



ALLIANCE FOR MICROBICIDE DEVELOPMENT

07 March 2008, Volume 9, Number 10

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

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

Its purpose is to:

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

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

Areas covered in this News Digest:

1. MEDIA COVERAGE OF MICROBICIDES

- Zimbabwe: And the greatest and best remains - prevention
- An audience with Tadataka Yamada

2. PUBLISHED RESEARCH: MICROBICIDE-SPECIFIC

- Cost-effective production of a vaginal protein microbicide to prevent HIV transmission
- Development of a comprehensive human immunodeficiency virus type 1 (HIV-1) screening algorithm for discovery and preclinical testing of topical microbicides

- Noncomparative contraceptive efficacy of cellulose sulfate gel

3. PUBLISHED RESEARCH: RELEVANT BASIC AND TRANSLATIONAL SCIENCE

- Could an open-source clinical trial data-management system be what we have all been looking for
- HIV drug development: the next 25 years
- Improved HIV-1 incidence estimates using the BED capture enzyme immunoassay
- Significant reduction in HIV prevalence according to male circumcision intervention in sub-Saharan Africa
- The estimated burden of HIV/AIDS in Uganda, 2005-2010

4. POLITICS AND POLICY

- Fighting HIV/AIDS in Africa requires more than 'Fruits of Science,' opinion piece says
- Concerns over blockbuster drugs Vytorin, Avandia prompt investigation of FDA review process
- Malawi seeks to oust fake AIDS healers
- NIH to lighten up heavy peer review process
- The Global Fund: growing pains

5. PHARMACEUTICAL INDUSTRY

- Drugs firms face new laws on test results

6. ANNOUNCEMENTS

- Gates Foundation seeking grant proposals for \$100M initiative to support research on infectious diseases, including HIV/AIDS
- Final Draft of the NIH 2007-2008 Peer Review Self-Study

1. MEDIA COVERAGE OF MICROBICIDES

"Zimbabwe: And the greatest and best remains - prevention"

Date: 01 March 2008

Source: *The Herald (Harare, Zimbabwe)*

Author(s): Editorial

<http://allafrica.com/stories/200803030071.html>

"Faith and hope and love we see, joining hand in hand agree but the greatest of the three and the best is love."

Above are strong words from one of the best hymns I have sung in life and one of those verses that try as one might, just embed themselves on the soul.

They also happen to be some of the truest words I have come across in life and as such, I hold them dear and try to let them guide me as I traverse along this arduous journey called life. They are a maxim, a principle and a value - something to hold onto even during the darkest hour. When things have gone so wrong that you lose all faith and hope and dislike and even hate begins to creep in, I often find myself remembering the days we sang this hymn in the

Queen Elizabeth Girls High Hall. Once again I am able to forget, forgive and open my heart to love - that way leaving the past with its hurts and hates behind.

Would it not be good if that is how we could all take Prevention in light of HIV and AIDS? If we could all design maxims such as Prevention, Treatment, Care and Support we need joining hand in hand agree but the greatest of them all and the best is Prevention. Letting the above statement guide each and everyone of us will go a long way towards cutting down new infections not only in Zimbabwe but in the whole of southern Africa. Agreed the whole package is essential in addressing HIV and AIDS for at any given time, there is need for prevention, treatment, care or support.

However at the very beginning, where our young people are found, where everyone who is HIV negative is, where most of those boys and girls who are just about to experiment with their lives are - there is and can be Prevention.

Last week another damper was thrown on HIV programming when news that the first **microbicide** candidate to reach the final phase of testing had failed to prevent HIV transmission. Testing of the **microbicide**, Carraguard, was carried out over a three-year period on 6000 women in South Africa and was completed in March 2007. But there was no difference in HIV infections between women in the group using Carraguard compared to those not using it. *Plus News* quotes Dr Khatija Ahmed, principal investigator of the trial saying "The trial was unable to demonstrate Carraguard's efficacy in preventing HIV transmission."

There had been hopes that a **microbicide** effective at reducing the risk of transmission was close to being discovered. This way many women would have been able to protect themselves by applying a gel to their genitalia before sexual contact. Unlike condoms, **microbicides** had brought excitement to women because one didn't have to tell their partner anything about wearing the gel unless they wished, which gave power to protect herself to the woman for once. Many women fail to advocate for the use of condoms in their relationships because of the power dynamics at play in our societies, which leave the decision to have sex, safer or unprotected, in the man's hands.

Before that it had been news that scientists were no closer to coming up with a vaccine for HIV and AIDS, which many among us in the HIV field had been hoping for. Again what this effectively means is that the best strategy that remains at our feet is that of Prevention. There are not that many options left to us.

Treatment is indeed essential in light of the fact that many people are already living with HIV and AIDS and by accessing treatment along with other care and support services, they can lead long, normal and healthy lifestyles. Before ARVs, many breadwinners, young people and those pushing industry were decimated by AIDS-related illnesses and today many more are faced with the same plight because of the unavailability and inaccessibility of the life-prolonging drugs.

That makes prevention also very essential especially when we consider that at 15,6 percent prevalence, many more people are HIV negative in this country, people who, if they don't recognise prevention for the important and crucial strategy that it is and should be, can also find themselves infected with HIV.

Research today will show that while more than 300 000 people are in desperate need of Antiretroviral treatment in

Zimbabwe, less than half that number are accessing it. If we were to add even 10 more people to the number of those who need treatment, is it realistic to expect that the country systems would then be able to cope?

Activists are doing well to lobby for treatment for everyone who needs it because human beings should have the right to access treatment in order for them to live long and healthy lives. However activists would do well to lobby for prevention too. According to the Executive director for Southern Africa HIV and AIDS Information Dissemination Service (SAfAIDS) Mrs Lois Chingandu, there is need to begin to reward people for being HIV negative. For a long time, societies have looked at one side of the coin, that of acknowledging and rewarding people living with HIV and AIDS, especially those who disclose, and it is high time both sides were looked at, she said.

