



# ALLIANCE FOR MICROBICIDE DEVELOPMENT

**13 June 2008, Volume 9, Number 23**

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/cs/weekly\\_news\\_digest](http://www.microbicide.org/cs/weekly_news_digest). If you would like to be removed from the *Digest* distribution list, please send an email to [digest@microbicide.org](mailto: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!

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#### **1. ALLIANCE UPDATES AND COMMUNITY NEWS**

**New Resources from the International Women's Health Coalition (IWHC)**

<http://www.iwhc.org/>

The International Women's Health Coalition (IWHC) is pleased to announce the following publications:

- **Triple Jeopardy: Female Adolescence, Sexual Violence, and HIV/AIDS** addresses the particular vulnerability of young women to sexual violence and HIV infection (<http://iwhc.org/resources/youngadolescents/triple-jeopardy.cfm>). This factsheet is the latest in the IWHC's series on Young Adolescents' Sexual and Reproductive Health and Rights (<http://iwhc.org/resources/youngadolescents>), which uses evidence about the sexual and reproductive knowledge and behaviors of 10- to 14-year-olds around the world to argue for more responsive programs and policies.
- **Child Marriage: Girls 14 and Younger at Risk**, underscores the realities of girls married at 14 or younger, including social and educational disadvantages, an elevated risk of contracting sexually transmitted infections including HIV, and complications in pregnancy and childbirth (<http://iwhc.org/resources/youngadolescents/childmarriage.cfm>; available in English, Spanish, Portuguese, and French).
- An updated version of **Women and Risk of HIV/AIDS Infection**, a factsheet highlighting the vulnerability of girls and women to HIV/AIDS (<http://iwhc.org/resources/hivaidsfactsheet.cfm>).

Please email [wwelshimer@iwhc.org](mailto:wwelshimer@iwhc.org) to request hard copies of the publications.

## **New Resources on the Alliance Website**

[www.microbicide.org](http://www.microbicide.org)

The Alliance has posted two new resources to its website. Please visit [www.microbicide.org](http://www.microbicide.org) to find further information about these and other **microbicide** topics:

- **Microbicide** Policy Update
- Gates Foundation Report - The Long Road to Success

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## **2. MEDIA COVERAGE OF MICROBICIDES**

### **"Clinical trials in Africa receive funding boost"**

**Date:** 06 June 2008

**Source:** *SciDev.Net*

**Author(s):** Naomi Antony

<http://www.scidev.net/en/news/clinical-trials-in-africa-receive-funding-boost.html>

The European and Developing Countries Clinical Trials Partnership (EDCTP) announced this week (3 June) that it will inject over 80 million euro (around US\$124 million) into African medical research.

Half of this sum has already been approved and will go towards malaria research and the development of tuberculosis (TB) vaccines. The remainder, expected later this year, has been earmarked for HIV and TB treatment and for the provision of vaccines and **microbicides**.

The combined sum will be the largest approved by the EDCTP since it was established in 2003, and should reinforce the European Union's partnership with Sub-Saharan Africa.

The EDCTP links 14 member states of the European Union, as well as Norway and Switzerland, to countries in Sub-Saharan Africa, largely by providing resources for joint clinical trials, capacity building and networking activities.

In particular, EDCTP funds projects to create and develop capacity for ethical review of clinical trials and to improve regulatory frameworks for drug approval.

Charles Mgone, executive director of EDCTP, told SciDev.Net that the new funding will go to help all these activities, with the "lion's share" being given over to clinical trials.

"Quite often when there is North-South collaboration, the ideas come from the North, the money comes from the North, even the principal investigators come from the North," says Mgone.

"These [EDCTP-funded] projects empower Africans, enabling them to take ownership over the projects and do the work. Looking at the 27 projects we have approved, around 24 of them have African principal investigators working in Africa."

Victor Mwapasa from the Malawi College of Medicine is one such example. He and his colleagues are looking at whether antimalarial drugs, specifically artemisinin-based combinations, are safe to use in two particular groups - those who are HIV positive and children aged under six months.

"Most studies looking at the safe use of antimalarials have tended to omit very young children, those who weigh less than five kilograms or are under six months old," Mwapasa told SciDev.Net. "But this is a high-risk malaria group."

Mwapasa says he is excited to be part of such a large collaboration with African and European researchers.

His team's research will also be carried out in Mozambique and Zambia. "We rarely do research together, despite sharing the same problems," he adds.

### **"Starting to gel"**

**Date:** 31 May 2008

**Source:** *Poz Magazine*

**Author(s):** Kellee Terrell

[http://www.poz.com/articles/2186\\_14600.shtml](http://www.poz.com/articles/2186_14600.shtml)

For positive people, an effective **microbicide** gel, applied vaginally or rectally to prevent HIV transmission, could one day reduce reliance on condoms. While two earlier **microbicides** proved ineffective, recent results from a three-year trial of Carraguard - a seaweed-based gel - offer both hope and disappointment:

- Carraguard was labeled "ineffective [in] blocking HIV transmission": Among women who used the gel, there were 134 new infections, compared to 151 for those using the placebo.
- Only 10 percent of participants used Carraguard during sex every single time, though, so the results may stem from poor adherence. Researchers plan to redesign trials to account for personal behavior.
- Carraguard was proved to be safe on women's genital surfaces - unlike some other **microbicides**, which damaged vaginal tissue, making it easier for HIV to penetrate. So Carraguard may provide a base for more potent HIV-preventing compounds in the future.

## "Prospects for HIV prevention"

**Source:** *Nat Med.* 2008 Jun 01;14(6):587. Editorial.

<http://www.nature.com/nm/index.html>

What are some options to halt the onslaught of AIDS in lieu of a vaccine? A recent article in the *Financial Times* reports that the World Bank is considering supporting a new approach to this problem: paying individuals to protect themselves. The plan would be a three-year trial in Tanzania in which participants are counseled on the prevention of sexually transmitted disease and are paid for periodically testing free of infection. A control arm would consist of individuals who receive only counseling.

A payment plan may prove better at preventing HIV infection than counseling - which, alone, has been largely ineffectual - but the approach will require careful evaluation.

Owing to the high cost of HIV tests, infection by other sexually transmitted pathogens, such as *Neisseria gonorrhoeae*, would be monitored. But if the incidence, transmission rates and detection accuracy of the sentinel pathogens are not equivalent to those of HIV, would the screening appropriately reflect the impact of the trial on HIV infection? Moreover, if individuals enroll in the hopes of receiving payments, the attrition rates for the two arms might differ dramatically, affecting the power of the study. And lengthy follow-up might be necessary to assess whether low-risk behavior is maintained in the long term or abandoned once payments stop.

In the US, the government is debating a different response to the global AIDS epidemic - whether or not to reauthorize the President's Emergency Plan for AIDS Relief (PEPFAR).

PEPFAR has provided \$15 billion over the past five years for AIDS treatment and prevention, making the US the largest contributor to AIDS relief in the world. Since its inception, PEPFAR has supplied antiretroviral treatment to almost 1.5 million HIV-infected individuals and aims, over the course of 10 years, to treat 2.5 million people, prevent

12 million new infections and care for 12 million persons affected by the AIDS epidemic. The bill's mandate expires this September, and the President has requested an additional \$30 billion for the next five years of the program.

In the past, the plan has garnered criticism because one-third of the funds are allocated to programs that promote abstinence - another approach that, by itself, has not halted the spread of HIV. In April, the US House of Representatives approved a bill that reauthorizes PEPFAR, increases its funding to \$50 billion and sensibly removes the one-third stipulation on the use of prevention monies, instead required more "balanced funding" of prevention measures. Reauthorization of the plan also expands its purview to support programs that help combat malaria and tuberculosis and improve health and education in general - efforts that are anticipated to indirectly affect the spread of AIDS.

