tolerated in this initial dose ranging safety study when used once daily for 6 days in sexually abstinent women. Five safety/pharmacokinetic studies of UC781 are currently underway in women and men, all utilizing UC781 concentrations less than 1%, with twice-daily dosing in some studies, and all involving careful monitoring of exposed epithelium.

"Aqueous extracts from peppermint, sage and lemon balm leaves display potent anti-HIV-1 activity by increasing the virion density"

Author(s): Geuenich S, Goffinet C, Venzke S, et al

Reference: N/A 5(1):27.

<http://highwire.stanford.edu/cgi/medline/pmid;18355409>

Published Abstract: BACKGROUND: Aqueous extracts from leaves of well known species of the Lamiaceae family were examined for their potency to inhibit infection by human immunodeficiency virus type 1 (HIV-1). RESULTS: Extracts from lemon balm (*Melissa officinalis* L.), peppermint (*Mentha x piperita* L.), and sage (*Salvia officinalis* L.) exhibited a high and concentration-dependent activity against the infection of HIV-1 in T-cell lines, primary macrophages, and in ex vivo tonsil histocultures with 50% inhibitory concentrations as low as 0.004%. The aqueous Lamiaceae extracts did not or only at very high concentrations interfere with cell viability. Mechanistically, extract exposure of free virions potently and rapidly inhibited infection, while exposure of surface-bound virions or target cells alone had virtually no antiviral effect. In line with this observation, a virion-fusion assay demonstrated that HIV-1 entry was drastically impaired following treatment of particles with Lamiaceae extracts, and the magnitude of this effect at the early stage of infection correlated with the inhibitory potency on HIV-1 replication. Extracts were active against virions carrying diverse envelopes (X4 and R5 HIV-1, vesicular stomatitis virus, ecotropic murine leukemia virus), but not against a non-enveloped adenovirus. Following exposure to Lamiaceae extracts, the stability of virions as well as virion-associated levels of envelope glycoprotein and processed Gag protein were unaffected, while, surprisingly, sucrose-density equilibrium gradient analyses disclosed a marked increase of virion density. CONCLUSIONS: Aqueous extracts from Lamiaceae can drastically and rapidly reduce the infectivity of HIV-1 virions at non-cytotoxic concentrations. An extract-induced enhancement of the virion density prior to its surface engagement appears to be the most likely mode of action. By harbouring also a strong activity against herpes simplex virus type 2, these extracts may provide a basis for the development of novel virucidal topical **microbicides**.

"Deciphering human immunodeficiency virus type 1 transmission and early envelope diversification by single-genome amplification and sequencing"

Author(s): Salazar-Gonzalez JF, Bailes E, Pham KT, et al

Reference: N/A 82(8):3952-70.

<http://jvi.asm.org/cgi/content/abstract/82/8/3952?maxtoshow=&HITS=2&hits=2&RESULTFORMAT=&andorexacttitleabs=and&fulltext=microbicide%2C+microbicides&andorexactfulltext=or&searchid=1&usestrictdates=yes&resourcetype=HWCIT&ct>

Published Abstract: Accurate identification of the transmitted virus and sequences evolving from it could be instrumental in elucidating the transmission of human immunodeficiency virus type 1 (HIV-1) and in developing vaccines, drugs, or **microbicides** to prevent infection. Here we describe an experimental approach to analyze HIV-1 env genes as intact genetic units amplified from plasma virion RNA by single-genome amplification (SGA), followed by direct sequencing of uncloned DNA amplicons. We show that this strategy precludes in vitro artifacts caused by Taq-induced nucleotide substitutions and template switching, provides an accurate representation of the env quasispecies in vivo, and has an overall error rate (including nucleotide misincorporation, insertion, and deletion) of less than 8×10^{-5} . Applying this method to the analysis of virus in plasma from 12 Zambian subjects from whom samples were obtained within 3 months of seroconversion, we show that transmitted or early founder viruses can be identified and that molecular pathways and rates of early env diversification can be defined. Specifically, we show that 8 of the 12

subjects were each infected by a single virus, while 4 others acquired more than one virus; that the rate of virus evolution in one subject during an 80-day period spanning seroconversion was 1.7×10^{-5} substitutions per site per day; and that evidence of strong immunologic selection can be seen in Env and overlapping Rev sequences based on nonrandom accumulation of nonsynonymous mutations. We also compared the results of the SGA approach with those of more-conventional bulk PCR amplification methods performed on the same patient samples and found that the latter is associated with excessive rates of Taq-induced recombination, nucleotide misincorporation, template resampling, and cloning bias. These findings indicate that HIV-1 env genes, other viral genes, and even full-length viral genomes responsible for productive clinical infection can be identified by SGA analysis of plasma virus sampled at intervals typical in large-scale vaccine trials and that pathways of viral diversification and immune escape can be determined accurately.

"Sulfated K5 Escherichia coli polysaccharide derivatives as wide-range inhibitors of genital types of human papillomavirus"

Author(s): Lembo D, Donalisio M, Rusnati M, et al

Reference: N/A 52(4):1374-81.

