



# ALLIANCE FOR MICROBICIDE DEVELOPMENT

**17 August 2007, Volume 8, Number 32**

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](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. MEDIA COVERAGE OF MICROBICIDES

##### "Microbicide trial: women get special treatment"

**Date:** 10 August 2007

**Source:** *New Vision*

**Author(s):** Irene Nabusoba

<http://www.newvision.co.ug/D/8/13/580715>

Women who got infected while participating in the failed trials of a **microbicide** gel designed to prevent the transmission of HIV, will receive free treatment.

Dr. Olive Sentumbwe, the national professional officer in charge of population and family planning at the World Health Organisation, announced this at the on-going fourth East African Sub-Regional African Women's Leadership Institute conference.

She said the results should not discourage other people from participating in future trials. "Research always has mishaps. It happens elsewhere but it does not mean you stop. The victims of the halted gel research will receive special treatment. They are martyrs. We should regard them as heroes because they have sacrificed their lives for the good of others."

**Microbicides** are substances that a woman can apply in her vagina before sexual intercourse to prevent HIV infection. They may include gels or creams. The trial of a **microbicide** was halted in Uganda recently because 25 women became infected despite using it, indicating that this particular product had no value in preventing HIV transmission. The same **microbicide** was tested in Benin, India, South Africa and Burkina Faso.

Sentumbwe said research should continue until scientists discover an effective **microbicide**. "We should adopt scientific research that can decrease HIV transmission in women. It is going to be difficult to empower women in fighting HIV/AIDS if we can't find special approaches for them." The annual event with the theme, 'women's right to health; contemplating sexual and reproductive health and rights', was organised by Akina Mama.

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## 2. PUBLISHED RESEARCH: MICROBICIDE-SPECIFIC

**"Can nucleic acid amplification tests be used to test for chlamydia and gonorrhoea in microbicide trials?"**

**Author(s):** Rizzo-Price P, Stamper PD, Wood BJ, et al

**Reference:** N/A 18(8):543-45.

<http://www.ingentaconnect.com/content/rsm/std/2007/00000018/00000008/art00007>

**Published Abstract:** **Microbicides** may interfere with detection of Chlamydia trachomatis (Ct) and Neisseria gonorrhoeae (Ng) in urine samples from women who use **microbicides**. The inhibitory effects of BufferGel, PRO2000 and PRO2000 placebo, in urine samples, were determined by nucleic acid amplification tests (NAATs). Uninfected urine was inoculated with different concentrations (10<sup>5</sup>-10<sup>1</sup> organisms/mL); **microbicides** were added to achieve final concentrations from 5% to 0.1%. Specimens were tested using strand displacement amplification (SDA) for Ct and Ng. Samples with BufferGel demonstrated no inhibition. Samples with PRO2000 showed inhibition at the 5% concentration when tested for Ct, whereas for Ng, PRO2000 showed inhibition at 5%, 2% and some 1% concentrations. The placebo showed no inhibition when detecting Ct, and variable inhibition at the 5% and 2% concentrations for Ng. The potential inhibitory effects of **microbicides** on the NAATs selected for detection of Ct and Ng should be considered in clinical trials involving topical **microbicides**.

### 3. PUBLISHED RESEARCH: RELEVANT BASIC AND TRANSLATIONAL SCIENCE

#### "Association between bacterial vaginosis and herpes simplex virus type-2 infection: implications for HIV acquisition studies"

**Author(s):** Nagot N, Ouedraogo A, Defer MC, et al

**Reference:** N/A 83:365-8.

<http://sti.bmj.com/cgi/content/abstract/83/5/365?etoc>

**Published Abstract:** *Objectives:* Bacterial vaginosis (BV) and Herpes simplex virus type-2 (HSV-2) have been linked to an increased risk of HIV-1 acquisition. Recent research suggests an association between BV and HSV-2 acquisition, but the converse has not been studied. Here, we investigate whether an association exists between BV and HSV-2 infection. *Methods:* We examined the determinants of BV occurrence in a cohort of female sex workers in Burkina Faso. Participants were followed every 3 months for diagnosis of genital infections and report of sexual behaviours. Factors associated with BV occurrence were assessed using generalised estimating equation models. *Results:* We enrolled 273 women (mean age, 28 years) and conducted 812 follow-up visits (mean 2.93 visit per woman). Baseline seroprevalence of HIV-1, HSV-2 and recent syphilis were 31.5%, 70.1% and 0.4%, respectively, while baseline prevalence of BV, *Trichomonas vaginalis* (TV) and *Candida albicans* were 20.5%, 3.3% and 2.5%, respectively. In multivariable analysis, HSV-2 (relative risk (RR) = 1.73, 95% CI 1.12 to 2.65), HIV-1 (RR = 1.76, 95% CI 1.30 to 2.40), TV (RR = 1.5, 95% CI 1.0 to 2.3), and having 3 sexual partners in the preceding week (RR = 2.2, 95% CI 1.1 to 4.6) were independently associated with BV, while hormonal contraception showed a protective effect (RR = 0.11, 95% CI 0.02 to 0.70). *Conclusions:* HSV-2 infection was associated with BV occurrence in this population. As HSV-2 is strongly linked to HIV-1 acquisition, studies assessing the cofactor effect of BV on HIV acquisition should control for the presence of HSV-2. Further studies are required to investigate the relative effect of asymptomatic HSV-2 shedding and/or genital ulcerations on BV occurrence.