But the bill must be approved by the US Senate, and seven senators seem intent on blocking its passage. At issue is the expansion of PEPFAR in both cost and scope. In a letter to the Senate Republican leader, the dissenting senators object to the funding increase, calling it "irresponsible," and claim it will benefit unduly program officers and consultants. To prevent this, they wish to restore a mandate that at least 55% of PEPFAR funds are used for treatment of HIV-infected individuals. The mandate was applied during the first five years of PEPFAR but removed in the reauthorization bill to give countries greater flexibility in spending decisions.

The senators reject the expansion of PEPFAR to projects addressing other health concerns, claiming that this "mission creep" turns PEPFAR into a development program and dilutes the focus on HIV/AIDS. And they attack the aid increase allocated to the UN to support the Global Fund to Fight HIV/AIDS, as well as the World Health Organization, which they state promotes "dubious health initiatives," such as needle exchange programs - and, apparently worse, HIV vaccine and **microbicide** research. The senators' objection to the bill may delay reauthorization of PEPFAR until 2009.

One critic accuses the senators of supporting human suffering through a lack of generosity and a conservative ideology that rejects practical HIV prevention measures. Tom Coburn, the senator leading the stand-off, insists that his intent is to secure treatment of HIV/AIDS. But the senators' letter undermines this contention - its criticism is squarely levied at the increased funding and breadth of PEPFAR, and its potential support of activities perceived by the senators to be morally suspect.

Coburn argues that "treatment is prevention," yet treatment alone is not curbing the spread of HIV, and prevention strategies of all forms are crucial to AIDS relief. And if distributing needles, condoms, and **microbicides** and improving the general health conditions of populations at risk are, in combination with treatment, the best bets in the war on AIDS in the absence of a vaccine, then such approaches - and PEPFAR's funds - should not be held hostage to the moral qualms of a few on the Senate floor.

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### 3. PUBLISHED RESEARCH: MICROBICIDE-SPECIFIC

**"Anti-Trichomonas activity of Sapindus saponins, a candidate for development as microbicial contraceptive"**

**Author(s):** Tiwari P, Singh D, Singh MM

**Reference:** N/A Epub ahead of print.

<http://jac.oxfordjournals.org/cgi/content/abstract/dkn223v1?maxtoshow=&HITS=4&hits=4&RESULTFORMAT=&andorexacttitle=and&andorexacttitleabs=and&fulltext=microbicide%2C+microbicides&andorexactfulltext=or&searchid=1&usestrictdates=yes&resourcetype=HWCIT&ct>

**Published Abstract:** Objectives: Trichomoniasis is the most common non-viral sexually transmitted disease and is caused by the protozoan *Trichomonas vaginalis*. In view of increased resistance of the parasite to classical drugs of the metronidazole family, the need for new unrelated agents is increasing. This study evaluates anti-*Trichomonas* activity of *Sapindus* saponins, a component of a herbal local contraceptive *Consap* recently marketed in India.

Methods: The parasites were treated with saponins for MIC determination. Anti-*Trichomonas* activity of the saponins was evaluated using a cytoadherence assay, the substrate gel electrophoresis method and RT-PCR analysis. The effect of saponins on the mitochondrial potential of the host was determined by fluorescence-activated cell sorter. Actin cytoskeletal staining was used to determine the effect on parasite cytoskeleton. Results: Using *in vitro* susceptibility assay, the MIC of *Sapindus* saponins for *T. vaginalis* (0.005%) was found to be 10-fold lower than its effective spermicidal concentration (0.05%). Saponins concentration dependently inhibited the ability of parasites to adhere to HeLa cells and decreased proteolytic activity of the parasite's cysteine proteinases. This was associated with decreased expression of adhesin AP65 and membrane-expressed cysteine proteinase TvCP2 genes. Saponins produced no adverse effect on host cells in mitochondrial reduction potential measurement assay. Saponins also reversed the inhibitory mechanisms exerted by *Trichomonas* for evading host immunity. Early response of saponins to disrupt actin cytoskeleton in comparison with their effect on the nucleus suggests a membrane-mediated mode of action rather than via induction of apoptosis. Conclusions: Findings demonstrate the potential of *Sapindus* saponins for development as a **microbicial** contraceptive for human use. Further studies are required to evaluate its **microbicial** activity against other sexually transmitted infections.

### "Engineering human vaginal lactobacillus for surface expression of two-domain CD4"

**Author(s):** Liu X, Lagenaur LA, Lee PP, et al

**Reference:** N/A Epub ahead of print.

<http://aem.asm.org/cgi/content/abstract/AEM.00104-08v1?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:** Women are at significant risk of heterosexually transmitted HIV infection, with the mucosal epithelium of the cervix and vaginal serving as a major portal of entry. The cervico-vaginal mucosa naturally harbors dynamic microflora composed predominantly of lactobacilli, which may be genetically modified to serve as a more efficient protective barrier against heterosexual transmission of HIV. We selected a vaginal strain of Lactobacillus, *L. jensenii* 1153, for genetic modification to display surface-anchored anti-HIV proteins. Genomic sequencing analyses revealed that the *L. jensenii* 1153 encodes several unique high-molecular-weight cell wall anchored proteins with a C-

terminal cell wall sorting LPQTG motif. In this report, we employed these proteins to express a surface-anchored two-domain CD4 (2D CD4) in *L. jensenii* 1153. Our studies indicated that the C-terminal cell wall sorting signal LPQTG motif alone is insufficient to drive surface expression of heterologous proteins, and display of surface-anchored 2D CD4 required native sequences of a defined length upstream of the unique C-terminal LPQTG cell wall sorting signal and the positively charged C-terminus in a *Lactobacillus*-based expression system. The modified *L. jensenii* displayed 2D CD4 molecules that were uniformly distributed on the bacterial surfaces. The surface-anchored 2D CD4 was recognized by a conformation dependent anti-CD4 antibody, suggesting that the expressed proteins adopted a native conformation. Establishment of this *Lactobacillus*-based surface expression system, with potential broad applicability, represents a major step toward developing an inexpensive, yet durable approach to topical **microbicides** for mitigation of heterosexual transmission of HIV and other mucosally transmitted viral pathogens.

**"Pre-clinical development as microbicide of zinc tetra-ascorbo-camphorate, a novel terpenoid derivative : Potent in vitro inhibitory activity against both R5- and X4- tropic HIV-1 strains without significant in vivo mucosal toxicity"**

**Author(s):** Saidi H, Jenabian M, Gombert B, et al

**Reference:** N/A 2(1):10.

<http://highwire.stanford.edu/cgi/medline/pmid;18522743>

**Published Abstract:** BACKGROUND: Terpenoid derivatives originating from many plants species, are interesting compounds with numerous biological effects, such as anti-HIV-1 activity. The zinc tetra-ascorbo-camphorate complex (or "C14"), a new monoterpenoid derivative was evaluated in vitro for its anti-HIV-1 activity on both R5- and X4- HIV-1 infection of primary target cells (macrophages, dendritic cells and T cells) and on HIV-1 transfer from dendritic cells to T cells. RESULTS: The toxicity study was carried out in vitro and also with the New Zealand White rabbit vaginal irritation model. C14 was found to be no cytotoxic at high concentrations (CC50 (greater than) 10 uM) and showed to be a potential HIV-1 inhibitor of infection of all the primary cells tested (EC50 = 1 uM). No significant changes could be observed in cervicovaginal tissue of rabbit exposed during 10 consecutive days to formulations containing up to 20 uM of C14. CONCLUSIONS: Overall, these preclinical studies suggest that zinc tetra-ascorbo-camphorate derivative is suitable for further testing as a candidate **microbicide** to prevent male-to-female heterosexual acquisition of HIV-1.