<http://aac.asm.org/cgi/content/abstract/52/4/1374?maxtoshow=&HITS=3&hits=3&RESULTFORMAT=&andorexacttitle=&andorexacttitleabs=&fulltext=microbicide%2C+microbicides&andorexactfulltext=or&searchid=1&usestrictdates=yes&resourcetype=HWCIT&ct>

Published Abstract: Genital human papillomaviruses (HPV) represent the most common sexually transmitted agents and are classified into low or high risk by their propensity to cause genital warts or cervical cancer, respectively. Topical **microbicides** against HPV may be a useful adjunct to the newly licensed HPV vaccine. A main objective in the development of novel **microbicides** is to block HPV entry into epithelial cells through cell surface heparan sulfate proteoglycans. In this study, selective chemical modification of the Escherichia coli K5 capsular polysaccharide was integrated with innovative biochemical and biological assays to prepare a collection of sulfated K5 derivatives with a backbone structure resembling the heparin/heparan biosynthetic precursor and to test them for their anti-HPV activity. Surface plasmon resonance assays revealed that O-sulfated K5 with a high degree of sulfation [K5-OS(H)] and N,O-sulfated K5 with a high [K5-N,OS(H)] or low [K5-N,OS(L)] sulfation degree, but not unmodified K5, N-sulfated K5, and O-sulfated K5 with low levels of sulfation, prevented the interaction between HPV-16 pseudovirions and immobilized heparin. In cell-based assays, K5-OS(H), K5-N,OS(H), and K5-N,OS(L) inhibited HPV-16, HPV-18, and HPV-6 pseudovirion infection. Their 50% inhibitory concentration was between 0.1 and 0.9 (micro)g/ml, without evidence of cytotoxicity. These findings provide insights into the design of novel, safe, and broad-spectrum **microbicides** against genital HPV infections.

[Return to Table of Contents](#)

3. PUBLISHED RESEARCH: RELEVANT BASIC AND TRANSLATIONAL SCIENCE

"Circumcision and risk of sexually transmitted infections in a birth cohort"

Author(s): Dickson NP, van Roode T, Herbison P, et al

Reference: N/A 152(3):383-87.

[http://www.jpeds.com/article/S0022-3476\(07\)00707-X/abstract](http://www.jpeds.com/article/S0022-3476(07)00707-X/abstract)

Published Abstract: *Objective* To determine the impact of early childhood circumcision on sexually transmitted infection (STI) acquisition to age 32 years. *Study design* The circumcision status of a cohort of children born in 1972 and 1973 in Dunedin, New Zealand was sought at age 3 years. Information about STIs was obtained at ages 21, 26, and 32 years. The incidence rates of STI acquisition were calculated, taking into account timing of first sex, and comparisons were made between the circumcised men and uncircumcised men. Adjustments were made for potential socioeconomic and sexual behavior confounding factors where appropriate. *Results* Of the 499 men studied, 201 (40.3%) had been circumcised by age 3 years. The circumcised and uncircumcised groups differed little in socioeconomic characteristics and sexual behavior. Overall, up to age 32 years, the incidence rates for all STIs were not statistically significantly different - 23.4 and 24.4 per 1000 person-years for the uncircumcised and circumcised men, respectively. This was not affected by adjusting for any of the socioeconomic or sexual behavior characteristics. *Conclusions* These findings are consistent with recent population-based cross-sectional studies in developed countries, which found that early childhood circumcision does not markedly reduce the risk of the common STIs in the general population in such countries.

"Genital ulcers facilitate rapid viral entry and dissemination following intravaginal inoculation with cell-associated simian immunodeficiency virus SIVmac239"

Author(s): Weiler AM, Li Q, Duan L, et al

Reference: N/A 82(8):4154-58.

<http://jvi.asm.org/cgi/content/abstract/82/8/4154?etoc>

Published Abstract: Here we report the results of studies in the simian immunodeficiency virus (SIV)-rhesus macaque model of intravaginal transmission of human immunodeficiency virus type 1 in the setting of genital ulcerative diseases. We document preferential association of vRNA with induced ulcers during the first days of infection and show that allogeneic cells of the inoculum traffic from the vaginal lumen to lymphatic tissues. This surprisingly rapid systemic dissemination in this cell-associated SIV challenge model thus reveals the challenges of preventing transmission in the setting of genital ulcerative diseases and illustrates the utility of this animal model in tests of strategies aimed at reducing transmission under these conditions.

"Herpes simplex virus type 2 acquisition during recent HIV infection does not influence plasma HIV levels"

Author(s): Cachay ER, Frost SD, Poon AF, et al

Reference: N/A 47(5):592-96.

<http://www.jaids.org/pt/re/jaids/abstract.00126334-200804150-00010.htm;jsessionid=HpJB2mSfL4p43WhJCJR2T5kHwyFrT1fqQd2HbVrhvnKXnJLHg5wx!1675702673!181195628!8091!-1>

Published Abstract: Summary: We assessed the effect of herpes simplex virus type 2 (HSV-2) acquisition on the plasma HIV RNA and CD4 cell levels among individuals with primary HIV infection using a retrospective cohort analysis. We studied 119 adult, antiretroviral-naive, recently HIV-infected men with a negative HSV-2-specific enzyme immunoassay (EIA) result at enrollment. HSV-2 acquisition was determined by seroconversion on HSV-2 EIA, confirmed by Western blot analysis. Ten men acquired HSV-2 infection a median of 1.3 years after HIV infection (HSV-2 incidence rate of 7.4 per 100 person-years of follow-up). The median time of follow-up after acquiring HSV-2 infection was 303 days. All men except 1 were asymptomatic during HSV-2 acquisition, and only 1 HSV-2 seroconverter, who was asymptomatic, had a transient increase in blood HIV load (0.5 log₁₀ copies/mL over 11 days). The HSV-2 incidence rate was high in our cohort of recently HIV-infected individuals; however, HSV-2 acquisition did not significantly change the plasma HIV dynamics and CD4 cell levels.

"Increased levels of HIV-1-infected cells in endocervical secretions after the luteinizing hormone surge"

Author(s): Benki S, Mostad SB, Richardson BA, et al

Reference: N/A 47(5):529-34.