#### "Effect of Human Papillomavirus 16/18 L1 viruslike particle vaccine among young women with preexisting infection"

**Author(s):** Hildesheim A, Herrero R, Wacholder S, et al

**Reference:** N/A 298(7):743-53.

<http://jama.ama-assn.org/cgi/content/full/298/7/743>

**Published Abstract:** *Context* Viruslike particle human papillomavirus (HPV) vaccines were designed to prevent HPV infection and development of cervical precancers and cancer. Women with oncogenic HPV infections might consider vaccination as therapy. *Objective* To determine whether vaccination against HPV types 16 and 18 increases the rate of viral clearance in women already infected with HPV. *Design and Setting* Phase 3, masked, community-based randomized trial conducted in 2 provinces of Costa Rica. *Participants* A total of 2189 women aged

18 to 25 years who were recruited between June 2004 and December 2005. Participants were positive for HPV DNA at enrollment, had at least 6 months of follow-up, and had follow-up HPV DNA results. *Intervention* Participants were randomly assigned to receive 3 doses of a bivalent HPV-16/18 L1 protein viruslike particle AS04 candidate vaccine (n = 1088) or a control hepatitis A vaccine (n = 1101) over 6 months. *Main Outcome Measures* Presence of HPV DNA was determined in cervical specimens by a molecular hybridization assay using chemiluminescence with HPV RNA probes and by polymerase chain reaction using SPF10 primers and a line probe assay detection system before vaccination and by polymerase chain reaction after vaccination. We compared rates of type-specific viral clearance using generalized estimating equations methods at the 6-month visit (after 2 doses) and 12-month visit (after 3 doses) in the 2 study groups. *Results* There was no evidence of increased viral clearance at 6 or 12 months in the group who received HPV vaccine compared with the control group. Clearance rates for HPV-16/18 infections at 6 months were 33.4% (82/248) in the HPV vaccine group and 31.6% (95/298) in the control group (vaccine efficacy for viral clearance, 2.5%; 95% confidence interval, -9.8% to 13.5%). Human papillomavirus 16/18 clearance rates at 12 months were 48.8% (86/177) in the HPV vaccine group and 49.8% (110/220) in the control group (vaccine efficacy for viral clearance, -2.0%; 95% confidence interval, -24.3% to 16.3%). There was no evidence of a therapeutic effect for other oncogenic or nononcogenic HPV categories, among women receiving all vaccine doses, among women with single infections, or among women stratified by the following entry variables: HPV-16/18 serology, cytologic results, HPV DNA viral load, time since sexual debut, Chlamydia trachomatis or Neisseria gonorrhoeae infection, hormonal contraceptive use, or smoking. *Conclusion* In women positive for HPV DNA, HPV-16/18 vaccination does not accelerate clearance of the virus and should not be used to treat prevalent infections.

### **"No evidence for consistent virus-specific immunity in Simian Immunodeficiency Virus exposed, uninfected Rhesus monkeys"**

**Author(s):** Letvin NL, Rao SS, Dang V, et al

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

[http://www.ncbi.nlm.nih.gov/sites/entrez?cmd=Retrieve&db=PubMed&list\\_uids=17686853&dopt=AbstractPlus](http://www.ncbi.nlm.nih.gov/sites/entrez?cmd=Retrieve&db=PubMed&list_uids=17686853&dopt=AbstractPlus)

**Published Abstract:** Defining the immune correlates of the protection against HIV-1 acquisition in individuals who are exposed to HIV-1 but do not become infected may provide important direction for the creation of an HIV-1 vaccine. We have employed the simian immunodeficiency virus (SIV)/rhesus monkey model to determine whether monkeys can be repeatedly exposed to a primate lentivirus by a mucosal route and escape infection, and if virus-specific immune correlates of protection from infection can be identified in uninfected monkeys. Five of 18 rhesus monkeys exposed 18 times by intrarectal inoculation to SIVmac251 or SIVsmE660 were resistant to infection, indicating that the exposed/uninfected phenotype can be reproduced in a nonhuman primate AIDS model. However, routine peripheral blood lymphocyte IFN $\gamma$  Elispot, tetramer, and ICS assays, as well as cytokine-augmented Elispot and peptide-stimulated tetramer assays failed to define a systemic antigen-specific cellular immune correlate to this protection. Further, local cell-mediated immunity could not be demonstrated by tetramer assays in these protected monkeys and local humoral immunity was not associated with protection against acquisition of virus in another cohort of mucosally exposed monkeys. Therefore, resistance to mucosal infection in these monkeys may not be mediated by adaptive virus-specific immune mechanisms. Rather, innate immune mechanisms or an intact epithelial barrier may be

responsible for protection against mucosal infection in this population of monkeys.