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#### **4. PUBLISHED RESEARCH: RELEVANT BASIC AND TRANSLATIONAL SCIENCE**

**"Maraviroc: The first of a new class of antiretroviral agents"**

**Author(s):** Macarthur RD, Novak RM

**Reference:** N/A Epub ahead of print.

<http://www.ncbi.nlm.nih.gov/pubmed/18532888>

**Published Abstract:** Maraviroc is the first US Food and Drug Administration-approved drug from a new class of antiretroviral agents that targets a host protein, the chemokine receptor CCR5, rather than a viral target. Binding of maraviroc to this cell-surface protein results in blocking human immunodeficiency virus type 1 (HIV-1) attachment to the coreceptor and prevents the virus from entering CD4(+) cells. In this review, we include the details of the discoveries that led to the development of this drug. The drug's pharmacology, including pharmacokinetics and drug interactions, is discussed, as are the clinical efficacy studies that led to licensure. HIV-1 mechanisms of resistance to maraviroc, assays to determine viral coreceptor use (tropism), drug safety, and clinical use of maraviroc are discussed at length.

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## 5. EPIDEMIOLOGY

### "Threat of global AIDS epidemic over, says WHO"

**Date:** 10 June 2008

**Source:** *The Times of India*

**Author(s):** Kounteya Sinha

[http://timesofindia.indiatimes.com/Threat\\_of\\_global\\_AIDS\\_epidemic\\_over\\_says\\_WHO/rssarticleshow/3115367.cms](http://timesofindia.indiatimes.com/Threat_of_global_AIDS_epidemic_over_says_WHO/rssarticleshow/3115367.cms)

A quarter of a century after AIDS first appeared, the World Health Organisation has for the first time said the threat of a global heterosexual pandemic outside Africa might have passed.

According to Dr Kevin de Cock, one of the world's leading epidemiologists and head of the organisation's HIV/ AIDS department, there has been a shift in the understanding of the risks posed by the virus.

HIV was earlier regarded as a risk to populations everywhere, irrespective of the percentages that practised unsafe sexual behaviour. But experts now believe that outside of sub-Saharan Africa, the disease is largely confined to high-risk groups like men having sex with men, sex workers and their clients.

Speaking to TOI from New York, Dr de Cock said, "If the virus had to cause an epidemic among the general population in India and China, as originally feared, why hasn't it happened till now? It doesn't look likely anymore."

Dr de Cock, who expressed doubts about predictions of an Africa-type situation developing in India, said prevention strategies need to be focused where HIV transmission is occurring. "India needs to look at who are getting infected more often and then target that section of society," he said. He called for massive investments in educating those most at risk rather than focus on a school AIDS programme. "Countries need to go where transmission is occurring, which they have not always been good at," he said.

The WHO expert said that unlike Africa, specially in its southern and eastern parts, where the virus has been found to be "self-sustaining" in the general population, a similar trend has not emerged in Asian countries. In these nations, the prevalence is mostly concentrated in groups at risk and their partners. "It is very unlikely that there will be a heterosexual epidemic in other countries outside Africa," Dr de Cock said, while emphasising that this should not breed complacency.

UNAIDS chief Dr Dennis Broun, too, agreed with Dr de Cock. He told TOI, "We made a mistake with our predictions.

However, the gloomy predictions were made seeing evidence that was available to us 10 years ago, which was minimal. Today, with all the accumulated information, it is unlikely that Asian countries will see a generalised epidemic."

Nearly 2.45 million Indians live with HIV with prevalence rate in the general population of 0.36%.

India is also home to nearly two lakh IDUs. Over 20% of them are HIV positive solely due to sharing of contaminated needles. India is also home to 2.5 million MSMs with HIV infection rates as high as 16%.

Critics of the global Aids strategy have always cried foul of the vast sums being spent educating people who were not most at risk from the disease when a far bigger impact could be achieved by targeting groups who are more vulnerable.

Dr de Cock admitted there were "elements of truth" to such criticism. There has been a view that UNAIDS had deliberately exaggerated the size and trend of the projected pandemic, besides hyping the potential for HIV in general populations creating an impression that just about everyone was at risk of AIDS.

"This led to billions of dollars being spent on AIDS rather than on other serious illnesses which face an acute fund crunch," a health ministry official said.

India's worries are concentrated in six states - Maharashtra, Tamil Nadu, Andhra Pradesh, Manipur, Karnataka and Nagaland.

**EDITOR'S NOTE: Another article reporting on this topic is available for public access at <http://www.nationalpost.com/opinion/story.html?id=577936>**

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## **6. HIV/AIDS VACCINES**

**"AIDS vaccines may not warrant tests in U.S. teens"**

**Date:** 09 June 2008

**Source:** *Bloomberg News*

**Author(s):** John Lauerma

<http://www.bloomberg.com/apps/news?pid=newsarchive&sid=aL1GqKdC0HDE>

Early testing of experimental AIDS vaccines in teenagers may be ethically justified in countries where the disease is spreading more quickly than in the U.S., scientific advisers said today.

The risks of such trials may not outweigh the benefits in the U.S., according to the panel advising the Food and Drug Administration.

The advisers to the FDA are seeking ways to improve research guidelines for clinical trials in children. The panelists began looking at ethical as well as medical questions that would arise in developing treatments for disorders such as asthma, finding medical uses for stem cells and creating potential AIDS vaccines.

"There was agreement that AIDS trials in adolescents should take place in countries where adolescents are at higher risk for AIDS and that's in other countries," including in Africa, said Norman Fost, a pediatrics professor at the University of Wisconsin in Madison. Fost is chairman of the panel meeting today and tomorrow in Gaithersburg, Maryland.

Children often don't respond to drugs the same way adults do, according to scientists. Congress passed legislation in 2002 granting drugmakers extended patents on medicines that have been tested in children and mandating that the FDA hire a pediatric ethicist to push for safe medical research in children.

Robert Nelson, who has held that position for the past 18 months, asked that the advisory panel's two-day session be held to discuss research that poses some risk to children while offering them the prospect of benefit.

#### *Review Boards*

The area hasn't been given adequate attention, and the meetings may lead to guidance documents for the institutional review boards, or IRB's, that oversee proposed research on humans, Nelson said.

"This morning's discussion started with the HIV case but moved into a discussion of principles that have more general applicability," he said in an interview at the meeting.

Experimental products such as AIDS vaccines can pose risks to study participants. Whitehouse Station, New Jersey-based Merck and Co. was forced to halt a study of an AIDS vaccine last year after 49 people who received it became infected with the virus that causes the disease, compared with just 33 people in a group that got placebo inoculations.

Researchers had considered adding adolescents to another study of the Merck vaccine in Africa, said Alan Fix, a panel member who is chief of the Vaccine Clinical Research Branch at the U.S. National Institutes of Health in Bethesda, Maryland. The issue was still under FDA consideration when the results from the Merck trial, called STEP, became public, and the African test was also halted, he said in a telephone interview.

#### *Considering Risks*

"There was interest in seeing how this could be done," he said. "Then the STEP results came out, so it became a non-issue."

Scientists and companies are discouraged from doing research on children that poses any significant risks because kids have limited legal standing and mental ability to make decisions for themselves. While that protection is valuable, it means that the effects of drugs and other therapies on children is often inadequately understood, said Eric Kodish, chairman of the department of bioethics at the Cleveland Clinic.

"In any disease, doctors who take care of adults have more scientific evidence to use than those taking care of children," Kodish said in a June 6 phone interview from his office.

The agency will also use the meeting to consider the risks and benefits of experimental treatment with powerful stem cells that can make any tissue in the body. The FDA put on hold in May a planned test by Menlo Park, California-based Geron Corp. of a stem cell therapy for patients with spinal cord injuries.