<http://www.jaids.org/pt/re/jaids/abstract.00126334-200804150-00001.htm;jsessionid=HpLfz2hmxSwQQxcZSXQ5VL5YCQtkSDTcd3ZhnyNQ2s1FCvnSrQJG!923867264!181195629!8091!-1>

Published Abstract: Summary: Levels of HIV-1 RNA in endocervical specimens fluctuate with the menstrual cycle, suggesting that cell-free HIV-1 levels may vary during the cycle, which could influence infectivity. Here, we examined daily changes in endocervical HIV-1-infected cells during 1 cycle. There were significant positive associations between the number of days from the luteinizing hormone surge and the number of HIV-1 DNA copies/swab ($P = 0.001$) and the number of total cells/swab (P (less than) 0.001) in endocervical specimens. These data suggest that sampling of cell-associated endocervical HIV-1 increases after the periovulatory period, which could result in increased exposure to HIV-1-infected cells during sexual contact.

"Mucosal irritation potential of personal lubricants relates to product osmolality as detected by the slug mucosal irritation assay"

Author(s): Adriaens E, Remon JP

Reference: N/A Epub ahead of print.

<http://highwire.stanford.edu/cgi/medline/pmid;18356773>

Published Abstract: BACKGROUND:: The slug mucosal irritation assay has recently been used as a sensitive measure of mucus membrane tolerance for vaginal **microbicide** products and carriers. In the current study, it was determined whether musosal irritation potency of personal lubricants is related to varying product osmolalities. METHODS:: Five commercial lubricants with an osmolality range were evaluated using the previously validated slug mucosal irritation assay. Specifically, *Arion lusitanicus* were treated with lubricants over 5 days to quantify mucus production and tissue damage, allowing assignment of each product into an irritation potency category (none, mild, moderate, or severe). RESULTS:: The irritation potency (assessed by the mucus production) of the lubricants showed a significant, quadratic relationship with the product osmolality ($P = 0.001$; $R = 0.99$). Femglide, a hypo-osmotic lubricant (32 mOsm/kg), caused a negative mucus production. Pre, an iso-osmotic lubricant (316 mOsm/kg), caused no changes. Two moderately hyperosmotic lubricants, Replens and K-Y jelly (2143 and 2463 mOsm/kg), induced mild and moderate irritation, respectively. The highly hyperosmotic lubricant Astroglide (5848 mOsm/kg) resulted in severe irritation and tissue damage. CONCLUSIONS:: Commonly used personal lubricants show a full range of mucosal irritation potential, which is related to product osmolality.

[Return to Table of Contents](#)

4. HIV/AIDS VACCINES

"AIDS vaccine testing at crossroads"

Date: 26 March 2008

Source: *The Washington Post*

Author(s): David Brown

<http://www.washingtonpost.com/wp-dyn/content/article/2008/03/25/AR2008032503153.html?wpisrc=newsletter>

The leaders of the federal government's effort to develop an AIDS vaccine said yesterday that more of their budget needs to be spent on basic lab research and less on testing the current crop of vaccines, none of which has proved useful in human trials.

The declaration made at a "summit meeting" is tantamount to an admission that almost no progress has been made in the search for an AIDS vaccine in the past 25 years and that something close to new start is necessary. The conference, held at the National Institutes of Health in Bethesda, was called after a much-touted vaccine tested in half a dozen countries not only failed to benefit people who received it but also may have actually increased their chance of becoming infected with HIV, the virus that causes AIDS.

"We need to turn the knob toward [basic scientific] discovery -- nobody should be unclear about that," said Anthony S. Fauci, head of the National Institute of Allergy and Infectious Diseases.

One of the co-chairmen of the meeting, Warner C. Greene of the University of California at San Francisco, was more definitive in his assessment. "There is no question the AIDS vaccine enterprise is in need of a major mid-course correction," he told the gathering of about 300 scientists, who came from as far away as South Africa and Kenya for the one-day meeting.

Carl W. Dieffenbach, the head of the NIH's Division of AIDS, acknowledged that "this summit does mark a change in our approach."

The meeting was called after two studies testing the same vaccine were stopped in September. The vaccine, made by the pharmaceutical giant Merck, used a crippled version of a common respiratory virus, called adenovirus type 5, to deliver a selection of HIV proteins to the immune system in the hope of inducing protection. The studies were stopped when early results suggested that people receiving the vaccine were more likely to become infected with HIV than people receiving placebo injections. The reason is unknown and the subject of intensive scientific study.

NIH is spending \$497 million on AIDS vaccine research this year, with about \$476 million going to researchers outside its campus. About 47 percent of the money funds basic research and 38 percent funds testing "candidate vaccines" in humans. Fauci said the ratio needs to be tipped more steeply in favor of basic research.

Although researchers have tested numerous AIDS vaccines on small groups of volunteers, only three vaccines have gone to large clinical trials with thousands of volunteers.

Earlier this decade, one product, called AIDSVAX, was found to be ineffective. The Merck vaccine, which showed promising results in monkeys, may have been harmful. A third vaccine, being tested in an experiment nearing completion in Thailand, is given little hope of working by most researchers, 21 of whom wrote a letter to the journal *Science* several years ago saying that the study should not even begin.

The search for an AIDS vaccine has proved difficult for several reasons. Successful vaccines mimic the protection the body normally provides when confronted with a virus, bacterium or other microbe. HIV, however, mainly attacks immune system cells, which are the ones a vaccine is trying to enlist for help. Furthermore, unlike most viruses, HIV stitches itself permanently into the DNA of some human cells after entering them. That means that if a vaccine does not provide full protection within days -- and possibly even hours -- of exposure, irreversible infection occurs.