**"Prevalence of circumcision and herpes simplex virus type 2 infection in men in the United States: the National Health and Nutrition Examination Survey (NHANES), 1999-2004"**

**Author(s):** Xu F, Markowitz LE, Sternberg MR, et al

**Reference:** N/A 34(7):479-84.

[http://www.ncbi.nlm.nih.gov/sites/entrez?cmd=Retrieve&db=pubmed&dopt=AbstractPlus&list\\_uids=17413536](http://www.ncbi.nlm.nih.gov/sites/entrez?cmd=Retrieve&db=pubmed&dopt=AbstractPlus&list_uids=17413536)

**Published Abstract:** OBJECTIVES: To study the prevalence of circumcision in the United States and to examine the association between circumcision and herpes simplex virus Type 2 (HSV-2) infection. METHODS: As part of National Health and Nutrition Examination Surveys from 1999 to 2004, 6174 men were interviewed about circumcision status and sexual behaviors, and were tested for HSV-2 antibodies. Medical artwork was used to aid the reporting of circumcision status. RESULTS: The overall prevalence of circumcision was 79% and varied by race/ethnicity (88% in non-Hispanic whites, 73% in non-Hispanic blacks, 42% in Mexican Americans, and 50% in others). For men born in the United States from 1940 through 1979, the prevalence of circumcision increased, with larger increases in non-Hispanic blacks and Mexican Americans than in non-Hispanic whites; the prevalence of circumcision decreased significantly in those born in the 1980s (84%) compared to those born in 1970s (91%) (P (less than)0.001). Circumcision status was not associated with sexual behaviors we assessed. In multivariate analyses, circumcision was not associated with HSV-2 infection (P = 0.47). CONCLUSIONS: The prevalence of circumcision apparently peaked in those born in the 1970s and declined in those born in the 1980s. Circumcision was not associated with HSV-2 infection.

**"Randomised controlled trial on whether advance knowledge of prostate-specific antigen testing improves participant reporting of unprotected sex"**

**Author(s):** Thomsen SC, Gallo MF, Ombidi W, et al

**Reference:** N/A 83(5):419-20. Epub 2006 Nov 29.

<http://sti.bmj.com/cgi/content/abstract/83/5/419?ct=ct>

**Published Abstract:** *Objectives:* To determine whether the process of informing research participants that they would be tested for the presence of a biological marker of semen exposure would reduce bias in their reports of unprotected sex. *Methods:* A randomised trial of 210 female sex workers from Mombasa, Kenya, was conducted, where half the group had advance knowledge (via the request for informed consent) that they would be tested for prostate-specific antigen (PSA) in their vaginal fluid before they reported on sex and condom use for the past 48 h. The other half were invited to participate (via additional informed consent) in the test for PSA after they had already consented to be questioned and reported on these sexual behaviours. A trained nurse instructed participants to self-swab to collect vaginal fluid specimens, which were tested for PSA using ELISA. *Results:* Reporting of unprotected

sex did not differ between those with advance knowledge of the test for PSA and those without this knowledge (14.3% v 11.4%, respectively;  $p = 0.27$ ). Surprisingly, more women with advance knowledge (15.8%) had discrepant self reports and PSA results than women without advance knowledge (9.1%); however, the difference was not statistically significant (OR 1.9; 95% CI 0.8 to 4.5). *Conclusions:* Knowing that one's answers to a questionnaire could be verified with a biological marker of semen exposure did not make respondents more likely to report unprotected sex.

### **"Vaccine platform for prevention of Tuberculosis and mother-to-child transmission of Human Immunodeficiency Virus type 1 through breastfeeding"**

**Author(s):** Im EJ, Saubi N, Virgili G, et al

**Reference:** N/A 81(17):9408-18.

<http://jvi.asm.org/cgi/content/abstract/81/17/9408?etoc>

**Published Abstract:** Most children in Africa receive their vaccine against tuberculosis at birth. Those infants born to human immunodeficiency virus type 1 (HIV-1)-positive mothers are at high risk of acquiring HIV-1 infection through breastfeeding in the first weeks of their lives. Thus, the development of a vaccine which would protect newborns against both of these major global killers is a logical yet highly scientifically, ethically, and practically challenging aim. Here, a recombinant lysine auxotroph of *Mycobacterium bovis* bacillus Calmette-Guérin (BCG), a BCG strain that is safer than those currently used and expresses an African HIV-1 clade-derived immunogen, was generated and shown to be stable and to induce durable, high-quality HIV-1-specific CD4<sup>+</sup> and CD8<sup>+</sup>-T-cell responses. Furthermore, when the recombinant BCG vaccine was used in a priming-boosting regimen with heterologous components, the HIV-1-specific responses provided protection against surrogate virus challenge, and the recombinant BCG vaccine alone protected against aerosol challenge with *M. tuberculosis*. Thus, inserting an HIV-1-derived immunogen into the scheduled BCG vaccine delivered at or soon after birth may prime HIV-1-specific responses, which can be boosted by natural exposure to HIV-1 in the breast milk and/or by a heterologous vaccine such as recombinant modified vaccinia virus Ankara delivering the same immunogen, and decrease mother-to-child transmission of HIV-1 during breastfeeding.

### **"When to stop treatment arms in a clinical trial assessing time to event with more than two arms against a common control"**

**Author(s):** Grobler AC, Carrara HR, Mwambi HG, et al

**Reference:** N/A 30(3):284-99.

<http://ehp.sagepub.com/cgi/content/abstract/30/3/284?ct=ct>

**Published Abstract:** Two-arm time-to-event (or survival) trials are powered to continue until a required number of events is reached. The authors discuss how the required number of events should be defined for a study with three or more arms with various pairwise comparisons and a common control arm. They advocate stopping one active arm when the required number of events is observed in the applicable pairwise comparison but continuing with the other active arm and the control arm until the required number of events is observed in that pairwise comparison, thereby

ensuring that the study continues until enough events are observed in each pairwise comparison. This article is the result of considerations during the design of a three-arm **microbicide** trial.