Indeed people living with HIV and AIDS (those brave men and women who I cannot help but applaud too) who disclose their status have been acknowledged and rewarded in some instances, but we are still to hear of cases where people who have tested negative have been recognised, or rewarded. Of course the negative result has been met with sighs of relief, vows to lead clean and healthy lives and ululations in many a family but have we as communities learnt to reward and pat our children, cousins, colleagues and comrades for "testing negative HIV."

For abstaining, practising safer sex all the time, for regularly getting tested, for protecting themselves from re-infection, for being open in all sexual matters and talking openly about HIV and AIDS issues, people must be acknowledged. For being responsible fathers and mothers who do not have extra-marital affairs and for being real about HIV and AIDS, people must be rewarded along with those who test positive and decide to do something positive with their lives after that result.

For taking this maxim close to heart: Prevention, treatment, care and support we need, joining hand in hand agree, but the greatest of them all and the best is Prevention: must we not applaud someone?

"An audience with Tadataka Yamada"

Source: *Nat Rev Drug Discov.* 2007 Dec;6(12):950.

<http://www.nature.com/nrd/journal/v6/n12/full/nrd2481.html>

Could you give examples of successes that the Gates Foundation has had in promoting the discovery and development of drugs for neglected diseases?

At this point we have one drug called paromomycin that has been approved for registration in India. Paromomycin is an old aminoglycoside that the Institute for OneWorld Health identified for its potential to treat visceral leishmaniasis. The Gates Foundation completely sponsored the drug through clinical development and we are about to launch it through a network of private providers called Janani.

From the Medicines for Malaria Venture there are four compounds in Phase III and we sponsored a GSK malaria vaccine called RTSS that will enter Phase III in 2008. Also, we have six vaccine candidates about to start Phase II

trials for Mycobacterium tuberculosis infection. Our portfolio has more than 70 new chemical entities or vaccines near clinical development.

What lessons have been learnt in drug discovery for neglected diseases over the past 7 years?

One key issue is the capacity for doing clinical trials in the developing world. For example, when conducting HIV prevention trials it is hard to find populations that are at a high enough risk for HIV so it becomes difficult to enrol enough patients. If you have many trials at the same time you easily exhaust the clinical trials capacity, which is what happened with our **microbicide** studies. We had four or five first generation **microbicide** studies at the same time, which made it difficult for us to start our second generation trials. Also, when you conduct HIV prevention trials you have to implement a comprehensive education strategy on the standard of care interventions against HIV, which means that the underlying incidence drops in the control group as well as in the test group. More patients are then needed to determine if the prevention product works.

Another important lesson is that although we have made large investments, not all are going to pay off. It is important to recognize that failure is more common than success.

How does the Gates Foundation engage industry to encourage the development of drugs for neglected diseases?

When we enter into a product development partnership with a pharmaceutical company we tend to support the research and development of the drug while the company retains its intellectual property. In return, we only ask for an affordable price for markets in the developing world.

Aside from our product development partnerships we have created funding mechanisms to ensure that industry is not penalized for participating in this area. One example is the Advanced Market Commitment directed at rewarding companies following success so their capital investment is reimbursed appropriately. Earlier this year we made our first advanced market commitment of \$1.5 billion for a pneumococcal vaccine.

Early in October the Gates Foundation announced a new fast-track grants programme to support innovative global health research. What are the main aims of this initiative and why is it needed?

First of all, we want to encourage novel ideas from anywhere in the world - Bill Gates often tells me that almost all technology innovation comes from China or India. However, in biomedical research most funding vehicles are in the United States or Western Europe. Second, we want a faster response to innovative thinking - traditional funding processes often give grants one or two years after the initial application. We also believe that peer review, although important, tends to stifle innovation because truly novel ideas have no peers. So the idea is to provide US\$100,000 grants within 3 months of submission of a two-page application that does not require preliminary data. We hope the grant reviewers will be creative people, reasonably versed in the sciences, who have demonstrated an ability to think about problems in a unique way.

We need this scheme because, if you look at a challenge like HIV, 25 years after the emergence of the disease we do not have a vaccine. I think we are mired in some old ideas and we need novel ideas to solve this problem.

From your experiences at GSK, what do you think are the major challenges for pharmaceutical companies to engage in addressing long-neglected health problems?

Traditionally these efforts have been looked on as costly, owing to the financial investment and the cost of applying people and useful resources against products that will not be profitable. From the shareholder perspective that might not be optimal. However, pharmaceutical companies have an important challenge to be committed to the people who are suffering across the world, whether or not they can make money from them. Over time there has been a tremendous loss of esteem for the industry which has translated to pressures on pricing, market access and on regulatory approval. By contributing meaningfully to the broad population of people who need help, the cost will be small measured against the returns in reputation, corporate self esteem and general satisfaction of employees. From the experience at GSK, helping address these problems gave the company a sense of pride and motivation - that positive impact is almost incalculable.

This is a unique time as nations, corporations, foundations and the general public have focused on global health, which has led to new sources of funding. Most importantly, science has advanced to the stage that solutions to difficult problems are possible with this coalescence of forces. It is imperative that the pharmaceutical industry be a partner in this. We need them, we value them and we want to look for ways that they can be rewarded for what they do. Their reward in return will be that they can help millions of people.

[Return to Table of Contents](#)

2. PUBLISHED RESEARCH: MICROBICIDE-SPECIFIC

"Cost-effective production of a vaginal protein microbicide to prevent HIV transmission"

Author(s): Ramessar K, Rademacher T, Sack M, et al

Reference: N/A Epub ahead of print.

