



Issue Number 372
October 19, 2001

Published twice monthly by
John S. James
AIDS Treatment News
1233 Locust St., 5th floor
Philadelphia, PA 19107
800-TREAT-1-2
Email: aidsnews@aidsnews.org

Contents

Tenofovir: FDA Hearing on Important New Antiretroviral 2

Report on the FDA advisory committee hearing on tenofovir (Viread(TM)), a new antiretroviral about to be approved.

Apparently Harmless Virus Associated with Reduced HIV Death 4

Infection with a virus that does not cause any known disease has been associated with a much better survival rate in persons with HIV. The mechanism of action is unknown. With further research, this finding might lead to a new class of drugs to help control HIV.

Retroviruses Conference: Major Deadlines Nov. 16 5

Anyone going to the Retroviruses conference next February either as community press or through the community scholarship program must apply by November 16. Applications from developing-country researchers and clinicians applying for international scholarships are also due on that date.

Barcelona International Conference, July 7-12, 2002: Time to Start Planning 6

Early applicants can get more convenient housing and a reduced admission price, and many international tickets go on sale early in the year.

"A Day for Women" Medical Information Meeting, November 3 in New York..... 6

A one-day meeting on women's HIV treatment issues will allow participants to ask questions of the experts. The meeting is free, but registration is required due to limited space.

New HIV Drugs: Extensive Lists, Additional Information 6

Here are links to lists of HIV drugs in development, and to an article about some of the most important ones.

Africa Access News 7

Much is happening in the fight for access to treatment in developing countries, especially countries in sub-Saharan Africa.

AIDS Treatment News

Published twice monthly

Subscription and Editorial Office:

AIDS Treatment News
Philadelphia FIGHT
1233 Locust St., 5th floor
Philadelphia, PA 19107
800-TREAT-1-2 toll-free U.S. and Canada
fax: 215-985-4952
email: aidsnews@aidsnews.org

Editor and Publisher: John S. James

Associate Editors: Tadd T. Tobias, R.N.

Statement of Purpose:

AIDS Treatment News reports on experimental and standard treatments, especially those available now. We interview physicians, scientists, other health professionals, and persons with AIDS or HIV; we also collect information from meetings and conferences, medical journals, and computer databases. Long-term survivors have usually tried many different treatments, and found combinations which work for them. *AIDS Treatment News* does not recommend particular therapies, but seeks to increase the options available.

Subscription Information: Call 800-TREAT-1-2

Businesses, Institutions, Professional offices: \$325/year. Includes early delivery of an extra copy by email.

Nonprofit community organizations: \$150/year. Includes early delivery of an extra copy by email.

Individuals: \$140/year, or \$80 for six months.

Special discount for persons with financial difficulties: \$54/year, or \$30 for six months. If you cannot afford a subscription, please write or call.

Outside the U.S., Canada, or Mexico, add air mail postage of \$20/year, or \$10 for six months.

Back issues, and discounts for multiple subscriptions, are available; contact our office for details.

Please send U.S. funds: personal check or bank draft, international postal money order, or travelers checks. VISA, Mastercard, and purchase orders also accepted.

To protect your privacy, we mail first class without mentioning AIDS on the envelope, and we keep our subscriber list confidential.

ISSN # 1052-4207

Copyright 2001 by John S. James. To assure accuracy, *AIDS Treatment News* requires permission for republishing articles. Readers may make up to 20 photocopies for persons with AIDS or HIV; if you want to reprint more, call or write to us. Bulk orders and bulk subscriptions are available. Our address and phone number must be included in any reprint. Brief passages may be quoted for review.

Tenofovir: FDA Hearing on Important New Antiretroviral

by John S. James

The FDA's one-day public hearing on tenofovir (brand name Viread(TM)), a new antiretroviral being developed by Gilead Sciences, took place October 3 near Washington D.C. (see *AIDS Treatment News* # 370, August 24, 2001). This meeting of the Antiviral Drugs Advisory Committee (a group of outside experts convened by the FDA) also included consultants selected for this particular meeting because of their special expertise.