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#### 4. EPIDEMIOLOGY

##### "AIDS rate in Kenya drops due to increased ARV use"

**Date:** 14 August 2007

**Source:** *Agence France Presse*

[http://news.yahoo.com/s/afp/20070814/hl\\_afp/kenyahealthaids\\_070814122904](http://news.yahoo.com/s/afp/20070814/hl_afp/kenyahealthaids_070814122904)

Kenya's AIDS prevalence rate has dropped to 5.1 percent last year from 5.9 percent in 2005 mainly due to the increased rollout of anti-retrovirals, the national AIDS council said Tuesday. The state-run National AIDS Control Council (NACC) said the growing use of life-prolonging therapy averted around 57,000 deaths in 2006.

"The annual death of adult AIDS deaths in Kenya reached a peak of about 120,000 in 2003. It would have stayed at that level for the next three years were it not for the increased number of people on anti-retroviral therapy," NACC said in a statement.

The council also reported a drop in new infections from 60,000 in 2005 to 55,000 last year, but stressed that most new infections were occurring among young people. At least 1.3 million people are currently living with HIV/AIDS in Kenya, 65 percent of whom are women between the ages of 19 and 45, according to NACC statistics.

Last year, President Mwai Kibaki announced that public hospitals would no longer charge HIV/AIDS patients for anti-retroviral drugs in a new bid to fight the deadly disease. Since 1984, at least 1.5 million people are said to have died from AIDS in Kenya, according to health ministry estimates.

Sub-Saharan Africa accounts for almost two-thirds of all people infected with HIV and 72 percent of global AIDS deaths, according to UNAIDS. As of June last year, around one million Africans were receiving antiretroviral drugs. This was still less than a quarter of the estimated 4.6 million people in need of the drugs on the continent.

##### "Women most affected by HIV-AIDS"

**Date:** 09 August 2007

**Source:** *The Namibian (Windhoek)*

**Author(s):** Kakunawe Shinana

<http://allafrica.com/stories/200708090241.html>

Many more women than men in Namibia are living with HIV-Aids, Caroline Thomas of the International Community of Women living with HIV-Aids (ICW) said at the Sister Namibia press briefing on Monday. Sister Namibia in collaboration with the Women's Leadership Centre organised a briefing on the impact of HIV-Aids on women and girls.

Thomas said this impact has resulted in women and girls being burdened with caring for the sick and the dying with little support, while providing for a rapidly growing number of orphans. "Young women are particularly at risk of new infections, because of the many cultural practices that involve sexual and other violation of their bodies," she said, adding; "Girls and young women in poverty are also exposed to HIV infection through 'sugar daddy' relationships with older men."

UNAIDS estimates that 62 per cent of people living with HIV are women, compared to 38 per cent men. Despite prevention campaigns over the years, the infection rate has not decreased. The Namibian Ministry of Health and Social Services conducted a national survey among pregnant women which shows a national average of 19,9 per cent of those tested in 2006 were HIV positive compared to 19,7 per cent in 2004. Figures vary greatly among the regions of Namibia, with the highest rate in the Caprivi Region amongst the age group 25 to 49. Almost 50 per cent of pregnant women tested in 2006 in Katima Mulilo were HIV positive.

Thomas said poverty drives many women and girls into prostitution, or they are trapped in unhealthy and often violent relationships as a means of survival. Gender inequality is in many ways sanctioned by cultural practices. Culture teaches boys to become men to rule over women and control their bodies, while girls are taught to be submissive and to be dependent on men, instead of promoting women's right to body integrity and choice.

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## 5. OTHER PREVENTION APPROACHES

### "Rare progress made in fight against HIV"

**Date:** 12 August 2007

**Source:** *The Miami Herald*

**Author(s):** Shashank Bengali

<http://www.miamiherald.com/news/world/story/200546.html>

In southern Africa for the past two decades, casual sex helped to fuel the worst epidemics of HIV and AIDS in the world. In Zimbabwe, however, fewer people are taking chances anymore, making this otherwise beleaguered nation an unlikely bright spot in Africa's battle against AIDS.

"Search every guy's wallet, and you'll find a condom," said Tinashe, a bespectacled, easygoing 28-year-old. "No one is having sex without a condom. People are scared of HIV."

That generational shift toward less casual sex and widespread condom use among young Zimbabweans has helped reduce HIV infections here even as they keep rising in neighboring countries. According to the most recent estimates by the Joint U.N. Program on HIV/AIDS, 1.5 million Zimbabwean adults were living with HIV in 2005, down from 1.6

million in 2003. In every other country in southern Africa -- home to 2 percent of the world's people but one-third of all HIV cases -- the number of infected people rose slightly or held steady.

"It really is a success story in a bleak situation," said Michael Chommie, the country director for Population Services International, an American nonprofit group that promotes condom use.