### **"Nonhuman primate models and the failure of the Merck HIV-1 vaccine in humans"**

**Author(s):** Watkins DI, Burton DR, Kallas EG, et al

**Reference:** N/A (14):617-21. Perspective Abstract.

<http://www.nature.com/nm/journal/v14/n6/abs/nm.f.1759.html>

**Published Abstract:** The adenovirus type 5 (Ad5)-based vaccine developed by Merck failed to either prevent HIV-1 infection or suppress viral load in subsequently infected subjects in the STEP human Phase 2b efficacy trial. Analogous vaccines had previously also failed in the simian immunodeficiency virus (SIV) challenge-rhesus macaque model. In contrast, vaccine protection studies that used challenge with a chimeric simian-human immunodeficiency virus (SHIV89.6P) in macaques did not predict the human trial results. Ad5 vector-based vaccines did not protect macaques from infection after SHIV89.6P challenge but did cause a substantial reduction in viral load and a preservation of CD4+ T cell counts after infection, findings that were not reproduced in the human trials. Although the SIV challenge model is incompletely validated, we propose that its expanded use can help facilitate the prioritization of candidate HIV-1 vaccines, ensuring that resources are focused on the most promising candidates. Vaccine designers must now develop T cell vaccine strategies that reduce viral load after heterologous challenge.

### **"The hunt for an HIV vaccine: time to rethink recent failures"**

**Source:** *Lancet*. 2008 Jun 07;371(9628):1897-98. Comment.

**Author(s):** Adriano Boasso, Gene M Shearer, Mario Clerici, et al

<http://www.thelancet.com/journals/lancet/article/PIIS0140673608608120/fulltext>

With no candidate vaccines for HIV so far proving to be successful, the much discussed failure of Merck's STEP trial<sup>1</sup> has exacerbated the sober mood in AIDS vaccinology. This depressed mood was much in evidence at the Conference on Retroviruses and Opportunistic Infections held in Boston, MA, USA, on Feb 3-6, 2008.

New, bold, revolutionary ideas are urgently needed in the design of novel vaccine approaches to HIV infection. The National Institute of Allergy and Infectious Diseases (NIAID) understands this need and called for a seminal meeting (Bethesda, MD, USA; March 25, 2008), in which experts in the field discussed how to face the problem. The agenda focused on vaccine development, animal models, and clinical trials, and the delegates emphasised that discovery and innovative research should lead the way over vaccine generation. This need for basic research appears even more stringent if one considers that the NIAID summit did not address the question as to why the immunisation strategies used so far have been unsuccessful. What is the purpose of designing new vaccines if we do not explore why the old ones have failed? Most vaccines are designed to induce immune responses that are stored as immunological memory, to rapidly recognise and clear the pathogen on subsequent exposure. Why is the same not happening for HIV? Even HIV vaccines successfully designed to induce efficient responses in healthy individuals do not appear adequate to prevent infection. It should be clear by now that an effective vaccine against HIV will require knowledge of the immunology of HIV infection that goes beyond the application of the immunisation-memory-response paradigm. This understanding should be a goal of the innovative research that the summit has recommended.

One contribution to vaccine failure could be HIV's ability to activate multiple mechanisms of immune downregulation.<sup>2</sup> HIV-associated disease is characterised by blunted immune responses, particularly those that require T cells.<sup>2</sup> It has been known since the early years of HIV research that immune responses against antigens to which the host had previously been primed are progressively lost during HIV infection.<sup>3</sup> Some of the mechanisms that contribute to this functional impairment have been identified as physiological immunoregulatory systems that control the immune balance and are kidnapped by HIV for its own advantage upon the first contact with the immune system.<sup>2,4,5</sup> If, during viral challenge, these immunosuppressive mechanisms are activated at the site of HIV entry, even efficacious vaccines might not fulfil their protective potential. An important example of such an event is the rapid depletion of mucosal CCR5+ CD4 T cells during the early stages of infection.<sup>6</sup> These cells in the immunological memory are the very ones that a vaccine is designed to trigger and expand.<sup>6</sup> How likely is it that immunological memory would protect the host, if, at the time of challenge, HIV not only resets the system into a suppressive mode, but also rapidly eliminates memory cells that the vaccine efficiently activated? Little if any consideration was given to this issue at the Bethesda summit.

The secondary immune response fails to anticipate and counteract HIV-mediated immunosuppression, and allows the virus to establish infection. The integration of the viral genome into the hosts poses further limits to HIV eradication. Although some immunisation strategies against simian immunodeficiency virus tested in the macaque model failed to protect against infection, they were efficient at inducing an immune response that limited viral replication, resulting in a slowly progressive disease.<sup>7</sup> This strategy, aimed at providing the immune system with the weapons to control infection rather than prevent it, represents a different concept, in that although infection may not be avoided, progression of disease may be slowed or stopped.

An efficient, protective immune response may have to block HIV-mediated immune suppression upon challenge. Besides the unfeasibility of treating a patient with immunomodulatory agents at the time of challenge, the limited knowledge of how HIV interferes with immune function and the risk of disrupting immune balance and inducing autoimmunity impede the design of immunotherapeutic approaches. A more efficient strategy might involve preventing or limiting the interaction of HIV with the immune system. The initial binding of the HIV envelope gp120 with its main cellular receptor, CD4, is essential for both HIV infection and immunopathogenesis.<sup>8-10</sup> Vaccine-induced mucosal antibodies that obstruct gp120-CD4 interactions might not only limit the infectious events, but also prevent HIV-

induced immunosuppression, thereby sparing other potentially protective components of adaptive immunity. An antibody barrier at the mucosal level, which protects immune cells from the adverse effects of their encounter with HIV, might allow the activation of T-cell-mediated responses of higher quality. Can mucosal antibodies gain some time for memory T-cell responses to be activated before HIV-mediated immune suppression occurs?

Consideration should be given to the fact that potentially efficacious HIV vaccines have already been developed and tested. However, their protective potential may have been frustrated by the rapid and powerful induction of suppressive mechanisms that block protective immunity at the site of viral entry. As noted in the NIAID meeting, this is the time for new thinking, the time to develop and test novel approaches with courage and resolve. Indeed, it is time for revolutionary, not evolutionary thinking.

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## 7. OTHER PREVENTION APPROACHES

### "HIV/AIDS implementers' meeting closes in Uganda; participants call for increased prevention efforts"

**Date:** 09 June 2008

**Source:** *Kaiser Daily HIV/AIDS Report*

[http://www.kaisernetwork.org/daily\\_reports/rep\\_index.cfm?DR\\_ID=52598](http://www.kaisernetwork.org/daily_reports/rep_index.cfm?DR_ID=52598)

The 2008 HIV/AIDS Implementers' Meeting in Kampala, Uganda, closed on Saturday with participants calling for an increase in efforts to prevent the spread of the virus worldwide, Xinhuanet reports. "Our chief weapon against HIV/AIDS has always been and must continue to be prevention," Ugandan first lady Janet Museveni said at the close of the conference, adding, "People need not only to learn but also be reminded constantly that their own line of defense against this killer disease, which has no cure, is to avoid contracting it in the first place." Joy Phumaphi, World Bank vice president of human development, said that prevention should be emphasized because HIV/AIDS treatment is expensive and has significant economic impacts. "It is more urgent for us to arrest the spread of [the] epidemic than it has ever been," she said (Xinhuanet, 6/7). George Tembo of UNAIDS also said treatment "costs much more (than prevention), and there is a huge need for" partners to invest "in this area." Tembo also called on governments to ensure that HIV/AIDS prevention, treatment and care are considered human rights issues (New Vision, 6/8).

Conference participants also said that countries should establish their own national prevention strategies because the factors that contribute to the spread of HIV are different in each country (Xinhuanet, 6/7). "Each country has a unique case; you can't say you are using one method for all countries," Phumaphi said. She added, "Let us carry the new ideas back to our countries and make careful and evidence-based decisions, especially in prevention." Phumaphi also said that HIV/AIDS has underscored the need to invest more resources to the development of health infrastructures. "There are not enough resources going to health care," Phumaphi said, adding that African countries should meet pledges made at a 2001 conference in Abuja, Nigeria, to devote 15% of their national budgets to health care (New Vision, 6/8).

