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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.

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Liver Fibrosis in HIV/Hepatitis C Coinfection: HIV Protease Inhibitors May Be Protective

by John S. James

A study of 182 patients at a major hospital in France suggests that HIV protease inhibitors may help to reduce liver fibrosis and cirrhosis in patients with both HIV and hepatitis C.[1]

This study, conducted in patients with both hepatitis C and HIV, was done to determine if protease inhibitors were really harmful to such patients, as had been reported in some cases. In fact, the opposite was found; use of protease inhibitors was associated with significantly less liver damage in this study. No one knows why, although the authors suggested several possible mechanisms. This new study is the first large, long-term followup of coinfected patients which included liver biopsy data -- which may help explain why it found different results.

The new study, published in the August 2000 *Hepatology*, analyzed a cohort of patients who had been treated at the hospital between 1995 and 2000, and on whom careful medical records had been kept. A statistical analysis found four independent predictors of progression to cirrhosis (severe scarring of the liver): absence of protease inhibitor therapy (relative risk 4.74), heavy alcohol use (greater than or equal to 50 grams per day -- about 5 drinks a day -- relative risk 4.71), CD4 count under 200 (relative risk 2.74), and age greater than 20 years at the time of hepatitis C infection (relative risk 2.74).

The protective effect of antiretroviral treatment was found only for protease inhibitors, not for nucleoside analog drugs. (There were not enough patients treated with NNRTIs, such as nevirapine or efavirenz, to make a comparison.)

The authors suggested that using protease inhibitors in HIV therapy, reducing alcohol consumption, and keeping CD4 counts high might be beneficial in coinfected patients.

This study was limited because it was not a randomized trial where patients were randomly assigned to use protease inhibitors or not, with long-term followup with liver biopsy. The authors noted that such as trial would be impossible for both ethical and practical reasons.

References

1. Benhamou Y, Di Martino V, Bochet M, and others. Factors affecting liver fibrosis in human immunodeficiency virus- and hepatitis C virus-coinfected patients: Impact of protease inhibitor therapy. *Hepatology*. August 2001; volume 34, pages 283-287.

Note

For more information on hepatitis C and coinfection with HIV, see *The Hepatitis Report* by Michael Marco and Jeff Schouten, available at http://www.treatmentactiongroup.org (click on "HIV/HCV Coinfection").

Tenofovir: FDA Hearing October 3, Public Comment Deadlines September 26

by John S. James

On October 3 the FDA's Antiviral Drugs Advisory Committee will hold a public hearing on tenofovir (full chemical name tenofovir disoproxil fumarate, or tenofovir DF; new brand name Viread™), an antiretroviral developed by Gilead Sciences and currently in pre-approval expanded access. Public comments are scheduled for the **October 3** hearing, and written statements can also be submitted. Both written comments, and sign-up to make an oral presentation, are due at the FDA by **September 26**. Details are included in the official announcement below.

[Name and drug class: The full chemical name of tenofovir is tenofovir disoproxil fumarate, or tenofovir DF; the new brand name is Viread™. Tenofovir is a *nucleotide* analog -- differing from the nucleoside analogs (AZT, d4T, etc.) in that it requires less processing within cells, and therefore is active in certain cells where the nucleoside analogs generally are not. Both nucleotide analogs and nucleoside analogs are reverse transcriptase inhibitors.]

On the following day, October 4, the same Advisory Committee will discuss another drug, voriconazole, for severe fungal infections.

Comment

Tenofovir is an important new HIV treatment because of its resistance profile, potency, apparently low side effects, and ease of use. The Committee is expected to recommend it for approval. (The FDA does not have to follow the recommendation of an Advisory Committee, but it almost always does.)