<http://www.pnas.org/cgi/content/abstract/0708841104v1?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: A series of small-molecule **microbicides** has been developed for vaginal delivery to prevent heterosexual HIV transmission, but results from human clinical trials have been disappointing. Protein-based **microbicides**, such as HIV-specific monoclonal antibodies, have been considered as an alternative approach. Despite their promising safety profile and efficacy, the major drawback of such molecules is the economy of large-scale production in mammalian cells, the current system of choice. Here, we show that an alternative biomanufacturing platform is now available for one of the most promising anti-HIV antibodies (2G12). Our data show that the HIV-neutralization capability of the antibody is equal to or superior to that of the same antibody produced in CHO cells. We conclude that this protein production system may provide a means to achieve **microbicide** ingredient manufacture at costs that would allow product introduction and manufacture in the developing world.

"Development of a comprehensive human immunodeficiency virus type 1 (HIV-1) screening algorithm for discovery and preclinical testing of topical microbicides"

Author(s): Lackman-Smith C, Osterling C, Luckenbaugh K, et al

Reference: N/A Epub ahead of print.

[http://aac.asm.org/cgi/content/abstract/AAC.01328-](http://aac.asm.org/cgi/content/abstract/AAC.01328-07v1?maxtoshow=&HITS=4&hits=4&RESULTFORMAT=&andorexacttitle=and&andorexacttitleabs=and&fulltext=microbicide%2C+microbicides&andorexactfulltext=or&searchid=1&usestrictdates=yes&resourcetype=HWCIT&ct)

[07v1?maxtoshow=&HITS=4&hits=4&RESULTFORMAT=&andorexacttitle=and&andorexacttitleabs=and&fulltext=microbicide%2C+microbicides&andorexactfulltext=or&searchid=1&usestrictdates=yes&resourcetype=HWCIT&ct](http://aac.asm.org/cgi/content/abstract/AAC.01328-07v1?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: Topical **microbicides** are self-administered, prophylactic products for protection against sexually transmitted pathogens. A large number of compounds with known anti-HIV-1 inhibitory activity have been proposed as candidate topical **microbicides**. To identify potential leads, an *in vitro* screening algorithm was developed to evaluate candidate **microbicides** in assays that assess inhibition of cell-associated and cell-free HIV-1 transmission, entry, and fusion. The algorithm advances compounds by evaluation in a series of defined assays that generate measurements of relative antiviral potency to determine advancement or failure. Initial testing consists of a dual determination of inhibitory activity in the CD4-dependent CCR5-tropic cell-associated transmission inhibition assay and in the CD4/CCR5-mediated HIV-1 entry assay. Activity is confirmed by repeat testing and identified actives are advanced to secondary screens to determine their effect on transmission of CXCR4-tropic viruses in the presence and absence of CD4 and their ability to inhibit CXCR4 and CCR5 envelope-mediated cell-to-cell fusion. In addition, confirmed active compounds are also evaluated in the presence of human seminal plasma, in assays incorporating a pH 4 to 7 transition, and for growth inhibition of relevant strains of Lactobacilli. Leads may then be advanced for specialized testing, including determinations in human cervical explants and in PBMCs against primary HIV subtypes, combination testing with other inhibitors and additional cytotoxicity assays. PRO 2000 and SPL7013 (the active component of VivaGel™), two **microbicide** products presently being evaluated in human clinical trials, were tested in this *in vitro* algorithm, and were shown to be highly active against CCR5- and CXCR4-tropic HIV-1 infection.

"Noncomparative contraceptive efficacy of cellulose sulfate gel"

Author(s): Mauck CK, Freziers RG, Walsh TL, et al

Reference: N/A 111(3):739-46.

<http://www.greenjournal.org/cgi/content/abstract/111/3/739?maxtoshow=&HITS=1&hits=1&RESULTFORMAT=&andorexacttitle=and&andorexacttitleabs=and&fulltext=microbicide%2C+microbicides&andorexactfulltext=or&searchid=1&usestrictdates=yes&resourcetype=HWCIT&ct>

Published Abstract: OBJECTIVE: To estimate the 6-month cumulative probability of pregnancy, short-term adverse effects, and acceptability of cellulose sulfate vaginal contraceptive gel. METHODS: Two hundred fertile heterosexual couples were enrolled in this single-center, phase II, 6-month noncomparative study conducted at the California Family Health Council in Los Angeles, California. Couples did not desire pregnancy, were at low risk for

sexually transmitted diseases, and agreed to use 3.5 mL of cellulose sulfate gel intravaginally before each coital act as their primary means of contraception. Scheduled follow-up visits took place after one menstrual cycle and at study completion, which occurred after 6 months and six menstrual cycles had elapsed. In addition, participants were instructed to call the site at the onset of each menses to review their diary cards. RESULTS: The cumulative probabilities of pregnancy during 6 months and six cycles of typical use were 13.4% (95% confidence interval [CI] 7.5-19.4%) and 13.9% (95% CI 7.7-20.2%), respectively, and during 6 cycles of correct and consistent ("perfect") use: 3.9% (95% CI 0.0-9.2%). Slightly over one fourth of the women and one man reported experiencing gel-related adverse events, two thirds of which were mild and only possibly related to the gel. Three quarters of women and men reported that they would buy cellulose sulfate gel for contraception. CONCLUSION: Cellulose sulfate **vaginal gel** yields pregnancy rates comparable to nonoxynol-9 and few adverse events among couples at low risk for sexually transmitted diseases.

[Return to Table of Contents](#)

3. PUBLISHED RESEARCH: RELEVANT BASIC AND TRANSLATIONAL SCIENCE

"Could an open-source clinical trial data-management system be what we have all been looking for"

Author(s): Fegan GW, Lang TA

Reference: N/A 5(3):e6.