Much of the decline, however, is due to people infected with the virus dying -- at a rate of more than 3,000 each week -- because antiretroviral drugs are unavailable or unaffordable. Nearly 600,000 Zimbabweans died of AIDS-related illnesses from 2004 to 2006, the third-worst toll after India and South Africa, according to U.N. figures. Many HIV carriers also have fled the country, part of a nationwide exodus of more than 3 million people since Zimbabwe's economic free fall began. Moreover, even with fewer new cases, 1 in 5 Zimbabweans has HIV, among the highest rates in the world.

Still, experts say that fewer Zimbabweans are contracting the virus now, thanks to near-universal awareness of AIDS and the risks of unprotected and casual sex. Last year, epidemiologists from Imperial College in London documented a dramatic reduction in the number of sexual partners among men in the eastern countryside of Manicaland. They also found that far fewer teenagers -- boys and girls -- had become sexually active. Experts suggest sex has become another casualty of the country's eight-year economic depression. Few men have the money to support extramarital affairs or, for bachelors, the late nights on the town often required to woo a woman.

"You have to spend to get sex," said Richard Chimhiri, who writes about HIV for the Financial Gazette, an independent newsweekly. "Some guys would have four or five girlfriends if they could. But the economic situation and the risk of HIV -- it's all conspiring to make people change their attitudes."

### **"Circumcision message could confuse gay community"**

**Date:** 08 August 2007

**Source:** *IRINNews.org*

<http://www.irinnews.org/Report.aspx?ReportId=73320>

Experts are warning Senegalese men who have sex with men not to get caught up in the hype about male circumcision after recent research indicated that the procedure could offer some protection against HIV, and are urging them to keep using other means of protection. In 2006, the results of three studies, one each in South Africa, Kenya and Uganda, showed that the risk of HIV infection was up to 60 percent lower among circumcised men. However, these studies were specific to heterosexual interaction.

The HIV prevalence among men who have sex with men (MSM) in Senegal is an estimated 21.5 percent, according to the French Institute for Applied Medicine and Epidemiology (IMEA), compared to a national average of 0.7 percent. AIDS campaigners worry that the preliminary data on male circumcision could lead to reckless sex and an even higher HIV prevalence.

In a 2003 study on stigma, violence and HIV among MSM by Dr Cheikh Niang of the Cheikh Anta Diop University in Dakar, the Senegalese capital, only 23 percent of MSM said they had used a condom during their last sexual

encounter.

"Within Senegal's cultural context ... where homosexuality remains a taboo subject, we do not want to encourage people to hide behind the idea that circumcision completely prevents the transmission of HIV," Jean-Louis Rodriguez, former executive secretary of And Ligeey, a Senegalese association working to protect the rights of gay men, told IRIN/PlusNews. He said the hidden nature of homosexuality in Senegal meant gay men often married or had girlfriends in order to fit into society, but still engaged in clandestine homosexual activity, putting many people at risk. In the IMEA study, 94 percent of participants also had sexual relations with women.

The results of observational research, published in the *Journal of Infectious Diseases* in 1993, suggested that the risk of circumcised homosexuals contracting HIV during sex could be halved; another study in 2005 in the United States reached the same conclusion. However, neither of these was as extensive as the three African studies that prompted the United Nations World Health Organization (WHO) to recommend male circumcision as a tool in the fight against the AIDS pandemic.

"We know nothing; [these] are observational studies; therefore, they prove nothing," Bertran Auvert, one of the authors of the South African study, said in an interview published on a gay rights website called 'The Warning'. "We can merely suppose that there is a certain level of protection."

The only thing the medical profession is sure of is that MSM run a considerable risk of HIV infection, especially since intercourse is often unprotected. Vigilance in prevention must be maintained

"Prevention must always be targeted, so that the message can be better understood and conveyed in the correct manner. When I hear all the media hype about circumcision, I get scared that people will get confused," said Rodriguez. "We have not yet worked on a specific statement to raise awareness, even if it were merely to tell people that condoms are the only thing that can offer protection."

Khoudia Sow, the HIV/AIDS focal point for the WHO in Senegal, commented that "It is certainly not a question of revising all our prevention techniques; circumcision could play a part in the range of existing measures, but in no instance would it substitute them."

The university's Dr Niang agreed. "MSM have to deal with many situations where they are excluded. Their lives are unstable, they are rejected by society and the health services, they do not have much control over negotiating their sexual relations, and drug use can also be an issue," he said. "These factors increase the risk of HIV infection a great deal more than whether or not they are circumcised."

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## 6. POLITICS AND POLICY

### "Official's firing revives S. African battles over AIDS"

**Date:** 16 August 2007

**Source:** *The Washington Post*

**Author(s):** Craig Timberg

<http://www.washingtonpost.com/wp-dyn/content/article/2007/08/16/AR2007081602215.html?referrer=emailarticle>

**EDITOR'S NOTE: THIS ARTICLE APPEARED ONLINE ON 16 AUG 2007, HOWEVER IS PUBLISHED IN THE 17 AUG 2007 WASHINGTON POST PRINT EDITION.**

South African President Thabo Mbeki's firing of a top health official with strong ties to AIDS activists has undermined a fragile, year-old truce over how to combat the epidemic, an issue crucial to the future of Africa's most prosperous nation. Mbeki has said he fired Deputy Health Minister Nozizwe Madlala-Routledge on Aug. 8 for attending an AIDS conference in Spain against his wishes. But activists say Madlala-Routledge initially fell out of favor because of her outspoken advocacy for more ambitious action against the HIV virus, which has infected an estimated 5.5 million people here, more than in any other nation.