A likely issue before the Committee will be whether to recommend a broad indication (such as "indicated in combination with other antiretroviral agents for the treatment of HIV infection"), or a narrow one that would limit the drug to advanced patients, where more data is available. In either case physicians would legally be permitted to prescribe the drug for any patient, but insurance reimbursement will often be a problem if the drug is labeled only for treatment-failure cases and physicians want to use it earlier. We believe that approval with a broad indication is important for several reasons:

* Tenofovir has already been shown to work well for advanced HIV patients, the most difficult to treat. While less information is available today for its use early in treatment, everything we know about antiretrovirals suggests that they work at least as well when used early in treatment, and with at least as good a safety profile.

* Many patients cannot tolerate existing regimens because of metabolic or other side effects. Their physicians may want to try changing their regimen early, for example when lipoatrophy (fat wasting) first begins to develop, to prevent long-term harm. Even though much remains unknown about metabolic side effects and how to manage them, doctors and patients should have more

options to try if necessary, without having to fight HMO red tape or pay for necessary drugs out of pocket.

* Some doctors are moving toward using stronger drug combinations first, instead of keeping them in reserve for when the other treatments fails -- and the patients have become more difficult to treat. Medical opinion is still largely unformed on this issue; no one knows for sure which strategy is better, and in practice we will probably learn from clinical experience before we learn from clinical trials. Reimbursement obstacles should not block clinical practice and experience.

* Adherence remains crucial, and is improved by regimens that are easy to take. Tenofovir is taken as one tablet once a day, so it can be a part of once-daily regimens, important for patients with adherence difficulties and also for tests of directly observed therapy.

* It has been hard to get companies to research new drugs for advanced patients. Most prefer to test their drugs earlier when it is usually easier to show viral-load changes and lack of side effects. Gilead did test tenofovir first in late-stage patients, and if it is punished with a restrictive label, other companies will become even more reluctant to test early for advanced patients, who need new options the most. (Gilead is now running a large trial, called Study 903, for treatment-naive patients, but data will not be available until 2002.)

One can never be sure what will come out of an advisory committee -- especially when the FDA has been under increasing pressure in recent years to be more conservative in its drug approvals. We hope HIV physicians will write or speak to the Committee about their need for new treatment options -- and tell the Committee and the FDA what labeling for tenofovir would be best.

FDA Meeting Announcement, Distributed August 21:

The Food and Drug Administration (FDA) will hold a public meeting of the Antiviral Drugs Advisory Committee on October 3 and 4, 2001, 8:30 a.m. to 5 p.m. at the Town Center Hotel, Maryland Ballroom, 8727 Colesville Road, Silver Spring, MD. For directions, or information about lodging, please call the hotel directly at (301) 589-5200.

On October 3, 2001, the committee will discuss new drug application (NDA) 21-356, for Viread™, (tenofovir disoproxil fumarate) Tablets, proposed for the treatment of Human Immunodeficiency Virus (HIV) infection. The sponsor is Gilead Sciences, Inc.

Additionally, on October 4, 2001, the committee will discuss new drug application (NDA) 21-266, for Vfend™ (voriconazole) Tablets, and (NDA) 21-267, Vfend™ I.V. (voriconazole) for Infusion, Pfizer Global Research and Development, proposed for the treatment of invasive aspergillosis, serious Candida infections, infections caused by Scedosporium spp. and Fusarium spp., rare and refractory infections and empirical treatment.

This meeting is free and open to the public. No prior registration is required to attend.

Interested persons are encouraged to present data, information, or views, orally or in writing, on issues pending before the committee.

If you would like to make an oral presentation, please send the following information to: Tara Turner, Pharm.D., Center for Drug Evaluation and Research (HFD-21), 5600 Fishers Lane, Lane (for express delivery: 5630 Fishers Lane, rm. 1093)Rockville, MD 20857, by FAX at 301-827-6776, or by e-mail to TurnerT@cder.fda.gov by September 26, 2001.

* Name of speaker (and organization/affiliation if appropriate)

* Address, phone and FAX numbers

* A brief summary statement of your comments

* Approximate amount of time you would like to speak

Oral presentations from the public are scheduled on both days between approximately 1 p.m. and 2 p.m. Time allotted for each presentation may be limited, depending on the number of speakers.