Everyone who spoke agreed that tenofovir should be approved; the FDA had no issue with approval, which is expected shortly. In clinical trials the drug has shown a 0.6 log decrease sustained for the length of the trial (up to a year so far), when added to an antiretroviral regimen which was failing to suppress the virus -- a difficult test for a drug, and probably not the way tenofovir will generally be used. (Usually at least some of the other drugs in the regimen would be changed, often after resistance testing -- although it is too early to know for sure how tenofovir will be used in practice.) Resistance to tenofovir seems slow to develop, although resistant viruses do occur. The drug is easy to use (it is taken only once a day, with food), and so far has shown excellent safety in human tests, with side effects comparable to those reported by volunteers who received the placebo.

One major issue at the hearing was whether the FDA should recommend tenofovir for combination use in HIV treatment for any patient -- including those starting antiretrovirals for the first time -- or only recommend it for advanced patients, where there is currently more data. All activists who spoke wanted the general indication, but for a variety of reasons the committee tended toward the more restrictive one (there was no formal vote). Activists want to free doctors and patients from possible reimbursement hassles if they decide to use the drug in front-line therapy; they also wanted to make sure the company was not punished for testing tenofovir first in ad-

vanced patients, which activists and the FDA have urged companies to do, since these patients most need new options.

But committee members were concerned that less is known about first-line use and more will be known next year, when the indication could be changed. Some felt that the lack of complete information about first-regimen use changed the risk/benefit ratio of using a new combination vs. a standard one. Others noted that ADAPs (the AIDS Drug Assistance Programs, run separately by each state) are unlikely to micromanage patients, so they will not deny reimbursement if a physician uses the drug outside of the indications formally approved by the FDA. Some saw the drug's indication as mainly a marketing issue. (Doctors are free to prescribe an approved drug for any patient, without being bound by the indications.)

Some observers think the FDA may approve the general indication but with a note saying that studies in treatment-naive patients are not yet complete.

Long-Term Safety Issues

Human safety data were very good -- in particular, there was none of the kidney toxicity that had been seen in adefovir when studied for HIV at doses of 60 and 120 mg daily. (Adefovir, a much less effective antiretroviral in the same drug class as tenofovir, is no longer being developed for HIV, but is a promising potential treatment for hepatitis B, in much smaller doses.)

But animal studies using tenofovir doses much higher than those given to people had found a bone problem, osteomalacia -- a lack of normal mineralization of the bone (this disease is called rickets in children, osteomalacia in adults). While the danger appears to be low -- the condition can be treated, and reversed completely in animals when the drug was stopped -- two bone experts brought by the FDA as consultants to the committee thought that certain steps should be taken now in order to head off possible problems in the future:

(1) Gilead should do some simple research to find out which potential mechanism caused the

problem in the animals. Was bone failing to mineralize properly because of a deficiency of the minerals in the body? Or was the drug interfering with enzymes involved in the mineralization process? The company might be able to learn much by analyzing samples already in its freezers.

(2) The bone specialists recommended that certain baseline tests be done before tenofovir is started -- at least to look for vitamin D deficiency and certain other simple nutritional problems that could easily be corrected with nutritional supplements or other treatments. One of the consultants listed baseline studies he would ideally like to do today -- probably too many to be feasible for widespread clinical practice -- but noted that once the mechanism studies had been done, much of that baseline testing could become unnecessary. Pregnant women and children could be at particular risk for any bone mineralization problem.

We left the hearing with the impression that this issue should not delay approval of tenofovir -- the drug is needed now, and the bone risks are not immediate if they exist at all. But the discussion pointed out the need for biochemical research on the mechanism of the bone changes in animals, and strongly suggested at least some baseline testing when the drug is started, for correction of relevant nutritional deficiencies if necessary.