Archived webcasts from the meeting will be available online at [kaisernetwork.org](http://kaisernetwork.org).

## **"Congo: You, me and the condom"**

**Date:** 06 June 2008

**Source:** *PlusNews*

<http://www.irinnews.org/Report.aspx?ReportId=78617>

After a long day's work at a printing office in Brazzaville, capital of the Republic of Congo (RoC), Andre Mikangou\* usually buys a bottle of beer at the local petrol station shop and gets some locally produced Ami-3 condoms from the vending machine.

"I slipped my 100 CFA franc (US\$0.28) coin into the vending machine and a three-pack of condoms dropped down," said Mikangou, who is in his fifties.

"Many people who have used this very simple service told me about this facility to get hold of condoms immediately. I didn't believe it, but now I can't doubt it any more. I am going to try these condoms that everyone is talking about," he told IRIN/PlusNews before finishing his beer in one go and heading off to catch a taxi.

The vending machine is located in a convenience store at petrol station that is open nearly 24 hours a day in Makelekele, a densely populated neighbourhood in the south of Brazzaville.

Condom dispensers are now found in most of the RoC's busiest towns, thanks to an initiative by the National AIDS Council (Conseil national de lutte contre le sida - CNLS), in partnership with the UN Population Fund, which has installed around 40 machines across the country to promote condoms.

"The term, 'Ami 3', comes from the fact that because of AIDS, the act of sex no longer involves two parties, but three: me, my partner and the condom, which is becoming unavoidable," said Maurice Ndefi, director of the association to support community health initiatives (Association pour l'appui aux initiatives de sante communautaire - AAISC).

AAISC, which runs Ami 3's marketing programme, set up a condom distribution and sales network in 2007, covering 12 states in the RoC, including Sangha State in the north, where 82 percent of the people living with HIV are found. The national HIV prevalence rate is estimated at 4.2 percent.

Last year about seven million male condoms were distributed by various outlets, 300,000 of which were bought from vending machines installed in areas frequented most regularly by young people, particularly dance bars, university campuses, theme parks and hotels. Petrol stations were also targeted, as taxi and bus drivers are one of the sections of society most exposed to infection, according to CNLS.

### *The third partner*

To make consumers more aware of the need to use condoms, an advertisement is aired every evening in a popular television programme from Cote d'Ivoire, broadcast on Congolese national television. "In the age of AIDS, relations with three parties, not two, are safer and more reliable," the characters from the series remind viewers.

The packs of three cost 100 CFA francs (\$0.28) from vending machines and 50 CFA francs (\$0.14) from other distribution points like hospitals and pharmacies. They are also handed out free at specific awareness events.

"Ami 3 is well received by young people. They are well lubricated, strong, extra-thin and do not tear easily," said Lydie Blanche Mahoundi, who is responsible for promotion, information, education and communication at AAISC.

Juliette Ngoma, a student at the Marien Ngouabi University in Brazzaville, agreed: "Even the packaging of Ami 3 is reassuring. It is really easy to use. It would only rip if the man was being violent."

Young people are not the only ones receptive to the condom promotion messages, and willing to take advantage of being able to buy them discretely and easily, said Achille Mongo, one of the people in charge of a petrol station with a vending machine.

"Young people and adults are coming down to the station all the time to buy their condoms," he said. "Some days there are more older people than young coming to stock up on supplies."

According to the last sentinel survey carried out by the national health authorities in 2003, with support from the World Bank, 95 percent of people living with HIV in Congo were infected while having sex. AAISC plans to make the same quantity of condoms available in 2008.

### **"Consistent condom use in married Zimbabwean women after a condom intervention"**

**Author(s):** Callegari L, Harper CC, van der Straten A, et al

**Reference:** N/A 35(6):624-30.

<http://www.stdjournals.com/pt/re/std/abstract.00007435-200806000-00019.htm;jsessionid=LPQQ20TBGrnxvDz6qLwwWZ2yBgPS17js1p80qf42YnJtLDdgtWx!-1809387994!181195628!8091!-1>

**Published Abstract:** Objectives: Condom use to prevent HIV in Africa has increased in nonmarital sexual encounters but remains low within marriage. Married women of reproductive age, however, are at high risk of HIV. Goal: This study investigated factors associated with consistent condom use after a brief intervention. Study Design: We conducted an HIV prevention condom intervention with a cohort of 394 married women, aged 17 to 47, recruited from clinics in Zimbabwe. Consistent condom users were ineligible. At enrollment, participants received education and were offered free male and female condoms and HIV testing. Women completed a follow-up questionnaire at 2-months. We used logistic regression analysis to measure the association of protected sex (i.e., 100% use of male or female condoms) at follow-up with condom attitudes, negotiation skills, HIV risk perception and testing. Results: At follow-up, 179 (48.5%) women reported consistent condom use throughout the study, and 318 (87%) reported condom use at last sexual episode; 72 women tested HIV-positive, only 4 of whom reported at enrollment that it was likely that they were infected. Results showed that women who tested positive were more likely to report consistent condom use (OR 2.9, 95% CI 1.7-5.2). HIV risk perceptions and condom negotiation self-efficacy increased postintervention, and were significantly associated with consistent condom use. Hormonal contraception was negatively associated with consistent condom use (OR 0.3, 95% CI 0.19-0.65). Conclusions: Married women reported significant increases in consistent condom use in response to a brief intervention, especially if HIV-positive.

## "Integrating multidimensional HIV prevention programs into healthcare settings"

**Author(s):** Temoshok LR, Wald RL

**Reference:** N/A 70(5):612-19. Epub ahead of print.

<http://www.psychosomaticmedicine.org/cgi/content/abstract/70/5/612?maxtoshow=&HITS=2&hits=2&RESU LTFORMAT=&andorexacttitle=and&andorexacttitleabs=and&fulltext=microbicide%2C+microbicides&andorexactfulltext=or&searchid=1&usestrictdates=yes&resourcetype=HWC>

**Published Abstract:** Effective secondary prevention programs to reduce HIV transmission risk-relevant behaviors among HIV-infected individuals must go beyond the traditional, common sense prevention components to develop biomedically and epidemiologically informed behavioral interventions as part of comprehensive, integrated, multidisciplinary HIV care. Incorporating and expanding on the Serostatus Approach to Fighting the Epidemic, a five-pronged strategy set forth by the Centers for Disease Control and Prevention in 2001, we discuss recent findings from the biomedical sciences on viral and host factors that influence infectiousness to support the idea that the most proactive prevention programs will explicitly integrate biomedical interventions and approaches designed to reduce infectiousness, and thus the sexual transmission of HIV. Based on studies of emerging and spreading drug-resistant HIV variants, we have posited the potential development of biodisparity as the biological entrenchment of disparities in socioeconomic status, access to care, and HIV risk-relevant behaviors that differentially affect minorities living with HIV in the US. It is clear that creative approaches based on an expanded behavioral medicine interface with the latest HIV biomedical and epidemiological research are needed to enhance the efficacy of HIV secondary prevention.

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## 8. POLITICS AND POLICY

### "U.N. Secretary-General calls for end of discrimination against, travel restrictions on people living with HIV/AIDS"

**Date:** 11 June 2008

**Source:** *Kaiser Daily HIV/AIDS Report*

[http://www.kaisernetwork.org/daily\\_reports/rep\\_index.cfm?DR\\_ID=52657](http://www.kaisernetwork.org/daily_reports/rep_index.cfm?DR_ID=52657)

United Nations Secretary-General Ban Ki-moon at the opening of the U.N. 2008 High Level Meeting on AIDS on Tuesday called on the international community to end discrimination against HIV-positive people, including travel restrictions, describing such practices as "an affront to our common humanity," Xinhuanet reports. Ban also said that such discrimination "drives the virus underground, where it can spread in the dark; as important, it is an affront to our common humanity" (Xinhuanet, 6/10). Ban said that 60 years after the adoption of the Universal Declaration of Human Rights, "it is shocking that there should still be discrimination against those at high risk, such as men who have sex with men, or stigma attached to individuals living with HIV."