Written submissions may also be sent to Dr. Turner by September 26, 2001.

Please call the FDA Advisory Committee Information Line, 1-800-741-8138 (301-443-0572 in the Washington, DC area), code 12531, for up-to-date information on this meeting.

Homocysteine, HIV, and Heart Disease

by Jennifer E. Cohn

[Note: Abnormally high levels of homocysteine in the blood are associated with increased risk of heart disease, and a number of other diseases as well. These high levels can be detected by a blood test, and are often caused by dietary deficiencies that can be corrected.

[Reducing disease risk by controlling homocysteine level is today considered experimental; for example, it is not part of the new NCEP (National Cholesterol Education Program) guidelines published May 16, 2001, probably because much of the data is just emerging and is sometimes contradictory. But because excessive homocysteine is strongly suspected to be unhealthy in many ways, because it can be easily controlled in many cases, and because vitamin B12 deficiency (which can cause excess homocysteine) is already an important risk for persons with HIV, we believe there should be more attention to this potential medical strategy.

[Therefore we asked Jennifer Cohn, a medical student in Philadelphia, to look into the literature on homocysteine and cardiovascular risk and prepare a brief report, to help raise awareness in the HIV community. JSJ]

* * *

Homocysteine is a non-essential amino acid; high levels have been associated with cardiovascular disease. Excessive homocysteine levels can be caused by a deficiency of folate and/or vitamin B12. Deficiencies of folate can arise because a person is not eating enough fruits and leafy green vegetables. Vitamin B12 deficiency can occur in vegetarians (since this vitamin is not found in plant sources), but deficiencies are more commonly caused by poor absorption, which can result from HIV disease, aging, and other causes.

Excess homocysteine may have varying effects on an individual's health. For example, increased levels of homocysteine have been associated with both increased risk of Alzheimer's and cardiovascular disease.[1,2] Furthermore, some preliminary studies have demonstrated that a certain form of homocysteine, called "reduced homocysteine," may increase HIV viral replication.[3] However, the literature on homocysteine levels and viral replication is inconsistent[3, 4] -- so this article will focus on one of the better documented effects of homocysteine: its effect on the cardiovascular system.

Many studies of non-HIV infected individuals have shown elevated serum homocysteine levels to be a risk factor for vascular disease. In particular, a review article by Boushey et al. (1995) highlighted homocysteine as a causal factor for arteriosclerotic vascular disease.[1] Individuals with a high level of serum homocysteine had 2.5 times the risk of developing vascular disease as those with a normal level; this makes serum homocysteine levels a stronger risk factor for vascular disease than serum cholesterol. In another study, Stubbs et al. (2000) demonstrated that for patients being admitted for acute cardiac events, serum homocysteine levels were an excellent predictor of later cardiac events such as another heart attack or death from a heart attack.[5]

The mechanism by which homocysteine acts is still unclear. However, research suggests that it affects the lining of blood vessels.[6] Increased serum homocysteine levels may damage this lining or make it hard for blood vessels to relax, making it easier for arteriosclerotic plaques to develop. Homocysteine may also change factors in blood itself so that the blood becomes more prone to clot.[1,6]

How does homocysteine affect people with HIV? Unfortunately, at the present time few studies are investigating this question. However, it is probably a reasonable assumption that homocysteine increases the risk of vascular disease in people with HIV in the same way as it does in people without HIV -- but if persons have already developed other risk factors for cardiovascular disease, high homocysteine levels may be even riskier for them. And persons with HIV may have a more difficult time absorbing Vitamin B12, leading to an increase in serum homocysteine.[7]

Some drugs may also increase homocysteine

levels. Examples of such drugs include nicotinic acid (niacin), theophylline (used for asthma, emphysema and bronchitis), methotrexate and L-Dopa.[8]

The most important and easiest treatment is taking dietary supplements of Vitamin B12, Vitamin B6, folic acid and TMG (betadine), in addition to eating a balanced diet including fruits and green leafy vegetables.[1,7] While there are suggested daily amounts of supplements, the only reliable way to know if a patient is taking the right amounts to control a high serum homocysteine level is by having a blood test for homocysteine.