A few people who become infected with HIV are able to survive without treatment indefinitely -- so-called elite controllers. Many non-human primates also tolerate the monkey equivalent of HIV without becoming ill. In both cases, how the immune system achieves that outcome is unknown.

"We do not have a vaccine now. . . . We are not only not there, we are not close," said James Hoxie, a researcher at the University of Pennsylvania, who summarized the view of a panel of basic researchers who spoke at the meeting.

One organization yesterday called for the money now spent on AIDS vaccine research to be used for HIV testing, treatment of HIV patients and research on the use of antiretroviral drugs to prevent infection.

"I think we should pull the plug on vaccine research," said Michael Weinstein, president of the AIDS Healthcare Foundation, a private, nonprofit group that provides treatment for people with HIV. "Do we have any other enterprise that has been studied for 25 years and for which we've spent billions of dollars where we have no results? There's no evidence we'll ever have an AIDS vaccine," he said.

However, Mitchell Warren of the AIDS Vaccine Advocacy Coalition, who attended the meeting, praised it as the beginning of a necessary readjustment of priorities.

"We are at a critical moment in the field. We've had a tremendous setback. But this field is not abandoning the research for a vaccine," he said. "This is not the end of the line for AIDS vaccine research. That was an important point for everyone."

Several people at the meeting said that they not only support greater spending on basic research, but also that the government must be willing to fund promising, yet unorthodox, proposals, or a generation of young scientists may abandon AIDS research in favor of fields that are less challenging.

EDITOR'S NOTE: The AIDS Vaccine Advocacy Coalition (AVAC) issued a comment on the AIDS Vaccine Summit, available at http://avac.org/pdf/summit_commentary_mar2008.pdf. AVAC will be including more in-depth analyses and discussions of issues raised at the Summit in forthcoming publications, including the next issue of *Px Wire*, *AVAC Report 2008*, and future updates on the *Advocates' Network*.

"Vaccine failure is setback in AIDS fight"

Date: 21 March 2008

Source: *The Washington Post*

Author(s): David Brown

<http://www.washingtonpost.com/wp-dyn/content/article/2008/03/20/AR2008032003398.html?referrer=emailarticlepg&sid=ST2008032101286>

The two-decade search for an AIDS vaccine is in crisis after two field tests of the most promising contender not only did not protect people from the virus but may actually have put them at increased risk of becoming infected.

The results of the trials, which enrolled volunteers on four continents, have spurred intense scientific inquiry and unprecedented soul-searching as researchers try to make sense of what happened and assess whether they should have seen it coming. Both field tests were halted last September, and seven other trials of similarly designed AIDS vaccines have either been stopped or put off indefinitely. Some may be modified and others canceled outright.

Numerous experts are questioning both the scientific premises and the overall strategy of the nearly \$500 million in AIDS vaccine research funded annually by the U.S. government.

"This is on the same level of catastrophe as the Challenger disaster" that destroyed a NASA space shuttle, said Robert Gallo, co-discoverer of the human immunodeficiency virus (HIV), which causes AIDS, and head of the Institute for Human Virology in Baltimore.

The recently closed studies, STEP and Phambili, used the same vaccine -- made from a common respiratory virus called adenovirus type 5 that had been crippled and then loaded with fragments of HIV. Both studies were halted when it became clear the STEP study was futile and possibly harmful. The results of the Phambili vaccine trial, which was conducted in South Africa, were revealed last month and only worsened the gloom. Although the number of new HIV infections in that study was far smaller than in STEP -- and too few to draw firm conclusions from -- those results,

too, hinted at a trend toward harm among vaccine recipients.

Many researchers are questioning the scientific premises on which all those studies were based and are wondering, along with AIDS activists, what effect this near-worst-case scenario might have on tests of future vaccines. The working hypothesis for what went wrong is that the vaccine somehow primed the immune system to be more susceptible to HIV infection -- a scenario neither foreseen nor suggested by previous studies.

The National Institutes of Health, which funded the STEP and Phambili trials, is convening a meeting next week to reassess its AIDS vaccine program. But some respected scientists have already reached a verdict.

"None of the products currently in the pipeline has any reasonable chance of being effective in field trials," Ronald C. Desrosiers, a molecular geneticist at Harvard University, declared last month at an AIDS conference in Boston. "We simply do not know at the present time how to design a vaccine that will be effective against HIV."

He told a rapt audience that he has reluctantly concluded that the NIH has "lost its way in the vaccine arena" and that he thinks it should redirect its AIDS vaccine funds to basic research and away from human trials.

In this fiscal year, the NIH's budget for AIDS vaccine research is \$497 million. The STEP and Phambili trials were each expected to cost about \$32 million. Pharmaceutical giant Merck and Co. has spent an undisclosed amount developing the vaccine and helping to manage the studies.

"We can't afford to have any more trials like this," said Mark Harrington, head of the activist Treatment Action Group and a longtime observer of AIDS research. "We have to stop and reassess and recommit to basic science, or people will begin to lose faith."

At the moment, only two things are certain. The first is that the vaccine, developed by Merck, could not have caused HIV infection because it contains only three proteins from HIV, not the entire virus. The second is that there are no obvious villains.

"I do not think that what happened in this trial is an example of scientists blindly rushing into dangerous things," said John P. Moore, an AIDS virologist at Weill Cornell Medical College, who has criticized vaccine trials he considered futile. "In the general HIV-research community, I didn't know anyone who said this was going to happen."