According to UNAIDS, 74 countries have travel restrictions in place for HIV-positive people, including a mention of the disease on their passports. Twelve countries -- Armenia, Colombia, Iraq, Oman, Qatar, Russia, Saudi Arabia, Solomon Islands, South Korea, Sudan, the U.S. and Yemen -- bar entry to people with HIV/AIDS, often citing public health concerns and the high cost of treatment. Three hundred forty-five nongovernmental organizations signed and sent a letter to worldwide leaders and ambassadors to urge countries that impose travel restrictions to lift them. President Elias Antonio Saca of El Salvador, who lifted travel restrictions in the country four years ago, said he supports the NGOs' petition. "I appeal to the international community and all governments for the scrapping of walls and barriers which restrict the free movement of people living with HIV," Saca said. Innocent Laison, a member of the Senegalese NGO AfriCASO, also denounced the travel restrictions, saying that countries that enforce them allow their own HIV-positive citizens to travel abroad (AFP/Yahoo! News, 6/10).

Also at the meeting, Anthony Fauci, director of NIH's National Institute of Allergy and Infectious Diseases, said that more efforts should be made to develop a safe and effective HIV/AIDS vaccine following the cancellation of a Merck trial last year. "Such disappointments are not unusual," Fauci said, adding, "Researchers normally experience numerous setbacks and disappointments, yet they persevere. Finding a safe and effective HIV vaccine requires the same kind of resolve" (Lauerman, Bloomberg, 6/10).

Archived webcasts of the sessions will be available after 5 p.m. ET on June 18 at [kaisernetwork.org](http://kaisernetwork.org).

### **"UNAIDS Executive Director Piot to step down"**

**Date:** 11 June 2008

**Source:** *Kaiser Daily HIV/AIDS Report*

[http://www.kaisernetwork.org/daily\\_reports/rep\\_index.cfm?DR\\_ID=52658](http://www.kaisernetwork.org/daily_reports/rep_index.cfm?DR_ID=52658)

UNAIDS Executive Director Peter Piot will step down from his position when his term is over at the end of the year, United Nations Secretary-General Ban Ki-moon announced on Tuesday at the United Nations 2008 High Level Meeting on AIDS in New York, Reuters reports. Piot has served as UNAIDS executive director since the organization's inception in 1995.

Piot's replacement has not been named, according to Reuters (Bases, Reuters, 6/10). The next executive director will be chosen by the chair of the UNAIDS Program Coordinating Board, which currently is the U.S., according to UNAIDS spokesperson Mahesh Mahalingam. The final decision is up to Ban, he added. Piot said that he likely will take a job in academia.

Piot in April informed the UNAIDS board that he would step down. According to Bloomberg, Piot told the board that an ongoing five-year evaluation of UNAIDS, as well as the preparation of a new budget and plan, presented an "opportune time" to leave. "Both of these developments provide space for my successor to shape the program as they see fit and under your guidance," Piot said.

According to Piot, his largest accomplishments were increasing attention paid to HIV/AIDS at the United Nations and in governments worldwide. This contributed to larger amounts of funding being allocated for prevention and treatment programs, according to Bloomberg. "I had three goals when I took this job," Piot said, adding, "One was to put AIDS

on the agenda, two was to form a broad coalition and three was to mobilize the money." Ban said that Piot's work has helped to increase the number of people in developing countries with access to antiretroviral drugs. Ban also said, "We need more leaders like Dr. Piot in every sector of society" (Lauerman, Bloomberg, 6/10).

### **"Africa: Women say regional AIDS plan falls short"**

**Date:** 10 June 2008

**Source:** *Inter Press Service News Agency*

**Author(s):** Nergui Manalsuren

<http://allafrica.com/stories/200806110003.html>

Despite the admirable progress made by some African countries in preventing and treating HIV/AIDS since 2000, 14 million Africans have died of AIDS in that time span, and an additional 17 million have been infected, says a new report on HIV/AIDS on the continent.

According to the report "Securing Our Future" launched Monday by the Commission on HIV/AIDS and Governance in Africa, the disease is reducing capacity in all social and economic sectors, undermining and slowing the overall development of the region.

It estimates that by 2020, the nine most severely hit sub-Saharan countries may lose 13-26 percent of their agricultural workers to AIDS -- people who are also household heads, mothers and fathers of young children, and have many more roles that contribute to their societies.

The report was released as heads of state, diplomats and civil society groups gathered at U.N. headquarters Tuesday for a two-day high-level meeting to review progress since the General Assembly issued a major declaration on HIV/AIDS in 2001 and to seek renewed commitments for funding and political will to tackle the disease. The commission on Africa presented an action plan calling for a stronger policy and programmatic response in the areas of prevention, treatment and financing, including a new donor framework for funding.

Speaking at a press conference, Peter Piot, the head of UNAIDS, said the report "addresses not only medical and health aspects", but also the impact of the disease on governance, answering questions such as: "What should African countries do? What are the impacts on society beyond the health sector? Does it affect the capacity of continuing resilience particularly in Southern Africa in terms of public service that can be provided, and private sector, and what it can do to labour, and et cetera?" However, some civil society representatives said the commission had fallen short in its mission.

"It is disappointing that the report does not focus on the key current challenges in Africa, such as governments' failure to meet their Abuja commitment to allocate 15 percent of their budgets to health, the threat to the funding and political commitment to the universal access [to treatment] goal by 2010," Aditi Sharma of Action Aid, an international NGO, told IPS. She also cited rising fatalities from tuberculosis, the threat posed by drug-resistant strains of HIV, and "the growing criminalisation of HIV transmission across the region."

Both Sharma and Olayide Akanni of the Nigerian group Journalists against AIDS said that although the report identified many of the key drivers of HIV/AIDS, it failed to offer concrete solutions on what should be done. "It's not that the recommendations are bad, but they are not strong enough and fail to address women's issues," Akanni told IPS. Both NGO representatives were very critical that the report did not pay enough attention to gender equality and violence against women as key aspects of the pandemic.

The commission was largely male-dominated, with women comprising only six of the 19 members. In light of the fact that 61 percent of those living with HIV/AIDS in sub-Saharan Africa are women and girls, Sharma told IPS that "it is very disappointing not to have a strong focus -- or even a separate chapter -- on women given the feminisation of the pandemic."

"We are condemning the lack of action and resources to tackle the feminisation of the pandemic by governments and calling on them to put in place specific programmes with dedicated budgets to promote and protect women's rights -- such as the right to health and education, the right to inherit property, the right to land and livelihoods, the right to live free of violence and sexual and reproductive health and rights," she told IPS. "I would've really expected, as an activist, a strong recommendation on how to improve in terms of political accountability of African governments," Sharma added. "We are also calling for greater involvement and leadership of women's rights advocates, especially women living with HIV, in the design and implementation of national and regional AIDS responses," she continued.

Speaking on Monday, U.N. Secretary-General Ban Ki-moon addressed the critical role of tackling the epidemic as "a prerequisite" for reaching almost all of the Millennium Development Goals set by world leaders in 2000 to significantly reduce hunger, poverty and malnutrition, and promote gender equality, among other things, by 2015. Progress toward the Millennium Development Goals at their midpoint will be reviewed by the General Assembly this September.

**EDITOR'S NOTE: The report "Securing Our Future" is available for public access at <http://www.uneca.org/chga/Report/CHGARReport.pdf>**

### **"Drop in FDA warning letters points to enforcement shift"**

**Date:** 06 June 2008

**Source:** *Wall Street Journal*

**Author(s):** Jared Favole

[http://online.wsj.com/article\\_email/BT-CO-20080606-711156-klyVDAtMEM4TzAtOTlwMDkwWj.html](http://online.wsj.com/article_email/BT-CO-20080606-711156-klyVDAtMEM4TzAtOTlwMDkwWj.html)

U.S. Food and Drug Administration warning letters to companies dropped by half in the last 10 years, highlighting a change in enforcement tactics at an agency facing criticism about its policing of the food and drug industries.