Published Abstract: *EDITORS' NOTE: Due to the length of this article, we have included only the first four paragraphs below. The full text, along with references and figures for this article, is available at*

<http://medicine.plosjournals.org/perlserv/?request=get-document&doi=10.1371%2Fjournal.pmed.0050006>

Difficulties in Meeting the Demands of Regulators and Guidelines

In Europe, it is a legal requirement to conduct clinical trials in accordance with the International Conference on Harmonisation's guidelines on good clinical practice (see <http://www.ich.org/>). A recent editorial reported that this directive has led to a decline in the number of trials being conducted by independent academic groups [1]. One possible reason for this is that reporting and documentation requirements are now so burdensome that the process has become unnecessarily complicated [2]. This is rather ironic, given that well-designed clinical trials should be amenable to very simple data handling and analysis [3]. Indeed the flowchart established by the CONSORT (Consolidated Standards of Reporting Trials) statement [4] for carrying out a properly randomised controlled trial has just four steps, which supports the approach of keeping it simple.

Following discussions with colleagues at various institutions (including Oxford University, the London School of Hygiene and Tropical Medicine, the International Aids Vaccine Initiative, and the Medical Research Councils of Uganda, South Africa, and the United Kingdom), one major difficulty comes up time after time: these, and many other, clinical trial groups do not have the skills or resources to establish and use software systems required to manage trial data in compliance with the International Conference on Harmonisation's guidelines. This situation is further exacerbated for non-commercial research groups based in developing countries, where basic information systems infrastructure and support tends to be even more limited [5].

There is little good independent information about what is available. Additionally, there is almost a complete absence of guidance from regulatory agencies such as the European Medicines Agency and United States Food and Drug Administration about how to evaluate the many competing systems available, and indeed what the actual requirements are for trials where the data will be needed for a regulatory submission. This is particularly important with respect to trials evaluating products for neglected diseases, which are often carried out by academic researchers and where the data would be needed to support a product license. The size of this issue can be somewhat ascertained from the results of a search that we did at the World Health Organization trials registration site (<http://www.who.int/trialsearch/>, accessed September 27, 2007): use of the term "Africa" returned 206 trials, and the term "Asia" returned 520.

Ideally, such a system would work as well for a single-centred investigator-led small trial as it would for large regulatory standard multi-centred randomised controlled trials. Furthermore, this system would need to be affordable to the public sector and modifiable and amenable for use with existing software already employed, particularly statistical and reporting software. This is quite a tall order. Put in this context, and considering the dialogue between research groups on this matter, it would seem prudent for international health research organisations to combine their efforts and spending power and assist with the development of systems that are open to all and truly fit for purpose. The daunting challenges of capturing, cleaning, extracting, and storing trial data would then be eased, with the added desirable benefit of improving quality and reliability of data. Perhaps we would then see more academics wanting to conduct clinical research...

"HIV drug development: the next 25 years"

Author(s): Flexner C

Reference: N/A 6:959-66.

<http://www.nature.com/nrd/journal/v6/n12/full/nrd2336.html>

Published Abstract: The development of drugs for HIV infection began soon after the virus was discovered 25 years ago. Since then, progress has been substantial, but numerous uncertainties persist about the best way to manage this disease. Here we review the current treatment options, consider novel mechanisms that can be exploited for existing drug targets, and explore the potential of novel targets. With a view to the next quarter century, we consider whether drug resistance can be avoided, which drug classes will be favoured over others, which strategies are most likely to succeed, and the potential impact of pharmacogenomics and individualized therapy.

"Improved HIV-1 incidence estimates using the BED capture enzyme immunoassay"

Author(s): Hargrove JW, Humphrey JH, Mutasa K, et al

Reference: N/A 22(4):511-8.

Published Abstract: OBJECTIVE: To validate the BED capture enzyme immunoassay for HIV-1 subtype C and to derive adjustments facilitating estimation of HIV-1 incidence from cross-sectional surveys. DESIGN: Laboratory analysis of archived plasma samples collected in Zimbabwe. METHODS: Serial plasma samples from 85 women who seroconverted to HIV-1 during the postpartum year were assayed by BED and used to estimate the window period between seroconversion and the attainment of a specified BED absorbance. HIV-1 incidences for the year prior to recruitment and for the postpartum year were calculated by applying the BED technique to HIV-1-positive samples collected at baseline and at 12 months. RESULTS: The mean window for an absorbance cut-off of 0.8 was 187 days. Among women who were HIV-1 positive at baseline and retested at 12 months, a proportion (epsilon) 5.2% (142/2749) had a BED absorbance < 0.8 at 12 months and were falsely identified as recent seroconverters. Consequently, the estimated BED annual incidence at 12 months postpartum (7.6%) was 2.2 times the contemporary prospective estimate. BED incidence adjusted for epsilon was 3.5% [95% confidence interval (CI), 2.6-4.5], close to the 3.4% estimated prospectively. Adjusted BED incidence at baseline was 6.0% (95% CI, 5.2-6.9) and, like the prospective estimates, declined with maternal age. Unadjusted BED incidence estimates were largely independent of age; the pooled estimate was 58% higher than adjusted incidence. CONCLUSION: The BED method can be used in an African setting, but further estimates of epsilon and of the window period are required, using large samples in a variety of circumstances, before its general utility can be gauged.

"Significant reduction in HIV prevalence according to male circumcision intervention in sub-Saharan Africa"

Author(s): Londish GJ, Murray JM

Reference: N/A Epub ahead of print.

Published Abstract: Background: Observations that reduced adult HIV prevalence in sub-Saharan Africa correlated with levels of male circumcision (MC), have suggested that MC could be used as a preventative measure against HIV infection. The exact benefits of this intervention are uncertain. Moreover if MC is not feasible for the whole male population, which groups should be targeted? Methods: A mathematical model simulated observed levels of HIV prevalence under the complete range of current levels of circumcision. Increased MC from 2007 was incorporated in this model and used to simulate HIV prevalence in 2020. Results: Complete coverage by MC could reduce HIV prevalence from 12 to 6% for an average population country in sub-Saharan Africa in 2020. This reduction is scaled proportionally when lower circumcision levels are achieved. These benefits are achieved mostly by circumcising men between 20 and 30 years of age (adult prevalence reduced from 12 to 10%), and those with riskier behaviour (8 to 6.9%). Complete negation of these benefits requires at least 40% of circumcised males to significantly increase risky behaviour. Conclusions: MC provides an effective intervention in sub-Saharan Africa to reduce HIV prevalence. It is most effective when applied to 20-30 year old risky males with diminishing returns with application to the wider male population.