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EDITOR'S NOTE: The full text of this article is available for public access at the above website. AVAC issued a response to this article, available at http://www.avac.org/pdf/WP_Response_mar2008.pdf

[Return to Table of Contents](#)

5. OTHER PREVENTION APPROACHES

"Religious leaders test for HIV/AIDS"

Date: 24 March 2008

Source: *The New Times (Kigali)*

Author(s): Eddie Mukaaya, Saul Butera

<http://www.newtimes.co.rw/index.php?issue=13472&article=4913>

The one-day meeting held at Hotel La Palisse, Nyandungu was aimed at emphasizing the role of religious leaders in the fight against AIDS and set strategies against the AIDS stigma.

Andrew Butare, the country representative of Christian Aid said the testing that was carried out on a voluntary basis was a sign of leading by example.

"If found positive, treatment will be guaranteed and they will be advised how to handle themselves in the society as well as spread the campaign of living positively," he said

Reverend Canon Gideon Byamugisha, who is also the regional ambassador for Christian Aid, revealed his status being positive since 1992, adding that had it not been the church's help, he would have been dead by now. He said that fighting the scourge was a joint operation that God supports since AIDS is un-Godly.

Dr. Agnes Binagwaho, the Executive Secretary of Rwanda's National AIDS Control Commission (CNLS) commended the exercise saying it was vital for religious leaders to get involved in the fight due to the influence they command in the general public. She added that since 90 percent of religious leaders were represented at the function, the fight should be widespread because they represented at least 98 percent of their congregations.

"Since statistics show that 15 percent of the sick are children below 18 years - and these are the leaders of tomorrow, religious leaders should fight the stigma and talk to the youths about sexuality in their own words," Binagwaho said. She urged religious leader to do whatever is in their powers to reach to people and to stop the scourge.

With the help of Christian Aid and CNLS, religious leaders will find measures to prevent the increase of HIV, non-judgmental care and treatment of people living with HIV and their families. They also have plans to increase advocacy for the rights of affected people.

[Return to Table of Contents](#)

6. NON-HIV STIS AND REPRODUCTIVE HEALTH

"An epidemic no one wants to talk about"

Date: 21 March 2008

Source: *The Washington Post*

Author(s): Robert E Fullilove, Adaora Adimora, Peter Leone

<http://www.washingtonpost.com/wp-dyn/content/article/2008/03/20/AR2008032003019.html>

A much-publicized study from the Centers for Disease Control and Prevention this month highlighted the high rates of sexually transmitted diseases among teenage Americans. But for those of us who work in public health, this "news" is already old.

A decade ago, the National Academy of Sciences' Institute of Medicine published a landmark report, "The Hidden Epidemic," examining sexually transmitted diseases in the United States. In 1995, the report noted, STDs accounted for 87 percent of cases of the 10 most frequently reported diseases in the nation. Despite the huge costs that such infections imposed on our health-care system, awareness of their importance was all but absent from the public consciousness. We fear that this latest study will have its 15 minutes in the spotlight and also fade from view.

Sadly, our national silence may be related to our difficulty discussing the roles that race and poverty play in these trends. In 2005, for example, the rate of gonorrhea (a curable STD) among African Americans was 18 times greater than the rate among whites. The contrast in rates for HIV-AIDS, syphilis and chlamydial infection among blacks and whites is only slightly less dramatic. These diseases cost tens of billions of dollars each year, but with the exception of HIV infection, STDs remain the elephant in the room when it comes to the national conversation about health and health care.

One obvious reason is that conversations about sexual behavior, race and sexually transmitted infections remain taboo. Another is that the incidence of many STDs, particularly HIV, is concentrated in poor, segregated neighborhoods that are characterized by high rates of incarceration. Inner-city populations of African Americans and Latinos account for almost two-thirds of the 2.2 million Americans in prison nationwide, and two disturbing trends are increasingly present in these communities.

One is the shift in the patterns of marriage and courtship that result when so many men are removed from a community. The other is an increase in the number of "multiple concurrent sexual partnerships," in which individuals are engaged in sexual relationships with more than one person at a time. In many communities, when one sexual partner is imprisoned, the person left behind chooses another partner. When widespread, this behavior creates an efficient, effective pattern for introducing and maintaining an STD through a network of sexual relationships.

Concurrent sexual partnerships, our research indicates, are a more effective engine for transmitting STDs than sequential partnerships. In the latter case, an infected individual is more likely to be diagnosed before a new partner is infected. In the former, an individual infected by one partner can immediately pass the infection on to another, potentially spreading it quickly through the network. As people move in and out of relationships and in and out of communities, such infections become almost impossible to treat efficiently. Movement in and out of prison aggravates these trends.

We can no longer have effective STD prevention campaigns in poor communities of color if they treat one person at a time or ignore the social conditions underpinning high rates of HIV and other STDs. For one thing, women in poor African American communities who engage in the lowest levels of risk behavior are dramatically more likely to acquire STDs than higher-risk women in communities with low background rates of infection. Where you live and choose sexual partners has an enormous impact on your risk, particularly if it is in a community with high incarceration rates. Imprisonment changes community male-female ratios, and these unbalanced numbers contribute to low marriage rates, a reluctance to negotiate "safe sex," formation of concurrent partnerships and the maintenance of STDs within the networks in which members choose partners.

Simply put, we will never rid the United States of HIV and other STDs if our only weapon is medical treatment. And if we are unable to engage in a national dialogue about the sexual health of our youths and the social dynamics that drive STDs, this epidemic will go largely ignored, and many more lives will be lost.