In 2002, the FDA changed its policies and required that all warning letters go through the FDA's chief counsel office, a move designed to strengthen the letters and make them legally consistent and credible.

The year before this change took effect, in fiscal year 2001, the agency issued 1,032 warning letters. In 2006, the FDA sent 538 letters, and in 2007 it sent 471, FDA data show. The FDA sends warning letters for an array of reasons, from the mislabeling of chocolate chip cookies to the improper manufacturing of blood bags.

Some members of Congress, FDA staffers and former FDA officials have criticized the change, suggesting it favored industry. Since taking control of Congress in 2007, Democrats have stepped up attacks on what they charge is the Bush administration's tendency to tolerate lax regulatory enforcement at the FDA and a number of other government agencies.

"The number of warning letters has always been one of the surrogate measures of FDA's enforcement performance," said David Kessler, who was FDA commissioner from 1990 to 1997 under President Bill Clinton. "It's not the only measure, but any significant drop raises significant questions of what's going on."

Though complying with warnings in the letters is voluntary, the violations could lead the FDA to seize a company's product or take them to court. In certain circumstances, the FDA could refuse to approve company's products.

#### *'Legally Credible'*

Dan Troy, former FDA general counsel and an architect of the policy change, said the legal review process was aimed at making the letters consistent and legally credible and countering industry sentiment that the FDA didn't always follow through on the warnings.

The current FDA commissioner, Andrew von Eschenbach, acknowledged the drop in warning letters, but said the agency sends them now for more serious deviations rather than minor ones.

"You may see a change in the number, but you're seeing a focus on a grain size," von Eschenbach said Wednesday. The letters now going out are for transgressions "that we think are going to be important," he added.

David Elder, director of the FDA's office of enforcement, warned against measuring the agency's enforcement success by counting warning letters.

"Numbers of warning letters are just conveniently easy to measure," Elder said. Measuring the agency's efforts to protect public health "is a much more complicated analysis," he said.

The decline in warning letters came as the FDA changed its enforcement approach. Rather than sending out individual warning letters to separate companies for similar violations, the FDA alerts the industry via press releases and other forms of communication when it notices a trend of problems, he said.

This method, Elder said, results in "more widespread" compliance than an individual warning letter.

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

#### **"NIH to overhaul peer review of grants"**

**Source:** *ScienceNow Daily News. 2008 June 06.*

**Author(s):** Jocelyn Kaiser

<http://sciencenow.sciencemag.org/cgi/content/full/2008/606/1?etoc>

The U.S. National Institutes of Health (NIH) today released a widely anticipated plan to improve its system for peer reviewing grant proposals. The plan generally follows the recommendations of two advisory committees, including shortening the grant application. But NIH rejected a more radical suggestion aimed at eliminating an apparent bias toward researchers who resubmit their grant applications. Instead, NIH will try other ways to fund the best ideas quickly.

One year ago, NIH Director Elias Zerhouni asked external and internal advisory panels for advice on how to cope with a record number of applications, a flat NIH budget, and a shortage of quality reviewers. The two panels issued recommendations this winter (*Science*, 29 February, p. 1169). NIH's response was presented today to the Advisory Committee to the Director by National Institute of Dental and Craniofacial Research Director Lawrence Tabak.

NIH agreed with the panels on the need to shorten the application--by more than half, from 25 pages to 12--and to emphasize the anticipated impact of the research over methods and other details. Applicants will also be given more explicit feedback on their proposals. To attract more reviewers, NIH will allow them to serve over 6 years rather than 4 years, test out online reviews to reduce travel (review committees currently meet in person), and give those who attend at least 18 meetings a grant supplement of up to \$250,000, about as much as 1 year of an average grant. NIH also plans to have reviewers segregate the applications of young investigators from the rest of the pool and assign a different NIH-wide cutoff point for funding them so that at least 1500 a year are funded.

However, NIH officials nixed the panels' recommendation to jettison a system in which unsuccessful applicants can resubmit their proposal two more times. Reviewers tend to favor these amended applications (A1s and A2s) over first-time awards (A0s) because the applicant responded to reviewers' comments or out of sympathy, the advisory committee found. Since the doubling of NIH's budget ended in 2003, the percentage of first-time applications funded has shrunk from 60% of the total pool to about 30%.

To level the playing field, the advisory committee recommended that all proposals be considered "new." The committee also urged that the weakest proposals be marked "not recommended for resubmission." Its goal was fewer resubmissions and a lighter workload on reviewers.

These two proposals didn't go over well with the community. "There was a huge outcry about this. People feel like they need a second chance, a third chance," Zerhouni told *Science*. Rather than throw out the current system, the agency plans to "carefully rebalance success rates among" the three types of submissions so as to fund a larger portion of high-scoring grants on the first round, according to Tabak's slides. Tabak said this will be done by an institute's advisory council, which makes the final decisions about which grants to fund.

NIH's selective adoption of the recommendations is a relief to many scientists, says Howard Garrison, public affairs director of the Federation of American Societies for Experimental Biology in Bethesda, Maryland. "We're not comfortable with changing the system radically to reduce the number of resubmissions," he says. Keith Yamamoto, the University of California, San Francisco, cell biologist who co-chaired the external peer-review advisory committee with Tabak, says he's "disappointed" that NIH didn't follow all his group's suggestions. But Yamamoto says "I'm basically happy with" the report. NIH says it will take 18 months to implement the changes.

## "Payments in planned HIV trial raise ethical concerns"

**Source:** *Nat Med.* 2008 June;14(6):593. News.

**Author(s):** Meredith Wadman

<http://www.nature.com/nm/journal/v14/n6/full/nm0608-593a.html>

An unusual HIV-prevention trial planned to take place in rural Tanzania has sparked questions from ethicists. In the proposed trial, approximately 3,000 Tanzanians between the ages of 15 and 30 are slated to receive monthly cash payments of \$45 as an incentive to avoid diseases transmitted through unsafe sex. That's serious money in a nation where, in 2006, the World Bank put per capita income at \$350.

Bioethicists say that any ethics committee signing off on the trial must address the question of coercion. By paying \$45 monthly in a country as poor as Tanzania, "are you paying them so much that they can't refuse your offer?" asks Arthur Caplan, a bioethicist at the University of Pennsylvania in Philadelphia.

Researchers from the Ifakara Health Research and Development Centre (IHRDC) in southeastern Tanzania plan to conduct the trial in conjunction with scientists from the University of California system. On the IHRDC website, researchers trumpet the trial's "conditional cash transfers" approach as "a big advance in efforts to test public health ideas more rigorously" and note that some participants in a control arm will not be offered payments.

Testing for other sexually transmitted diseases will serve the trial as a proxy for determining HIV infection status. IHRDC researchers declined to elaborate further on the proposed trial when contacted by Nature Medicine.

The proposed three-year trial could potentially receive funding support from the World Bank. But Eric Chinje, manager of communications for the region of Africa at the World Bank, says that the institutions involved are still assessing the trial and "there is no consensus on its viability."

Karen Maschke, who focuses on ethics and science policy at the Hastings Center in Garrison, New York, points out that the behavior being encouraged by the payments is not entirely risk-free: "In some conditions, you are putting women at risk [of violence] for demanding safety during sex."

Bioethicist Stuart Rennie of the University of North Carolina at Chapel Hill agrees that the trial raises a list of issues, including the practical concern of how to keep a new infection confidential in a family counting on the income from the trial. Still, he says, the trial has clinical promise: "I think they should pilot it."