(According to Gilead, much of this work had already been done but was not presented at the hearing because the FDA was already comfortable with the data. And bone markers are now being measured in study 903, a clinical trial of tenofovir in treatment-naive patients.)

Other Possibilities

Tenofovir may have other important uses than the HIV treatment for which it will be approved:

* Hepatitis B. Tenofovir may prove to be an effective hepatitis B treatment. One activist urged that this use be planned for in co-infected people, instead of left to chance, so that the hepatitis B as well as HIV treatment could be optimized, to reduce the risk of patients developing tenofovir-resistant hepatitis B.

* Mother-to-infant transmission. One committee member noted theoretical reasons why this drug might be effective. If so it would have an advantage over nevirapine, in that resistance to tenofovir is much slower to develop. [We would also like to know if adding a single dose or very short course of tenofovir to the single dose of nevirapine could make the regimen more effective in preventing maternal transmission -- a possibility which would seem to be quite feasible to test, because of the safety of tenofovir, the fact that nevirapine is far from 100% effective (allowing a better regimen to be detected), and the fact that everyone in the trial would get at least the accepted nevirapine regimen.]

* Microbicide use? PMPA, the active form of tenofovir, proved very effective in preventing HIV infection in early animal studies (tenofovir is a chemical modification of PMPA, designed so that the drug could be given orally, as PMPA cannot). We do not recall microbicide possibilities coming up at this hearing, which had a different focus; but PMPA is now being studied by the U.S. National Institute of Allergy and Infectious Diseases as a possible vaginal microbicide. An effective microbicide would have a great impact on the global HIV epidemic because it would provide a prevention method controlled by women.

For More Information

A summary and a transcript will be on the FDA Web site, at:

<http://www.fda.gov/ohrms/dockets/ac/acmenu.htm> (click on '2001', then 'Anti-Viral Drugs Advisory Committee').

Usually the transcript is available 30 days after the meeting, the summary approximately 90 days after. Some other information about the October 3 meeting is already on this site.

Apparently Harmless Virus Associated with Reduced HIV Death

by John S. James

Two independent studies published September 6, 2001, in the *New England Journal of Medicine*^{1,2} found that persons with HIV who were also infected with a virus not known to cause disease had a much lower death rate than those who were not infected -- with the risk of death being reduced about two to four times, depending on how the comparisons were done. The mechanism of this effect is not known, although there are some hints from laboratory studies. An accompanying editorial includes a warning against attempts to infect people deliberately, at least until more is known³.

The finding is not new; five early studies had reported a similar result, and one had failed to find it (that study was done differently); for references, see the Discussion section of the September 6 Tillmann paper².

The virus, called GB virus C, is fairly common; it is found in about 1.8% of healthy blood donors, 15% of persons positive for hepatitis C, and up to 35% of persons with HIV³. This virus was first found in 1995, and is sometimes called hepatitis G virus, but that name is used infrequently since the virus does not appear to cause hepatitis or any other disease. Most people infected with GB virus C clear the infection normally; then they have antibodies, but no live virus can be found. Persons who have cleared the infection seem to have a somewhat reduced death rate from HIV, but not as much protection as those whose GB virus C infection is still active.

Comment

The importance of this finding is that it offers a window to a possible new understanding of HIV and a new way of controlling it.

HIV not only develops resistance to most drugs fairly rapidly; it also seems to evolve similarly to get around the patient's immune system. But GB

virus C infection is associated with lower viral loads and improved survival even years later (although it is probably not associated with higher T-cell counts). If this virus is causing these effects, it is doing so in some way that HIV cannot easily evolve around.

Perhaps there is no causal relationship, and GB virus C infection gives no benefit but is only a marker for something already in the patient that is responsible for the better outcome. Even in this case there would still be an unknown mechanism in the patient that is not easy for HIV to evolve around, and that might be exploited to develop a new kind of drug treatment -- one probably closer to immune-based therapy than to traditional antiretrovirals.

The hardest kind of clinical trial to conduct is one that shows a survival benefit. Here we already have a clear survival benefit -- and thousands of patients who could be studied with nothing more intrusive than a blood draw.