The episode has reignited old battles over Mbeki's controversial views about AIDS and the fitness of Health Minister Manto Tshabalala-Msimang -- long vilified as "Dr. No" because of her reluctance to embrace lifesaving antiretroviral drugs -- to lead the nation's battle against the epidemic. Above all, activists and experts say, the incident and the uproar it caused, including renewed calls for Mbeki to fire Tshabalala-Msimang, has been a huge distraction after a year of steady progress toward a unified national approach to AIDS.

"It's quite clear that internal politicking takes precedence over the nation's health," said Francois Venter, president of the Southern African HIV Clinicians Society. "The one person who actually gave people hope and led from the front is now gone."

Madlala-Routledge was not in charge of AIDS policy within the health department but was vocal about the urgency of the epidemic, publicly taking an HIV test even though Mbeki has declined to. She often sounded like an AIDS activist herself despite serving in a government that has frequently engaged in legal and political battles with the nation's most prominent activist group, the Treatment Action Campaign.

Her firing outraged activists who were just beginning to trust Mbeki's government. Early in his administration, he was widely denounced for appearing to question the scientific consensus that the HIV virus causes AIDS and that the disease's symptoms can be safely treated with antiretroviral drugs. That controversy had died down, but "now he's right back in it," said Karima Brown, political editor of the Business Day newspaper. "All the goodwill is gone."

Even before recent incidents, Madlala-Routledge was an unusual figure in a government where, analysts say, loyalty to Mbeki's policies is paramount and many insiders keep a low profile. Her first senior job was as deputy defense minister, though she was a Quaker and an avowed pacifist. As deputy health minister, Madlala-Routledge repeatedly clashed with Tshabalala-Msimang.

In a publicly released dismissal letter, Mbeki questioned her ability to work with others and chastised her for attending the conference in Spain without his permission. She has said that Mbeki scolded her for an unannounced visit in July to the troubled maternity ward at a government hospital -- whose conditions she said amounted to "a national emergency." The firing of Madlala-Routledge has marked a dramatic return to prominence for Tshabalala-Msimang.

Top government officials, weary of repeated controversies surrounding her, effectively removed Tshabalala-Msimang from overseeing AIDS policy last year. Deputy President Phumzile Mlambo-Ngcuka took control of the issue, and Madlala-Routledge gained a more prominent role as well.

A series of personal health problems further sidelined Tshabalala-Msimang, raising hopes among activists that her influence over AIDS policy was coming to an end. But after a liver transplant, Tshabalala-Msimang has gradually regained authority in recent months. Activists suspect that she engineered the firing of Madlala-Routledge.

Calls for the removal of Tshabalala-Msimang, once common but rarely heard for nearly a year, have returned. They have grown louder since South Africa's Sunday Times newspaper reported last weekend on allegations of heavy alcohol use by Tshabalala-Msimang, including alleged smuggling of whisky and red wine into her hospital room during a 2005 stay for shoulder surgery.

Activists and government officials have made back-channel efforts to keep these controversies from undermining the nation's newly adopted national AIDS policy, which includes ambitious targets for treating the disease and preventing new HIV infections, said Mark Heywood, a founding official for the Treatment Action Campaign and a member of the South African National AIDS Commission. "TAC is not going to say, 'Okay, all the bridges are burned. Let's go back to war,' " Heywood said. "And I don't think the government is either."

## "Keeping science on top in drug evaluation"

**Source:** *N Engl J Med.* 2007 Aug 16; 357(7):633-5.

**Author(s):** Jerry Avorn

<http://content.nejm.org/cgi/content/full/357/7/633?query=TOC>

In many sectors of American life - energy, defense, finance, pharmaceuticals - the government stands poised between powerful industry groups and the needs of the citizenry. But in only one of these areas, prescription medications, is there a formal public mechanism for integrating science into the national decision-making process. At their best, U.S. drug-approval procedures include an open system in which outside scientists come together as advisory committees to the Food and Drug Administration (FDA), publicly evaluate the available evidence, and render opinions to guide the agency's decisions. The approach is based on the insight that a deep reservoir of knowledge and judgment exists in the academic and clinical communities about often arcane matters of drug benefits and risks - a kind of expertise that would be impossible to equal inside any government agency. In theory, the FDA's advisory committee system aspires to the Platonic ideal of a group of disinterested experts giving freely of their wisdom to guide the republic's decision making.

Of course, the system doesn't always perform as well as it should. In recent years, the FDA has been less stringent about allowing the participation of committee members who have commercial conflicts of interest, despite evidence that such ties help shape opinions.<sup>1</sup> Science may also be defeated at later stages of the policymaking process, as when the FDA commissioner overruled the nearly unanimous recommendations of both internal and external scientists about the safety of emergency contraception (the morning-after pill). Unfortunately, the upcoming reauthorization of user-fee funding at the agency will lock in 5 more years of dependence on support from

pharmaceutical manufacturers to pay the salaries of the FDA's internal drug-review staff, renewing concern about the relationships between science, commerce, and federal policy and making the independence of external advisers even more critical.<sup>2</sup>

But though the quiet voice of science may often be no match for powerful vested interests or ideology, some encouraging signs may be in the air. The same reauthorization bill, disappointing in so many respects, may tighten somewhat the conflict-of-interest rules for outside advisers. In addition, some recent committee decisions provide interesting contrasts with recommendations made several years ago about similar drugs.