There is some precedent for cash incentive programs, albeit not involving sexual practices: In Mexico in the late 1990s, a government-sponsored program boosted class attendance significantly by offering cash rewards to poor families that sent their children to school. And, in the United States, a growing number of states provide financial incentives to encourage people receiving Medicaid to use preventive services and combat smoking and obesity. Whether these US interventions are effective, however, has not been proven in rigorous studies.

## 9. PHARMACEUTICAL INDUSTRY

### "Adaptive designs in the real world"

**Date:** 10 June 2008

**Source:** *Bio-IT World.com*

**Author(s):** Deborah Borfitz

<http://www.bio-itworld.com/issues/2008/june/cover-story-adaptive-trial-designs.html>

Among the broad array of statistical methodologies being piloted in clinical research, none draw as much hope and consternation than adaptive designs that involve interim data analysis. (See "Real-Time Trials," Bio-IT World, June 2006).

The potential of this approach is promulgated by vendors including Cytel and Tessella, which sell the accommodating software, together with a handful of evangelists within big pharma. Virtually unknown, however, is how these adaptive clinical trials (ACTs) play out in the real world and the overall tenor of regulatory agencies on the matter.

Aside from debate about the promise of ACTs in reducing development timelines and costs by utilizing actionable information sooner, much of the dialogue occurs behind closed doors. The FDA, which has been promising guidance on ACTs for more than a year, is currently handling novel designs on a "case by case basis" to give the agency "experience and definitions that will be useful for later advice," states Crystal Rice, spokesperson for the FDA's Center for Drug Evaluation and Research. The FDA does not track the number of adaptively designed protocols it evaluates, but "most all of the medical areas are receiving some protocols that have some aspect of the novel adaptive design associated with them."

Generically, an ACT describes an assortment of statistical approaches, including widely accepted designs such as "early stopping" and "dose-finding," says Donald Berry, head of the division of quantitative sciences and chairman of the department of biostatistics at the University of Texas MD Anderson Cancer Center. (Berry is also an independent adaptive design consultant.) Seamless trials, notably oncology studies that combine phases I and II, are also fairly common. Given the problems pharmaceutical companies have had in accurately establishing dosage, the FDA actively encourages adaptive approaches in early phase trials.

But in later stage ACTs, Berry says the FDA worries about the intrusion of bias and the inability to accurately read a treatment's false positive rate. "Almost all of [the ACTs] I've done," says Berry, "occurred before the confirmatory aspect kicked in." The exceptions were a few seamless phase II/III trials.

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

## "Drugs for developing countries"

**Date:** 03 June 2008

**Source:** *International Herald Tribune*

**Author(s):** Ellen 't Hoen

<http://www.ihf.com/articles/2008/06/03/opinion/edlet.php>

Oxfam is not, as Benedetto Della Vedova incorrectly asserts in his article "Patents are the wrong target" (Views, May 28), seeking to "scrap" the patent system.

Patents often lead to high prices for medicines in developing countries, yet developing countries can use the intellectual property system to address these concerns.

In 2001, all countries agreed to the Doha Declaration on Trade Related Aspects of Intellectual Property Rights, which stated that intellectual property rules do not and should not prevent countries from taking measures to protect public health.

Nevertheless, multinational pharmaceutical companies and rich countries have lobbied at times to discourage developing countries from using legal rules to ensure poor people have access to affordable medicines.

All countries must identify additional ways to ensure that pharmaceutical innovation works for poor countries. Stricter patent protection in developing countries will not lead to innovation that benefits the poor. The World Health Organization has declared that there is little to no evidence that patent rules boost research and development for medicines that address diseases that predominantly affect poor people.

They are not an attractive market for the pharmaceutical industry, so the medicines they need will not be provided under this system.

Even greater efforts than those few examples cited by Vedova will be required to overcome these critical gaps.

Bernice Romero, Washington Campaigns director Oxfam International

Benedetto Della Vedova argues that the World Health Assembly (WHA) should advance policies that are based on evidence when it comes to increasing access to essential medicines for people in developing countries. We could not agree more.

In 2003, the WHA created a commission that was tasked to look into ways to improve the current pharmaceutical research and development system so that desperately needed medical innovation takes place, and patients can access the fruit of this innovation.

Three years later, the commission concluded that the current patent system fails to deliver on both these points, and that there is no evidence stronger patent protection in developing countries will help.

These findings form the basis for the new WHO Strategy on Public Health, Innovation and Intellectual Property, which governments agreed to at the recent WHA meeting.

Every day, medical staff members of Medecins Sans Frontieres (MSF) witness first hand the failures of a market-driven pharmaceutical system, which caters to those who can pay large sums for their drugs, but leaves those who can't out in the dark. Tuberculosis is the poster child for these failures, where the newest drugs available were developed in the 1960s, and the most-commonly-used method to diagnose this curable disease - which continues to kill 1.7 million people each year - was developed nearly 130 years ago.

Changing the rules of the game will mean separating the cost of research and development from the price of products. MSF, other NGOs and some pharmaceutical companies have made proposals to improve the situation. We could establish prizes, a fund for neglected diseases, patent pools and not-for-profit drug development organizations. But Della Vedova's proposal to award innovation by giving marketing monopolies using the Orphan Drug Act - which allows the company to charge high prices - is absurd. How is increasing the price of new medicines for neglected diseases going to help the people that cannot afford to pay?

*Ellen 't Hoen, Paris Policy and Advocacy director Campaign for Access to Essential Medicines Medecins Sans Frontieres*

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## 10. ANNOUNCEMENTS

### 8th Annual Global Health Mini-University

[www.maqweb.org](http://www.maqweb.org)

Save the Date! Please join us for the 8th Annual Global Health Mini-University, sponsored by the United States Agency for International Development (USAID) Bureau for Global Health in collaboration with the George Washington University School of Public Health and Health Services. The event will be held on Friday, September 12, 2008 from 8:00am - 4:30pm at the George Washington University School of Public Health and Health Services, Ross Hall, 2300 Eye St NW, Washington, DC 20037.

Registration: Online registration will begin in mid-August at [www.maqweb.org](http://www.maqweb.org). This event is free and attendance is open to anyone interested in international health!

What is the Mini-University? The Mini-University is a day-long forum offering over 60 different sessions highlighting evidence-based best practices and state-of-the-art information from a variety of technical areas across the Global Health field. The forum is divided into four hour-long blocks, each offering 14 concurrent presentations. In addition, five exciting brown bag sessions are offered during the lunch break. The day culminates with a Knowledge Extravaganza session and the N'Lightening Round, a lively competition during which take-home messages from the sessions are presented and prizes are awarded for the top three.

Need CEUs? This year participants may choose from several courses offering Continuing Education Units from the American College of Nurse Midwives. More information will be available soon!

Questions? Contact Liz Greene at [egreene@usaid.gov](mailto:egreene@usaid.gov) or Chelsea Smart at [csmart@usaid.gov](mailto:csmart@usaid.gov)

## **Foundation Welcomes Dr. Nicholas Hellmann**

<http://www.pedaids.org/>

The Elizabeth Glaser Pediatric AIDS Foundation is pleased to announce the appointment of Dr. Nicholas Hellmann as Executive Vice President of Medical and Scientific Affairs.

In his role as Executive Vice President of Medical and Scientific Affairs, Dr. Nicholas Hellmann will provide leadership and strategic direction for the program implementation and research initiatives of the Elizabeth Glaser Pediatric AIDS Foundation, a worldwide leader in the fight against pediatric AIDS. In addition to guiding overall technical policy, Dr. Hellmann will work with members of the Foundation's leadership team to ensure an integrated approach to the Foundation's strategic goals.

Dr. Hellmann has a wealth of experience in HIV/AIDS issues, and was most recently at the Bill and Melinda Gates Foundation. He received his M.D. from the University of Kentucky, and completed his Internal Medicine Residency and Infectious Disease Fellowship training at the University of California, San Francisco, where he became an Assistant Professor in the Internal Medicine/Infectious Diseases Division.

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