References

1. Xiang J, Wunschmann W, Diekema DJ, and others. Effect of coinfection with GB virus C on survival among patients with HIV infection. *New England Journal of Medicine*. September 6, 2001; volume 345, number 10, pages 707-714.

2. Tillmann HL, Heiken H, Knapik-Botor A, and others. Infection with GB virus C and reduced mortality among HIV-infected patients. *New England Journal of Medicine*. September 6, 2001; volume 345, number 10, pages 715-724.

3. Stosor V. and Wolinsky S. GB virus C and mortality from HIV infection. *New England Journal of Medicine*. September 6, 2001; volume 345, number 10, pages 761-762.

Retroviruses Conference: Major Deadlines Nov. 16

The important 9th Conference on Retroviruses and Opportunistic Infections will take place February 24-28, 2002, at the Washington State Convention and Trade Center in Seattle, Washington. This conference has always been full, and this year will be limited to 3,800. Registration is also limited to certain categories of people. Important deadlines for "community" participation, as well as international scholarships, are November 16. Researchers and clinicians have other deadlines.

These applications must be received by November 16:

- * Community scholarships -- Applicants must meet certain conditions, and provide an appropriate letter of support. See complete information on the conference Web site, below

- * Community press -- AIDS newsletters, etc. must register by November 16. See information on the conference Web site as to how to do so. It may be difficult to be accepted if one's publication is not already known to the conference.

- * International scholarships -- "Researchers and clinicians from developing countries working in the area of AIDS research who, without financial support, would be unable to participate in the conference" must apply for these scholarships by November 16.

After being accepted applicants must meet other deadlines to register for the conference and for housing.

If you want to go to the conference, be sure to check the Web to confirm this information and to learn how to apply. The conference Web site is: <http://www.retroconference.org/2002/>.

The Retrovirus Conference Secretariat is: West-over Management Group, Inc., 115 South Saint Asaph St., Alexandria, VA 22314, 703-535-6862, fax 703-535-6899, email info@retroconference.org.

Barcelona International Conference, July 7-12, 2002: Time to Start Planning

The XIV International AIDS Conference will take place in Barcelona, Spain, July 7-12, 2002; this conference meets in different countries every even-numbered year. While not difficult to get into, the International Conference is expensive except for media (due to frills which developed early and have resisted protests since -- protests especially strong last time, in Durban, South Africa). It helps to register early in order to get housing closer to the meeting and minimize the daily travel time to get to one's hotel room and back. And early registration costs less: \$850 before February 1, \$950 February 1 and before May 1, and \$1050 starting May 1, with a much lower rate for students. Note that international airfares typically go on sale early in the year.

For information about this conference see <http://www.aids2002.com>.

Comment

While we certainly agree that the cost of the international AIDS conferences needs to be lowered, we think that what is most important is to improve the use of online communication throughout the year -- allowing education and collaboration around the world at far less expense than attending any international conference. Then the conferences could focus more on facilitating working groups, and less on lectures in auditoriums.

"A Day for Women" Medical Information Meeting, November 3 in New York

The 2nd annual women's conference by NATAP (National AIDS Treatment Advocacy Project) will take place Saturday November 3, 9:30 a.m. to 4:00 p.m. at the New York University Medical Center, Auditorium E & F, 401 East 30th St (between 1st Avenue and FDR Drive). There is no charge, but preregistration is required and seating is limited. To register, call NATAP at 212-219-0106, or 888-26-NATAP. You are requested to enter at 550 1st Avenue and bring valid photo ID.

Speakers include Judith Currier, M.D., on women's complications, lipodystrophy, and vaccines; Janet Mitchell, M.D., on GYN and women's infections and care; Kathleen Squires, M.D., on women's HIV treatment, epidemiology, and natural history, and Valerie Stone, M.D., on HIV treatment and adherence. There will be morning and afternoon breakout sessions for questions and answers.