During the 1999 approval process for rofecoxib (Vioxx, Merck), FDA internal reviewers noted early signals of a possible increase in cardiovascular risk. But the advisory committee focused instead on the hope that the drug would have less gastrointestinal toxicity than other nonsteroidal antiinflammatory drugs (NSAIDs), though such an advantage had not yet been convincingly demonstrated. When a quadrupling of the rate of myocardial infarction was documented a year later in a clinical trial comparing rofecoxib with naproxen, the agency allowed the company to imply that this was because of the cardioprotective effect of naproxen.

Fast-forward to 2007, when the same company sought FDA approval for etoricoxib (Arcoxia), a new drug in the same class. Merck had initially proposed - and the agency had approved - a study comparing etoricoxib with diclofenac, an NSAID that many worried carried its own cardiac risk. Several years and millions of dollars later, Merck presented the FDA with trial evidence that etoricoxib caused roughly the same number of cardiac events as diclofenac. But this time, the FDA allowed its sharpest internal critic, David Graham, to present data to the advisory committee on the implications of approving another cyclooxygenase-2 inhibitor with potentially dangerous cardiac side effects. Had the company used a more appropriate comparator, naproxen, Graham and the others argued, the increased cardiovascular risk would have been clear (see table). The committee voted overwhelmingly against approval. If diclofenac also presented a cardiac risk, the committee agreed, then the FDA should not approve a new product with no proven advantage that might confer the same hazard.<sup>3</sup> Not only did this decision fly in the face of the original study design, it was also a sharp departure from the conventional FDA view that a new drug in an established class need not be any safer or more effective than its predecessors. The committee's vote was so lopsided that the agency, still embarrassed at having missed the risk of myocardial infarction associated with rofecoxib during 5 years of widespread use, could not but agree with its recommendation.

A decision in the diet-drug category provides another indication of renewed assertiveness by the FDA's external advisers. In 1995, the FDA reviewed an application for dexfenfluramine, later marketed as Redux (Interneuron). Its parent compound, fenfluramine, led to negligible weight loss and caused potentially fatal pulmonary hypertension; there was no clear evidence that its new D-isomer would be any better in either respect. In a single clinical trial, the manufacturer showed that patients randomly assigned to receive dexfenfluramine lost about 6 lb more than those given placebo - hardly a medical breakthrough. The company claimed that on a population basis, such weight loss could result in less hypertension, diabetes, and heart disease, but no trial data were presented to substantiate this hope. Only 2 months after an advisory committee recommended disapproving the drug, the FDA convened another meeting of the same group to reconsider the question. No important new data were presented, but several skeptical committee members couldn't attend the second meeting, and the drug was approved. Redux proved to be an unimpressive appetite suppressant; the expected pulmonary hypertension indeed occurred, along with unexpected heart-valve damage. The drug was withdrawn from the market after just 1 year; its manufacturer has since paid more than \$20 billion in damages to affected patients and their lawyers.<sup>4</sup>

A different fate has met the most recent entry into the lucrative diet-drug market, rimonabant. Advocates said it could reduce appetite, improve lipid levels, and help people quit smoking. Faced with such a potential embarrassment of riches, its manufacturer, Sanofi-Aventis, entered the blockbuster lottery by trying for an appetite suppressant indication. Rimonabant worked slightly better than dexfenfluramine - clinical trials demonstrated a weight loss of 13 lb more than that achieved with placebo - but the drug also seemed to raise the risk of depression (sometimes severe), suicidality, anxiety, and insomnia. Despite these adverse effects, FDA staff issued an encouraging "approvable" letter in February 2006. But when an advisory committee reviewed the evidence in June 2007, it voted unanimously against the drug.<sup>5</sup> Soon thereafter, the manufacturer withdrew its application.

The agency is now addressing yet another follow-on drug as the glitazone story evolves. In 1997, the first entry in this class of antidiabetic agents, troglitazone (Rezulin, Parke-Davis), was observed to cause fulminant hepatic necrosis, sometimes fatal. Regulatory authorities throughout the world quickly concluded that the product had an indefensible risk-benefit ratio, and it was withdrawn from the market, often within just a few months of approval. Yet the FDA and its advisory committee were swayed by the arguments of the manufacturer and kept it in use in the United States for 2 years after it had been made unavailable in nearly every other country.<sup>4</sup> Now, a decade later, troglitazone's younger sibling, rosiglitazone (Avandia, GlaxoSmithKline), has been implicated in raising the risks of congestive heart failure and myocardial infarction, without impressive evidence of a countervailing advantage in clinical outcomes. An advisory committee meeting on July 30, 2007, did not fuel hopes for a new era of data-driven reform. The committee voted, 20 to 3, that rosiglitazone increases cardiac ischemic risk in type 2 diabetes but then recommended, by a 22-to-1 vote, that the drug remain in use. The decision was more suggestive of Rezulin redux (and of Redux) than it was of resolve. Although Avandia has been prescribed widely since 1999, several participants noted that neither the manufacturer nor the FDA had carried out enough safety studies to permit a clear conclusion.