7. POLITICS AND POLICY

"FDA denies it is risk-averse on drugs"

Date: 26 March 2008

Source: *Financial Times (London)*

Author(s): Andrew Jack

http://www.ft.com/cms/s/0/7ae3646a-fad6-11dc-aa46-000077b07658.html?nclick_check=1

The newly appointed head of medicine approvals at the US Food and Drug Administration has insisted that science rather than politics or pricing is behind the growing difficulties facing new pharmaceuticals attempting to reach the market.

Janet Woodcock, head of the Centre for Drug Evaluation and Research, one of the most senior jobs at the FDA, rejected claims from drug companies that her unit was rejecting new medicines because the agency was too risk-averse.

Ms Woodcock's spirited defence follows intense criticism of the FDA in recent months. With a large number of new drugs rejected or delayed, pharmaceutical companies and a number of patient associations have accused the agency of being too risk-averse, partly in response to politicians and consumer groups which have attacked it for approving medicines and failing to identify dangerous side effects, such as with the painkiller Vioxx.

She acknowledged that the rate of success in bringing new drugs to market had declined in recent years in a way that is putting pressure on pharmaceutical company executives and depressing investor interest in the sector as existing medicines come off patent.

She said that when the FDA rejected new medicines, it did so based on an assessment of their safety and -efficacy, not as a result of political pressure or greater conservatism.

She told the *Financial Times*: "We have a different story from the companies. We understand that [they] have productivity issues but [we] stick to the same safe and effective criteria as our bedrock. Pharma is having a difficult time but we are seeing drugs that have a lot of questions."

Ms Woodcock conceded that the size and length of clinical trials had grown substantially in recent years but argued that was a result of better understanding by regulators of how best to identify risks. "We're smarter now [but still] humbled by what we don't know."

She said the FDA would unveil proposals this autumn on reducing drug development costs by standardising the format and content of clinical trial data. "We need to learn from Henry Ford. Companies collect too much information because they are worried that the FDA will ask for it."

While endorsing a recent move towards greater post-marketing surveillance studies - with continued obligations on companies to study safety risks even after a drug has been launched - she allayed concerns about their extent.

"The fear that there will be a huge number is misplaced. We think very hard about every case," she said.

She denied industry claims that the FDA was turning down experimental drugs simply because they were more expensive or less cost effective than existing treatments but said: "If there are choices out there and a new drug is less safe, we will not put it on the market unless there is some advantage."

Ms Woodcock acknowledged that FDA staffing and funding for the inspection of foreign manufacturing sites for medicines remained "thin", warning of the -dangers of globalisation highlighted by concerns over Chinese-sourced ingredients for the anti-clotting agent Heparin.

"We now rely on a risk-based approach. Regulators share information but that does not totally compensate. There has been no increase [in inspectors] to the field."

She also defended the use in many instances of the FDA's gold standard of placebo-controlled trials, where a new drug is tested against a sugar pill rather than an existing approved medicine for the same disease. "If you compare with a treatment that is not proven to be effective, you don't know if either drug is effective," she said.

"UK to force drugmakers to share info"

Date: 25 March 2008

Source: *Associated Press*

Author(s): Maria Cheng

<http://ap.google.com/article/ALeqM5hP6zVeQeBkSt2SrG6Dg-oiy7JrsQD8VK24V81>

Britain plans to force pharmaceutical companies to share more information with regulators about clinical trials after an investigation recently concluded that GlaxoSmithKline PLC deliberately withheld information about an antidepressant.

The four-year probe by the Medicines and Healthcare products Regulatory Agency, completed earlier this month, said the British company should have revealed more quickly that Seroxat sometimes increased the suicide risk in teenagers - by more than six times. But without stronger legislation in place, the MHRA admitted there is no chance of prosecuting the company for what the agency perceives as an ethical lapse.

"I remain concerned that GSK could and should have reported this information earlier than they did," MHRA chief executive Kent Woods said in a statement.

GlaxoSmithKline rejected the suggestion that it withheld information.

"We firmly believe we acted properly and responsibly," said Dr. Alastair Benbow, the company's European medical director.

British legislation only obliges companies to report side effects in patients for which drugs are officially recommended.

Because Seroxat was only recommended for adults, GlaxoSmithKline was not required to report on any dangerous side effects it found in adolescents. But Seroxat can still be given to adolescents if prescribed by a doctor. About half of psychiatric drugs are prescribed "off-label," meaning that doctors give them to patients for whom the drug is not strictly intended.

The MHRA said it sifted through more than 1 million pages of evidence after requesting details of clinical trials held between 1994 and 2002. In response, Britain's government declared that by the end of the year, it will tighten laws forcing companies to share all their relevant safety research with regulators.

"Companies that conduct clinical trials should not compromise people's health by withholding information," public health minister Dawn Primarolo said. The new laws will require companies to disclose a drug's side effects in all patients tested, Primarolo said.

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EDITOR'S NOTE: The full text of this article is available for public access at the above website.

"HIV/AIDS threatening democracy, governance in southern Africa, study says"

Date: 20 March 2008

Source: *Kaiser Daily HIV/AIDS Report*

http://www.kaisernetwork.org/daily_reports/rep_index.cfm?DR_ID=51062

The Institute for Democracy in South Africa recently released a study that found HIV/AIDS is threatening democracy and governance in some Southern African countries, South Africa's Mercury reports.

For the study, Kondwani Chirambo, head of the Governance and AIDS Program at IDASA, and colleagues examined the impact of HIV/AIDS in Malawi, Namibia, South Africa, Tanzania, Zambia and Zimbabwe (Savides, Mercury, 3/19). The study, titled "The Political Costs of AIDS in Africa," found that in Malawi, Tanzania, Zambia and Zimbabwe, deaths from undisclosed causes among Members of Parliament younger than age 55 was the main cause of vacancies during the last 15 years. In South Africa, 23 MPs had died of various causes since 1994, the study found.