References

1. Boushey CJ, Beresford SA, Omenn GS, and others. A quantitative assessment of plasma homocysteine as a risk factor for vascular disease: Probable benefits of increasing folic acid intakes. *JAMA*. October 4, 1995; volume 274, number 13, pages 1049-57.

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4. Balzarini J, De Clercq E, Serafinowski P, and others. Synthesis and antiviral activity of some new S-adenosyl-L-homocysteine derivatives. *Journal of Medical Chemistry.* November 27, 1992; volume 35, number 24, pages 4576-83.

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7. Remacha AF, Riera A, Cadafalch J and others. Vitamin B-12 abnormalities in HIV-infected patients. *European Journal of Haematology.* July 1991; volume 47, number 1, pages 60-4.

8. Cardiovascular Consultants Medical Group: Homocysteine and the Heart, July 30, 2001, http://www.cardiacconsultants.com/homocysteine.htm.

AIDS Treatment Activists Form New Coalition

by John S. James

Twenty-one U.S. AIDS treatment activists met for three days in August and began to outline a new coalition to improve AIDS research, treatment access, and empowerment of new activists in communities most affected by the epidemic. The August 17-19 meeting, hosted by The Center for AIDS: Hope and Remembrance Project in Houston, Texas, resulted from earlier community meetings held at the annual Retroviruses conference in 2000 and 2001.

The new organization, tentatively named AIDS Treatment Activist Coalition, will address several concerns:

* There is no national organization or meeting of AIDS treatment activists to discuss and develop overall strategy. (NATAF, the North American AIDS Treatment Action Forum, serves another purpose, educating new activists and advocates.)

* Each year there are at least a dozen pharmaceutical company meetings with AIDS treatment activists. These meetings are called by different companies, each of which sets the agenda and decides who will be invited to represent patients and the public. U.S. activists want to move toward the European system of ongoing, structured meetings with the companies, where the community selects its own representatives and invites the company whose products will be discussed, instead of letting industry determine who will

represent the community at major company/community meetings. ATAC also hopes to improve communication about the discussions that take place at these meetings, so that activists who do not attend can be informed.

* Treatment activists must be more representative of the demographics of the epidemic (including more people of color, women, and young people). The new organization will emphasize mentoring, educating, and empowering new activists -- and may require members to recruit others from underrepresented groups.

* Today a small number of highly experienced activists are overcommitted. We need to help provide more opportunities for treatment education, and otherwise make it feasible for more people to become treatment activists.

ATAC will focus on biomedical research, including diagnostics, vaccines and microbicides as well as drugs, and will include AIDS-related illnesses such as hepatitis C and tuberculosis, as well as HIV infection and its complications.

Membership policies, bylaws, and other specifics are still being determined. For example, it is likely that membership will be open to all persons with HIV and their advocates, with members joining as individuals (not as representatives of organizations) and paying nominal dues; but there might or might not also be a separate category of organizational member for nonprofit organizations. The organizers are seeking input from the public and can be reached through the email addresses below.

Standing committees so far are Bylaws; Communication; Fundraising; Membership; Mentoring; and Research, Development, and Access.

For More Information; Contacting ATAC

ATAC has started a Web site at http://www.atac-usa.org; you can also send email to info@atac-usa.org

ATAC has a temporary steering committee, and you can also contact the members individually:

Parrish Crosby Parrishfc@yahoo.com
Yvette Delph YvetteDelph@aol.com
Larry Diaz sadatatx@hotmail.com
Mike Donnelly MrDonnelly@aol.com
Gregg Gonsalves greggg@gmhc.org
Michael Marco Mikemarco@aol.com
Bob Munk bobmunk@ix.netcom.com
Claire Rappoport clairer@itsa.ucsf.edu

Notes:

(1) This writer participated in the organizing meeting in Houston, and drafted the statement above with the assistance and approval of the group.