The approval, prescribing, and safety surveillance of prescription drugs involve a complicated mix of science, regulatory law, clinical judgment, business, and politics. It is not easy to ensure that science dominates in such a heady brew, but despite missteps such as the latest move with respect to rosiglitazone, an open model holds more promise for data-driven public decision making than those followed in the energy, finance, and defense sectors, among others. As Congress persists in allowing industry funding to dominate the FDA budget (and, many fear, its perspective as well), it will be especially important for the scientific community to remain independent, conduct rigorous analyses, and make its voice heard clearly to ensure that drug-review decisions are driven solely by the data.

Dr. Avorn reports having served, pro bono, as an expert witness for plaintiffs in Vioxx-related lawsuits.

#### *Source Information*

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## 7. PHARMACEUTICAL INDUSTRY

### "Canadian companies agree to share generic AIDS drugs with Rwanda"

**Date:** 09 August 2007

**Source:** *Globe and Mail (Canada)*

**Author(s):** Lisa Priest

<http://www.theglobeandmail.com/servlet/story/RTGAM.20070809.waccess09/BNStory/National/home>

AIDS drugs could be heading for Rwanda as soon as November under a Canadian program that allows generic-drug companies to send copies of brand-name medicines to poor countries. GlaxoSmithKline Inc. said yesterday it had given consent to Apotex Inc. to manufacture an antiretroviral medication for the treatment of HIV/AIDS patients in Rwanda. Consent, through Canada's Access to Medicines Regime, was needed as GSK has patent rights for two of the three molecules in the medication.

"We have made a commitment, we have the drug and if we can get the green light, we will move quickly on it," said Elie Betito, director of public and government affairs for Apotex Inc.

Though Canada's Access to Medicines Regime was created three years ago to help supply inexpensive drugs to developing nations facing public health threats such as HIV/AIDS, not one pill has been exported. Critics say it is due to legislative flaws and an inordinately cumbersome process.

Whatever the case, yesterday's development is good news for Rwanda, a country where 250,000 people are infected with HIV. If the agreement goes through, 15 to 16 million tablets of Apotex's triple combination AIDS medicine will be sent. Mr. Betito said that's enough to treat 21,000 Rwandans for one year or 200,000 for one month. It would be sold on a no-profit basis: It costs roughly 40 cents a tablet to make, he said.

Mr. Betito cautioned that there are still outstanding issues, among them the need to reach an agreement with one group of patentees associated with the medicine nevirapine, which also appears in the triple combination therapy.

"The bottom line is that the patentees have not lifted all of the barriers to shipment," Mr. Betito said. "Apotex cannot ship tomorrow."

Yesterday, Joanne Csete, executive director of Canadian HIV/AIDS Legal Network, said the process is a reminder of how "enormously complicated" the law still is. "It took three years and it's practically a miracle it has gotten to this point."

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## **8. ANNOUNCEMENTS**

### **AIDS Vaccine Development: Challenges and Opportunities**

<http://www.horizonpress.com/hsp/books/hivv.html>

This book reviews the scientific challenges that have impeded the search for an effective AIDS vaccine and discusses current novel research that is accelerating progress. In a series of mini-reviews by the world's leading experts in AIDS vaccine research the book is essential reading for everyone interested in the current progress and future direction of AIDS vaccine development.

Publisher: Caister Academic Press

Editor: Wayne Koff, Patricia Kahn and Ian D. Gust\* International AIDS Vaccine Initiative, New York and \*University of Melbourne, Australia

Publication date: Feb 2007

Price: GB £49 or US \$99 (paperback).

Pages: xiv + 151

### **Post IAS 2007 Conference Feedback-Save the Date**

The Department of Prevention and Community Health and The George Washington University HIV/AIDS Institute in collaboration with Clinical Care Options presents:

Post IAS 2007 Conference Feedback

Where: Crowne Plaza Hotel, Washington D.C.

When: Wednesday, August 29th: 6pm - 9pm

Note: Free Registration, More details to follow in formal invitation

### **WHO Expert Committee on Specifications for Pharmaceutical Preparations**

<http://www.who.int/bookorders/anglais/detart1.jsp?sesslan=1&codlan=1&codcol=10&codcch=937>

This report presents the recommendations of an international group of experts convened by the World Health Organization to consider matters concerning the quality assurance of pharmaceuticals and specifications for drug substances and dosage forms.

The report is complemented by a number of annexes. These include: a list of available international chemical reference substances and international infrared spectra; supplementary guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms; updated supplementary guidelines on good manufacturing practices for the manufacture of herbal medicines; supplementary guidelines on good manufacturing practices for validation; good distribution practices for pharmaceutical products; a model quality assurance system for procurement agencies (recommendations for quality assurance systems focusing on prequalification of products and manufacturers, purchasing, storage and distribution of pharmaceutical products); multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability; a proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms; and additional guidance for organizations performing in vivo bioequivalence studies.

Fortieth Report, Technical Report Series, No 937

Price: CHF 50.00 / US\$ 45.00

Developing countries: CHF 35.00

English, 2006, 471 pages

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