"The estimated burden of HIV/AIDS in Uganda, 2005-2010"

Author(s): Hladik W, Musinguzi J, Kirungi W, et al

Reference: N/A 22(4):503-10.

Published Abstract: OBJECTIVES: To estimate the burden of HIV disease in Uganda and the effect of HIV/AIDS control programmes to mitigate it. DESIGN: Mathematical modelling and projecting using surveillance and census data. METHODS: Using antenatal clinic surveillance (1986-2002) and a recent population-based survey (2004-2005) data, we modelled the adult national HIV prevalence over time (1981-2004), and kept prevalence constant at 6.4% for the years 2004-2010. Using Spectrum software and census data, we estimated the national burden of HIV disease and the effect of selected HIV-related prevention and treatment programmes. RESULTS: In 2005, we estimated that there were 135,300 new HIV infections (adult HIV incidence 0.96%), 691,900 asymptomatic prevalent infections, 88 100 AIDS cases, and 76 400 AIDS deaths. An estimated 647,000 (80%) HIV-infected adults were unaware of their infection; one third of all adult deaths were HIV related. As a result of population growth, by 2008 a similar number of people will be HIV infected (1.1 million) as during the peak of the epidemic in 1994. Although antiretroviral therapy (ART) coverage is expected to rise from 67,000 (2005) to 160,000 (2010), the number of persons needing but not receiving ART will decrease only slightly from 127,600 (2005) to 111,100 (2010). The use of single-dose in 2005 nevirapine probably averted only 4% of the estimated 20 400 vertical infections. CONCLUSION: HIV/AIDS continues to be a leading cause of adult disease and death in Uganda. Universal ART access is probably unachievable. With the absolute burden of HIV disease approaching the historic peak in the early 1990s, more effective prevention programmes are of paramount importance.

[Return to Table of Contents](#)

4. POLITICS AND POLICY

"Fighting HIV/AIDS in Africa requires more than 'Fruits of Science,' opinion piece says"

Date: 05 March 2008

Source: *Kaiser Daily HIV/AIDS Report*

http://www.kaisernetwork.org/daily_reports/rep_hiv_recent_rep.cfm?dr_cat=1&show=yes&dr_DateTime=05-Mar-08#50764

The "fruits of science" and antiretroviral drug programs alone will not curb the spread of HIV in Africa, Jonny Steinberg -- author of "Sizwe's Test: A Young Man's Journey Through Africa's AIDS Epidemic" -- writes in a *Los Angeles Times* opinion piece. Antiretroviral programs should "heed the frailty and complexity of the human beings they aim to reach," Steinberg writes. He adds, "In particular, for men who have been disabled by shame, treatment needs a new face, one that presents AIDS not as the core of a new political identity but as a chronic illness like any other."

Raising issues such as the possibility that HIV/AIDS is seen by some Africans as an "attack on a man's generative capacity" or a "white conspiracy" is "uncomfortable for two reasons," Steinberg writes. "First, they suggest that helping a continent in need is complicated and difficult," he writes, adding, "Second, asking why sick Africans do not always rush to get treatment requires thinking and speaking about them anthropologically, which brings its own special fear: the fear of patronizing them, of blaming them and their indigenous ways for their illness."

According to Steinberg, no one in the U.S. "has seriously argued that medicine single-handedly" helped control the HIV/AIDS epidemic among men who have sex with men. Before advances in treatment, MSM "entered into a collective dialogue that slowly and painfully re-examined the fundamentals of their identities and sexual practices," according to Steinberg. MSM "were forced to think about themselves anthropologically and to recalibrate their relation to themselves and the world," he writes, adding, "And so it will have to be with Africans."

Steinberg notes that the need to make antiretrovirals universally accessible in Africa is "urgent," but the "odds are stacked against these drugs becoming the harbinger of a wider African redemption." Africa needs "fortification against the comforting Western fantasy" that it "will be saved by science alone," Steinberg writes. He adds that a "great epidemic by its nature assembles people into difficult relations with themselves and one another," concluding, "There is no substitute for working through this terrain. Africans, after all, are as complicated" as white MSM (Steinberg, *Los Angeles Times*, 3/5).

A kaisernetwork.org interview with Steinberg is available online at http://www.kaisernetwork.org/health_cast/hcast_index.cfm?display=detail&hc=2514.

"Concerns over blockbuster drugs Vytorin, Avandia prompt investigation of FDA review process"

Date: 04 March 2008

Source: *Associated Press*

Author(s): Matthew Perrone

<http://www.signonsandiego.com/news/business/20080304-1111-drugapproval-investigation.html>

The government's watchdog agency is investigating whether the Food and Drug Administration's drug-review process cleared two blockbuster medications without sufficient proof of their safety or effectiveness. Sen. Charles Grassley said Tuesday the Government Accountability Office has agreed to study a much-debated method for approving drugs used to clear GlaxoSmithKline PLC's diabetes pill Avandia and Merck & Co. Inc. and Schering-Plough's cholesterol drug Vytorin. The Iowa Republican requested the investigation after recent studies suggested the drugs may not lower the risk of heart attack and artery-clogging plaque, as assumed by millions of patients and doctors. "There's enough of a pattern of problematic drugs to ask for an independent review of how the FDA follows up on the effects of medicines that it's approved," said Grassley, in a statement.

FDA cleared Avandia because it helped control blood sugar, which many doctors believe decreases diabetics' risk of heart attack. But the agency came under fire last year when an analysis showed Avandia could actually increase heart attack risk. FDA argued that it has never required diabetes drugs to show lower heart attack risk, and that lowering blood sugar alone is an important benefit.