For more information, call NATAP at 212-219-0109 between 10am - 6pm, Monday thru Friday.

New HIV Drugs: Extensive List, Additional Information

The most complete recent list we have seen of anti-HIV drugs in development -- over 60 total, including the approved drugs -- was posted recently by Ben Cheng of Project Inform, on the Web site of the new AIDS Treatment Activist Coalition.

The list, at <http://www.atac-usa.org/RDACCommittee.html> (scroll down, or click on "Chart on drugs in development", has the generic or chemical name of each compound, the class of drug (nucleoside analog, protease inhibitor, etc.), the phase of development (preclinical, phase I, phase II, phase III, or approved), and the pharmaceutical company doing the work.

For another extensive list of drugs in (or formerly in) development, see the Treatment Action Group (TAG) Web site: <http://www.aidsinfonyc.org/tag/science/pipeline.html>.

For more information about some of the more prominent new drugs currently being researched, see "New Agents for Anti-HIV Therapy," by Joseph J. Eron Jr., M.D., and Robert L. Murphy, M.D. It is available on the Medscape site, <http://hiv.medscape.com> (click on 'New Agents for Anti-HIV Therapy' if this link is still there, or search the site for the author's last name, and look for the title in the results returned). Note: The Medscape site requires registration, but registration is free, and it need be done only once (provided you remember the user ID and password you choose). Most articles on continuing-education medical sites remain online for one year.

Africa Access News

by John S. James

Online Petition Through November 2

See note at the end of this article.

Huge Mining Company Says It Cannot Treat Low-Income Workers

According to an October 9 article in the *Financial Times*, the London-based company Anglo American decided it could not provide antiretroviral treatment to most of its employees in South Africa. Only about 14,000 senior staff will be eligible for the AIDS medicines. The company employs about 160,000 people in Africa, most of them in South Africa -- where about 21% of the employees have HIV.

"The saving you achieve can be substantial, but we really don't know how it will stack up," said one official. "We feel that the cost will be greater than the saving." The company said it would need funding from international donor agencies to distribute AIDS treatment further.

The National Union of Mineworkers (South Africa) called the policy "inherently racist and discriminatory, with beneficiaries of the scheme being, in the main, white workers and the black elite. The foot soldiers who generate wealth in the bowels of the earth are excluded."

South Africa: Glaxo Offers Voluntary License on AZT/3TC

On October 7 GlaxoSmithKline said it would grant a voluntary license to Aspen Pharmacare, South Africa's largest generic drug company, to manufacture and sell AZT and 3TC -- a move sought by activists as well as by Aspen. Apparently this license will only allow the drug to be sold to government and NGO (nonprofit) organizations in South Africa -- not in other African countries. Glaxo will charge a royalty of 30% of net sales, which will be donated to nonprofits fighting AIDS in the country.

The final price of the Aspen drugs is not known but is widely expected to be much higher than prices available from generic manufacturers in India; however, the agreement will avoid legal obstacles that have kept the Indian drugs out of the South Africa. (India has patent laws designed to encourage pharmaceutical manufacturers to compete in low-cost production methods -- a system which has worked very well in providing low-cost medicines for that country, but now may have to be ended because of the World Trade Organization treaty, which requires all countries to adopt a U.S./European patent system even for domestic drug production.)

Note: In a separate announcement on October 3, not related to AIDS, GlaxoSmithKline offered discounts averaging 30% for U.S. elderly persons with limited income and without prescription coverage. Those who qualify must be 65 or older, and with income no greater than 300% of the federal poverty level (which today means less than \$26,000 for individuals and \$35,000 for couples). Qualifying persons will receive a card which they will present at pharmacies. Other companies may be under pressure to match these discounts, since otherwise their products will now become more expensive than competing Glaxo products for the eligible patients.

Generic Company Charges Patent Abuse in South Africa

On or around October 7, a South African affiliate of Cipla, the Indian generic pharmaceutical company, filed legal action in South Africa, accusing GlaxoSmithKline and Boehringer Ingelheim, the maker of nevirapine, of abusing their patents to keep prices high.