"Not a single elected representative has been known to" have died of AIDS-related causes, "despite that this mortality profile seems to mimic the pandemic's effect," the study said (SAPA/Polity.org.za, 3/19). The study said that "because there is no further information on whether these deaths were as a result of disease, car accidents or other causes, no inferences have been drawn by IDASA regarding trends." However, the study noted that there are "higher levels of stigma and discrimination" related to HIV/AIDS "among political elites, given that not a single elected representative has been known to live with or die" from AIDS-related illnesses (Mercury, 3/19).

Because of the increased number of deaths among MPs in the countries studied, organizational and financial restraints have left the positions vacant for longer periods of time, the SAPA/Polity.org.za reports. The vacancies also have "opened the door" to less qualified replacements, which might affect the quality of service, the SAPA/Polity.org.za reports. "A viable option would be to simply allow political parties to replace the deceased through appointment," IDASA said (SAPA/Polity.org.za, 3/18). In addition, Chirambo said that new electoral models should be

developed to address the effect of HIV/AIDS on Africa (Mercury, 3/19).

The study also found that deaths from AIDS-related causes among voters have hindered the ability to maintain registers. "AIDS is a much bigger problem than simply a health crisis," Chirambo said. He added that there are a "number of worrying revelations in this study," including the "large number of younger voters who have died; the rising deaths among MPs and the loss of representation attributed to these deaths; the impact on small or under-resourced opposition parties; and the implications for democratic accountability (SAPA/Polity.org.za, 3/18).

"Adaptive clinical trials: more talk than action"

Date: 17 March 2008

Source: *Bio-IT World.com*

Author(s): Deborah Borfitz

<http://www.bio-itworld.com/ecliniqua/2008/03/17/adaptive-clinical-trials-adoption.html>

Lack of regulatory guidance may be the main, if not the only, barrier to widespread adoption of adaptively designed clinical trials across study phases.

The statistical and technological know-how necessary to conduct adaptive clinical trials (ACTs) already exists. PC-compatible, open-source software known as WinBUGS accommodates the Bayesian statistical method with which ACTs have become more or less synonymous, says Jay Herson, PhD, senior associate in biostatistics at Johns Hopkins University. Simulation technology using programming language R also exists so companies doing ACTs can adequately plan for a multiplicity of possible sample sizes, outcomes, and resource consumption scenarios.

Regulatory authorities have only to give blessing to the use of specific ACTs through guidance, says Herson. For the foreseeable future, there won't be a shortage of sufficiently skilled Bayesian loyalists to handle the complex calculations associated with ACTs.

The big unknown is precisely how many ACTs have actually been done or are now under way, says Herson. "All the big pharmaceutical companies push for adaptive designs. PhRMA [Pharmaceutical Research and Manufacturers of America]... pretends the 'time is here' in hopes of intimidating the FDA politically. The strategy is not working and appropriately so."

Based on an initial survey last year of 13 mid- and large-size pharmaceutical companies, PhRMA's Adaptive Design Working Group came up with 37 examples of ACTs, says Judith Quinlan, co-chair of the group's case study work stream. Of those, three were Phase I, one combined Phase I and II, fifteen were Phase II, two combined Phase IIA and IIB, nine combined Phase II and III, four were Phase III, and three were Phase IV.

"All but one focused adaption on dose," says Quinlan. The exception adjusts on population. Nine of the 37 used Bayesian statistics, including seven of the fifteen Phase II trials. The combined Phase II and III adaptive designs were a mix of "operationally seamless" trials and those combining information from two phases. The survey also found that FDA interactions only occurred with the Phase II examples if the information was expected to be used for a regulatory submission.

The admittedly biased sample underrepresented early phase trials, which respondents saw as less "interesting," and late-phase confirmatory trials, due to confidentiality issues, says Quinlan. "I don't think we'll have clean metrics for some time."

Additional case studies are now being collected from clinical research organizations working on behalf of smaller companies, says Quinlan. The new case studies include about 20 trials (half for devices) contributed by Don Berry, chairman of the department of biostatistics and applied mathematics at the University of Texas M.D. Anderson Cancer Center, and another 10 or so contributed by biostatistical consultancy and software company Cytel.

Among them will be a large Phase III "population enrichment" trial involving platelet inhibition for acute coronary syndrome being done by Cytel on behalf of The Medicines Company, a small pharmaceutical company based in Parsippany, NJ. Subjects are sub-grouped according to their medical condition, and the drug gets randomized only to those groups it is found to benefit, says Cytel President Cyrus Mehta. The trial can adapt "up to 15,000" patients.

[Return to Table of Contents](#)

8. HIV/AIDS FUNDING

"In search of new ideas for global health"

Source: *N Engl J Med.* 2008 Mar 27;358(13):1324-25. *Perspective.*

Author(s): Tadataka Yamada

<http://content.nejm.org/cgi/content/full/358/13/1324>

The recent failure of another potential vaccine against human immunodeficiency virus (HIV) underscores the enormous challenges of tackling diseases whose heaviest burden falls on the developing world. A quarter of a century after the first report of AIDS, our knowledge about how an HIV vaccine might work is still distressingly limited. It seems clear that neither current dogma nor traditional thinking is likely to get us to the next step. Truly creative ideas will be required.