The agency approved Vytorin, which combines Schering-Plough's Zetia with Merck's older cholesterol drug Zocor, based on its cholesterol-lowering capability. But a study released earlier this year showed Vytorin was no more effective at limiting plaque buildup in neck arteries than Zocor alone, which is now available as a low-cost generic.

At issue now is whether FDA should approve drugs based on biological measures, like cholesterol and blood sugar, without evidence they improve more meaningful measures like survival. FDA's Director for Medical Policy Robert Temple said the agency has used several alternate study goals, often called surrogate endpoints, to approve drugs for decades. For example, HIV drugs are cleared based on their virus-lowering power, an effective predictor of survival.

Drug industry advocates favor shorter study goals because they involve smaller, less expensive and faster trials. Longer trials, they say, may actually jeopardize patients. "It's probably unethical to do an overall survival study where you're going to have HIV patients taking a placebo for 10 years," said Alan Goldhammer, vice president with the Pharmaceutical Research and Manufacturers of America.

But those who criticize FDA's handling of Avandia and Vytorin say surrogate endpoints aren't the problem. Rather, it's when FDA doesn't demand follow-up studies to prove drugs delivered on the predicted benefits. "These studies are often never done, so we're left without the knowledge we need to use these drugs wisely," said Dr. Steve Nissen, chairman of cardiovascular medicine at the Cleveland Clinic. "And obviously we've paid the price for that with the safety issues and lack of efficacy issues with Avandia and Vytorin."

Nissen wrote the analysis that showed Avandia raised the risk of heart attack. Last year FDA said the drug's risks were still unclear and asked GlaxoSmithKline to study its effect on the heart. Results from that trial aren't expected until 2014 - 15 years after the drug was approved.

Schering-Plough and Merck are working on a study to determine if Vytorin extends patients' lives. Results from that study, which FDA did not request or require, are expected in 2011.

When the agency does require follow-up studies of drugs, its track record is poor for making sure companies complete them. A 2006 investigation by the Health and Human Services Department inspector general concluded FDA could not readily identify what progress companies made on the studies. In its most recent report, FDA said 900 of more than 1,200 studies required of drug makers had not even begun. Under a law that takes affect next month FDA can fine companies up to \$1 million for failing to honor drug study commitments. Grassley argued for higher fines, and in his request to GAO asked investigators whether FDA needs more authority.

The agency shows no sign of scaling back its use of surrogate endpoints. Last month FDA cleared Genentech Inc.'s drug Avastin for use in breast cancer patients who have not taken other drugs. Agency reviewers based their decision on Avastin's ability to slow the spread of cancer. Previously FDA had approved drugs as a first-choice option for cancer patients if they extended, or improved the quality, of patients' lives.

"Malawi seeks to oust fake AIDS healers"

Date: 04 March 2008

Source: *Agence France Presse*

http://www.mg.co.za/articlepage.aspx?area=/breaking_news/breaking_news__africa/&articleid=333868&referrer=RSS

Malawi lawmakers on Tuesday began examining draft legislation aimed at ridding the HIV/Aids-plagued country of quacks claiming to cure the pandemic through such remedies as sex with virgins, health authorities said. "When it passes into law, all traditional healers claiming to cure Aids will be dealt with," Mary Shaba, head of HIV/Aids issues for Malawi's Health Ministry, told a parliamentary committee asked to provide input to the measure before it is submitted to the full 193-member Parliament later this year. "The Act will regulate and protect people from healers who prescribe sex with albinos, the disabled or virgins as a cure for HIV and Aids," she said of the Bill drafted in collaboration with traditional Malawi healers and the World Health Organisation.

Shaba did not specify possible sanctions against bogus healing claims for a virus that has devastated this Southern African country, infecting more than one in 10 people. But under the draft legislation, the country's 30 000 traditional healers -- many of whom operate in towns and villages where hospitals are few and far between -- would be required to register with a board set up by the Health Ministry.

Besides direct solicitation by healers, newspaper and radio advertisements for Aids cures are also common in Malawi.

Last year, a United Nations-funded study found that about 60% of people aged between 15 and 49 lacked knowledge about HIV prevention. Fourteen percent of Malawi's population of 12-million is infected with HIV, which causes Aids, according to official figures, and there are about 78 000 Aids-related deaths and 100 000 new infections every year.

"NIH to lighten up heavy peer review process"

Date: 03 March 2008

Source: *in-Pharma Technologist.com*

Author(s): Wai Lang Chu

<http://in-pharmatechnologist.com/news/ng.asp?id=83667-nih-research-grants>

Researchers applying to the US National Institutes of Health (NIH) for research grants could find the complicated peer-review process easier to navigate in the future under new proposals designed to revamp the outdated system. The move aims to speed up grant delivery, currently a painfully slow process that can take as long as 18 months to go through the system. The situation is further exacerbated as proposals are placed in a queue as older applications go back and forth to the applicants for rewrites and amendments before final approval.

The process began in the summer of last year, when NIH Director Elias Zerhouni called on researchers to air their gripes and share ideas about how to make the system better. The formal list of recommendations is expected to be complete by April.

In a preliminary report documented by the NIH, a list of challenges and recommendations has already been compiled in collaboration with internal and external working groups. These groups mainly comprises of researchers, advocacy

groups, professional society groups, and NIH staff. Broad strategies mentioned include reducing the administrative burden of applicants, reviewers, and NIH staff; enhancing review and reviewer quality; optimising support at different career stages and types and for different scientific approaches; and the need for continuing to review the peer review system in the future. "The fine details of implementation were purposefully not considered during this phase of the project and it would be premature to consider issues of this type today," NIH stated in the report, titled *A Self-Study by the NIH in Partnership with the Scientific Community to Strengthen Peer Review in Changing Times*.