The action, described by observers as "legally groundbreaking" and "a major move," could potentially open the door to South African sales of HIV medications at prices much lower than those which will result from the voluntary licensing agreement announced the same day.

Note: For a legal analysis arguing that South Africa is permitted under international trade rules to take "certain legal steps to ensure meaningful reductions in drug prices," see *Tripping Over Patents: AIDS, Access to Treatment and the Manufacturing of Scarcity*, by Jonathan Michael Berger, University of Toronto. It can be downloaded from www.tac.org.za/archive.htm (go to Research Papers).

Also on international patents (although perhaps not

relevant to this South African case) note *Patent Politics*, by Michael H. Davis, Cleveland State University College of Law. Davis argues that the "ordinary practitioner" test of nonobviousness, which determines that some patents are granted and some are not, is inherently subjective, allowing patent laws to implement national industrial policy without democratic oversight -- and also making patent law not rationally transferable across national borders. The abstract and link to the full article are available through the Social Science Research Network, at:
http://papers.ssrn.com/sol3/cf_dev/AbsByAuth.cfm?per_id=230701

UN Secretary General, Pharmaceutical Companies Issue Joint Statement

On October 5 United Nations Secretary General and executives of seven major pharmaceutical companies met and issued an 8-point joint statement on access to treatment. It is at:
<http://www.un.org/News/Press/docs/2001/sgsm7982.doc.htm>

Comment: we find it good as far as it goes -- though it does not go very far.

South Africa: Major Conflict Over Death Report

A report by the Medical Research Council (South Africa's government medical-research institution, like the U.S. National Institutes of Health) found that AIDS had become the largest single cause of death in the country, and that 40% of the deaths last year of South Africans age 15-49 were AIDS related. The South African government under President Thabo Mbeki -- which has refused to provide antiretroviral treatment through the public health system, even for prevention of mother-to-infant transmission -- refused to release the report, which was leaked to the press.

The report also predicted that in 10 years AIDS in South Africa would cause more than double the deaths of all other causes combined, and that life expectancy in the country would drop from 54 years to 41.

On October 16, after extensive protests over its suppression, the report was released at:
<http://www.mrc.ac.za>

On October 17 the Guardian (UK) covered the controversy:
<http://www.guardian.co.uk/Archive/Article/0,4273,4278717,00.html>

UK Poll Shows Strong Support for Dual Pricing

On October 8 the British charity Voluntary Service Overseas released a survey showing that 87% of people who responded thought it was right for people with HIV in poor countries to pay less for the medicines than people in the UK, according to *The Guardian*, UK, October 8.

We do not know of a similar U.S. poll, but almost certainly a large majority here would agree.

For More Information

For more information on treatment access in Africa, see the Web site of the Treatment Action Campaign (TAC), the leading AIDS treatment activist group in South Africa, at <http://www.tac.org.za/>

Action Alert: Online Petition on Drug Patent Rules Open Until November 2

A petition by Oxfam America, "The World Demands Fairer Rules on Patents," is open for signatures at the Oxfam America site:
<http://www.oxfamamerica.org/petition/petition.html>

Or you can sign at the Global Treatment Access site: <http://www.globaltreatmentaccess.org>

The complete text of the petition is:

"14 million people in the developing world die every year from treatable diseases, including HIV/AIDS, malaria, and tuberculosis. The high cost of medicines is a key factor. World Trade Organization patent rules are pushing up the price of these medicines. I urge WTO members, in particular the United States, to demonstrate their commitment to put health before wealth by changing and clarifying the global patent rules at the forthcoming WTO summit conference."

Note: The reference to the WTO summit is to the Ministerial Conference of the World Trade Organization (WTO), which occurs every two years; the last meeting was in Seattle in 1999. The next meeting is scheduled for November 9-13 in Doha, Qatar, but might be moved to Singapore for security reasons.