I must confess to having learned the hard way that embracing new thinking, as difficult as it may be, is crucial for the advancement of science and medicine. As a gastroenterologist, I was one of the many who believed as gospel truth that peptic ulcers were caused by gastric acid. When two scientists from Australia came along and argued that it was actually a bacterium, *Helicobacter pylori*, that produced ulcers, those of us in the "Acid Mafia" rejected their claims out of hand. But Robin Warren and Barry Marshall persisted. Marshall even drank a solution of *H. pylori*, became ill, took antibiotics, recovered, and wrote a paper about it, just to get others in the field to pay attention. You know the ending to this story - these scientists were proved right and went on to win a Nobel Prize in 2005.

New ideas should not have to battle so hard for oxygen. Unfortunately, they must often do so. Even if we recognize the need to embrace new thinking - because one never knows when a totally radical idea can help us tackle a problem from a completely different angle - it takes humility to let go of old concepts and familiar methods. We have seemed to lack such humility in the field of global health, where the projects related to diseases, such as HIV, malaria,

and tuberculosis, that get the most funding tend to reflect consensus views, avoid controversy, and have a high probability of success, if "success" is defined as the production of a meaningful but limited increase in knowledge. As a result, we gamble that a relatively small number of ideas will solve the world's greatest global health challenges. That's not a bet we can afford to continue making for much longer.

Incremental innovation has its place, of course. Many important lifesaving advances have been made by taking one crucial step forward at a time. Consider the worldwide effort to eradicate polio, for example. In 1955, Jonas Salk's vaccine showed that we could induce protective immunity against poliovirus by injecting people with inactivated viral strains. Because his vaccine required injections, it wasn't well suited to use in developing countries, but Albert Sabin's oral polio vaccine took us a step further and allowed the first global eradication campaigns to begin. Both Salk's and Sabin's solutions, however, would have been impossible had it not been for a great leap - an essentially transformative idea - that had occurred centuries earlier in the mind of Edward Jenner, who observed that milkmaids who had been exposed to cowpox became immune to smallpox, a far more deadly disease.

How can we capture such transformative innovation in order to address the problems in global health? First, it is clear that innovation does not take place only in the United States or Western Europe. In the realm of information technology, for example, many of the most important recent advances have been made in India or China. Innovation comes from every discipline. If only the anointed experts are permitted to address a problem, their field becomes locked in unchallenged dogma. An engineer or a physicist could have brilliant insights into a difficult biomedical problem. Innovative ideas might exist in the minds of people who could never navigate their way through a grant application for the National Institutes of Health. Moreover, new ideas can be fleeting, and waiting a year for funding in order to test them can have a serious dampening effect. Innovation frequently arises from the lessons of repeated failure, so if we are not willing to take risks and fail often, we will miss many opportunities to capture novel approaches that can transform a field. Above all, unfortunately, peer review can kill truly novel ideas because they are, by definition, peerless.

To help promote a more adventurous approach to research, the Bill and Melinda Gates Foundation, where I am president of the Global Health Program, is willing to take risks as well. We are launching a \$100 million initiative called Grand Challenges Explorations, which will supplement our current grant making by funding hundreds of innovative early-stage projects over the course of 5 years, investing \$100,000 in each one. We want bold ideas - even seemingly wacky ones - that need just a little help to get tested. Proposals will require creative thinking but no preliminary data. The applications are only two pages long, and we'll make a funding decision within about 3 months after the May 30 submission deadline. We'll run each idea past two groups of reviewers - one composed of internal scientists, and another of partners and advisers with a history of identifying creative solutions to difficult problems. We expect many of these projects to fail, but we stand ready to put substantial funding behind those that succeed.

We will begin taking submissions on the Grand Challenges in Global Health Web site on March 31 for a first set of four ambitious challenges. We're seeking new ways to protect against infectious diseases, drugs and delivery systems that limit the emergence of resistance, new ways to prevent or cure HIV infection, and an understanding of the basis for latency in tuberculosis. We'll issue new challenges at least twice a year going forward. We hope to hear from researchers of every age, on every continent, and from disciplines that don't typically focus on global health or even biomedical research - for history has taught us that great ideas can come from anywhere.

Each year, 9.7 million children die before 5 years of age, 4 million of them within the first month of life and the vast majority of them in the poorest countries in the world. These numbers are staggering to contemplate, let alone comprehend. Most of these deaths can be averted with the application of existing tools, but in some cases only new ideas will provide practical and effective solutions. Through initiatives like Grand Challenges Explorations, we hope to breathe life into the best of these new ideas.

[Return to Table of Contents](#)

9. ANNOUNCEMENTS

AVAC Launches Px Wire

<http://avac.org/pxwire/2008/jan-mar.pdf>

AVAC recently launched *Px Wire*, which will track key developments in the field of HIV prevention research, including the launch of new trials, results of ongoing studies, and an up-to-date tally of trials going on worldwide.

Px Wire is designed to complement AVAC's other publications and to help advocates stay on top of the ever-changing field of HIV prevention research. It is the first one-stop source for information on the full range of HIV prevention research going on worldwide, including vaccines, **microbicides**, pre-exposure prophylaxis (PrEP), herpes simplex virus-2 treatment, male circumcision, cervical barrier methods, and partner treatment.

Every three months, *Px Wire* will provide:

- A center foldout poster with:
 - An updated comprehensive timeline of efficacy trials of new biomedical HIV prevention trials worldwide
 - A world map showing where various strategies are being tested
- A tally of experimental prevention strategies in all phases of clinical development
- Brief news bulletins and "AVAC's take" on current events
- A calendar of upcoming meetings

The first issue is available at <http://avac.org/pxwire/2008/jan-mar.pdf>. Additional resources including the *Px Wire* archive, information about subscribing, reprint requests and bulk orders can be found at www.pxwire.org.

[Return to Table of Contents](#)