The proposals are not without its critics who believe the changes may make things worse. The fears are the system will reward superficiality at the expense of solid, critical work. The response section of resubmissions, a part of the process threatened with the axe, is considered the most meaningful part of the grant and researchers believe its absence will not give the applicant a chance to explain why a criticism is wrong.

However, feedback from scientists suggest that a review of the process is long overdue, with many believing the process too conservative, time-consuming, spotty in quality, and insufficiently supportive of young scientists and clinical research. "One goal is to focus on the merit of the science as presented in the application and not on the 'potential improvements' realised following additional rounds of review," the NIH commented. "To deal with that, the NIH may recommend removing the 'special status' of amended applications and consider all applications as being 'new.'" In removing the application's special status, researchers would be allowed to re-apply without revising, allowing reviewers to develop more concise reviews.

Other areas of concern on the agenda include improving the rating system and review and reviewer quality. Shortening the application (to an as-yet-unspecified length) was also mentioned as is reducing the emphasis on preliminary data and methodological details.

The report recommended engaging at least four reviewers per application, giving reviewers incentives for participating.

"The Global Fund: growing pains"

Source: *Lancet Infect Dis.* 2007 Nov;7(11):695.

The sound bites and spin coming from the latest replenishment round of the Global Fund to Fight AIDS, Tuberculosis and Malaria have done little to evoke confidence in the Fund's future support. Despite positive press statements from the Global Fund and donor governments at the recent donor replenishment meeting - rather cruelly known as the begging round - in Berlin (Sept 26-28), many governments pledged substantially less than they had previously committed to. But there is no time to brood. Next comes the round 7 meeting (Nov 11-13) where the Global Fund will examine funding proposals for the coming year.

By contrast with the enthusiasm from donors 5 years ago when the Global Fund was founded, the current lack of support is disappointing - and dangerously short sighted. In just a few years, the Global Fund has established itself as the major player in the fight against the "big three" infectious diseases. For example, it currently funds through its

grants programme 20% of the HIV programmes in the world, constituting about 60% of its own budget. To date, programmes supported by the Global Fund have provided treatment for 1.1 million people living with HIV/AIDS and 2.8 million people with tuberculosis. According to the Fund's own estimations, these programmes have averted 2 million deaths worldwide. So in light of all this lifesaving work, donor apathy is unacceptable.

However, it is easy to be distracted by the Global Fund's financial worries and there are other key factors at play that may limit its effectiveness. Although the Global Fund's remit has always been clear, and its organisational principles are impressive, from its conception the Global Fund was set up as a financial instrument, not an implementation agency. Its aim was to raise and give additional resources for the treatment of HIV/AIDS, tuberculosis, and malaria - according to former UN Secretary General Kofi Annan, it was to be a war chest. The Global Fund would operate transparently and administer funds through a rapid performance-based grant process. Crucially, it would support country-led plans and priorities, form innovative public-private partnerships, and thereby support people and communities living with these diseases. These principles and its focus on the big three has made it unique among international institutions.

Yet despite its best efforts to remain true to its founding principles, the Global Fund has learned through experience that putting these principles into practice is fraught with difficulty. Furthermore, many believe that its tight remit is increasingly becoming a straight jacket. Considerable criticism has been directed at the Global Fund's narrow disease-specific approach by civil society groups and others; an approach which many say distorts comprehensive health planning and diverts resources from other diseases and priorities (for example, other sexually transmitted infections), and which does not contribute to overall health-system strengthening. In response, the Global Fund implemented a stand-alone grant application process for health-system strengthening in 2005. However, after complaints from donors that this should not be an activity of the Global Fund, rather than fighting its corner, this grant scheme was subsequently stopped. Nevertheless, for the current funding round, guidelines state that applicants can request funds for health-system strengthening if these activities are essential to reducing the impact and spread of HIV/AIDS, tuberculosis, or malaria. This is a welcome step - it shows that the Global Fund is ready to take more of a whole-systems approach that will help make a long and lasting impact on the burden of infectious diseases in resource-poor countries.

Yet there is the opportunity to do more in the seventh round talks and the Global Fund must once again be bold enough to expand its remit. Recommendations made by civil society groups to the Global Fund board have called for institutional support for integrating sexual and reproductive health interventions into HIV/AIDS programmes. The Global Fund has supported very few applications for sexual and reproductive health interventions and has turned down requests for funding for sexual infections other than HIV/AIDS. Several countries have now submitted proposal requests that include such integration. For example, Rwanda has proposed to incorporate gender-based violence, a major driver of the HIV/AIDS pandemic, as an element of its sexual and reproductive health services.

The only sound public health and human rights approach for the Global Fund to take is to start dealing with the wider factors involved in tackling the big three. Expanding its remit to include a greater focus on the wider issues would be the right thing to do. It is time for the Global Fund to rise to the challenge.

5. PHARMACEUTICAL INDUSTRY

"Drugs firms face new laws on test results"

Date: 06 March 2008

Source: *The Guardian*

Author(s): Martin Hodgson, Nicholas Watt

<http://www.guardian.co.uk/science/2008/mar/06/medicalresearch.drugspolicy>

A major tightening of the law governing the oversight of drugs companies will be announced today when the government says GlaxoSmithKline delayed informing the authorities that a controversial drug increased the likelihood of suicide among teenagers. The health minister Dawn Primarolo will tell MPs that new legislation will be introduced by the end of the year to ensure drugs companies pass on results of clinical trials as soon as the alarm is raised about one of their medicines.

The government is to intervene after a four-year investigation by the drug regulatory body into the way GSK withheld the full results of their trials of the antidepressant Seroxat on children. The trial data, which was finally handed to the Medicines and Healthcare Regulatory Authority (MHRA) in May 2003, identified two problems of which the company had been aware as early as 1998:

- A higher risk of suicidal behaviour among under 18s using Seroxat rather than a placebo.
- Seroxat was ineffective in dealing with depressive illness among under 18s.

Primarolo will announce that GSK should have told the MHRA earlier than it did about the results. But GSK will not face criminal prosecutions, she will say, because the legislation in this area is insufficiently clear on whether and when drugs companies should inform the regulator. The minister will announce that new legislation will be introduced by the end of the year placing a greater obligation on companies to disclose results of trials.

The MHRA's investigation asked whether GSK had informed the regulatory body in reasonable time. It shows that the drug company had the information about the potentially suicidal effects of Seroxat and concludes that GSK should have informed the MHRA earlier. However, it finds that the company acted within the letter of the law by withholding data that would have shown up a problem. The failure to take stronger action against GSK will anger the many critics of the regulatory body, who say it is not up to the job of policing the pharmaceutical industry.

Patients and some doctors have been urging a tough line against GSK ever since the MHRA suddenly announced, in June 2003, that doctors must not give Seroxat to children and under 18s. The agency said it was acting within two weeks of being given the full set of data from trials of Seroxat in children. The statistics contained in those results showed that the drug was no better than a placebo in alleviating depression in children and that those on the drug

were more likely to develop suicidal tendencies than those on placebo. In one of the trials, 6.5% of those taking Seroxat became suicidal compared with 1.1% in the placebo group. A leaked internal document from GSK, dated to 1998, said the company would have to "effectively manage the dissemination of these data in order to minimise any potential negative impact". In the United States, GSK was sued by the New York state attorney general, Eliot Spitzer, and settled for \$2.5m (Ã,Â£1.25m) and an agreement to publish all its trial results - negative or positive - on a publicly available database.

Critics have called for big changes to the MHRA. In its report into the influence of the pharmaceutical industry, the Commons' health select committee expressed concern that the MHRA did not get all the information it needed from manufacturers before it licensed drugs. It called for a new regime of random audits of the raw trial data collected by companies and for more staff to be employed.

GSK has always completely rejected allegations that it improperly withheld data on the drug. It said Seroxat had never been approved by EU or US regulators as a medicine for those under 18, and that the company had therefore never marketed the drug for that age section. It also said its trial results had been submitted to regulators and were presented publicly in journals and on its website.

[Return to Table of Contents](#)

6. ANNOUNCEMENTS

"Gates Foundation seeking grant proposals for \$100M initiative to support research on infectious diseases, including HIV/AIDS"

Date: 04 March 2008

Source: *Kaiser Daily HIV/AIDS Report*

http://www.kaisernetwork.org/daily_reports/rep_index.cfm?DR_ID=50733

The Bill & Melinda Gates Foundation on Monday announced that it will begin accepting grant proposals on March 31 for the first round of its \$100 million initiative to fund research on infectious diseases, including HIV/AIDS, the AP/*Houston Chronicle* reports. The Grand Challenges Explorations is an expansion of the Grand Challenges in Global Health initiative, which was launched in 2003 to support new technologies to advance global health, according to the AP/*Chronicle* (AP/*Houston Chronicle*, 3/3).

Grand Challenges Explorations, announced in October 2007, targets scientists in Africa and Asia -- where diseases such as HIV/AIDS, tuberculosis and malaria are widespread -- but will accept proposals from scientists worldwide. The program uses a shorter application form that will be reviewed in a few months, compared with six months or more for typical grant applications. The grants will support hundreds of early-stage research ventures that involve scientists from multiple disciplines. The program also will focus on quickly evaluating a large number of ideas that could lead to new vaccines, diagnostics, drugs and other technologies (*Kaiser Daily HIV/AIDS Report*, 10/10/07).

First-round grants will consider proposals in four areas:

- Innovative approaches to HIV prevention or treatment methods that go beyond current vaccine research, antiretroviral drugs and other strategies;
- Original approaches to understanding latent TB, with the goal of finding new processes to detect and eradicate latent infection and prevent transmission;
- Unproven methods aimed at protecting against infectious diseases, such as using natural or synthetic immune responses or eliminating the need for an effective immune response; and
- New techniques for discovering or delivering drugs that limit the development of resistance (Gates Foundation release, 3/3).

The Gates Foundation will accept proposals for the first round of funding through May 30. Each initial grant will total \$100,000, and projects that prove successful will be eligible for additional funding of \$1 million or more (*AP/Houston Chronicle*, 3/3).

The Gates Foundation will select and award grants within about three months of the May 30 deadline. "Breakthrough ideas can come from anywhere, and we hope this new process will encourage a broad range of scientists from around the world to bring their ideas to the table," Tachi Yamada, president of the Gates Foundation's Global Health Program, said, adding, "We're especially interested in reaching people who work outside the field of global health, innovators in the developing world and young investigators" (Gates Foundation release, 3/3).

EDITORS' NOTE: *Full descriptions of the initial topic areas and application instructions are available at www.gcgh.org/explorations.*

Final Draft of the NIH 2007-2008 Peer Review Self-Study

On February 28, 2008, the Final Draft of the NIH 2007-2008 Peer Review Self-Study was submitted to Dr. Elias Zerhouni, Director of NIH, marking the end of the diagnostic phase of the peer review enhancement effort. To obtain the PDF file of Final Draft Report, please go to the Peer Review Website: <http://enhancing-peer-review.nih.gov> (Persons with disabilities experiencing problems accessing portions of the above PDF file should contact Kerry Brink at 301-435-2641. This Final Draft Report identifies the most significant challenges facing the NIH peer review system and proposes recommended actions. If you wish to comment on the Final Draft, please send your comments no later than Monday, March 17, 2008, via:

Electronically: PeerReviewRFI@mail.nih.gov

OR United States Mail:

Penny Wung Burgoon, Ph.D.

Senior Assistant to the Deputy Director
Office of the Director, NIH
One Center Drive,
Building 1, Room 114
Bethesda, MD
20892-0183

[Return to Table of Contents](#)