(2) We are especially impressed that this coalition has started useful work immediately, within a week of its organizing meeting; see http://www.atac-usa.org

Action Alert: Global AIDS Funding

by John S. James

It is especially important now for U.S. citizens to let their two Senators know they are concerned about funding to control AIDS and other infectious diseases around the world. The Democrats have been worse on this issue than the Republicans -- not because they are opposed, but because they do not think people care. Calls before Labor Day are most important. But it never hurts to let Congress know that their constituents care about AIDS in Africa and elsewhere, and infectious diseases everywhere.

Background

An August 20 alert from the Treatment Action Network of Project Inform summarizes the situation:

"On April 26th, 2001, United Nations Secretary General Kofi Annan launched the 'Global AIDS and Health Fund'. This international fund is intended to treat and prevent HIV/AIDS, tuberculosis, and malaria for those without access to medicine, health care, and

prevention programs.

"This spring, President Bush pledged a $200 million contribution to this fund. While a small step forward, this amount falls well short of the $2 billion asked of the United States and lowered the bar for other contributors. Major donors have scaled back their contributions and the momentum has slowed. Advocates have turned to Congress to increase this pledge.

"While the process hasn't finished in the House of Representatives or the Senate, it appears that the House will approve about the same amount as the President has pledged. It is critical that the Senate propose a much larger amount. The House and Senate will have to meet to negotiate a final amount to send to the President for approval. To prepare for these negotiations, it is crucial that the Senate come to the table with a large number, rather than the smallest!

"Constituent pressure is essential to ensure that elected officials make the global AIDS crisis a priority. If everyone who cares about the international AIDS epidemic meets with, calls, or writes a letter to their Senators this month, we could have a major impact in focusing their attention on this issue. Please take a few minutes to respond to this Alert!

... "You can find contact information for your two U.S. Senators by accessing their individual websites through the main U.S. Senate website. Go to www.senate.gov, then click "List Senators By State". You'll find links to both of your Senators underneath your state. Each website will have Washington and district phone, fax, and mailing addresses."

Notes:

(1) It is best to avoid email to political offices unless you know that they are prepared to include email in their counts of public opinion on issues. If you do email your Senators, include your street address so they will know it is coming from a constituent. You might call their office and ask if email is a good way to communicate with them -- or if you should write or call instead.

(2) This alert is intended for the month of August (before Labor Day). But it is never too late to let your representatives know that you care about AIDS in Africa and elsewhere, and infectious diseases throughout the world.

Doing our part to control epidemics is entirely feasible and is the right thing to do, and it makes us all safer in an increasingly populated, mobile, and interconnected world.

NATAF Scholarship Deadline August 31; You Can Apply Online

"The 2001 North American AIDS Treatment Action Forum (NATAF) will be held December 2-5 at the Sheraton Vancouver Wall Centre Hotel, Vancouver, Canada. The forum is designed to educate individuals interested in becoming HIV/AIDS advocates and educators; to enhance their skills and knowledge; and to develop inclusive, national strategies to ensure the continuity and success of the treatment advocacy movement.

"NATAF 2001 is open to anyone interested in broadening their knowledge of HIV/AIDS research and treatment issues, and learning to use this knowledge to advocate on behalf of everyone living with HIV/AIDS. Participants include the volunteers, staff, and board members of community-based organizations, case managers, social workers, AIDS educators and outreach workers, pharmaceutical and government representatives, healthcare professionals and people living with HIV/AIDS.

"Scholarships Deadline August 31st: Deadline for scholarships application is 6:00 PM (Eastern) on August 31, 2001. For information about scholarships or to apply online, please go to http://www.nmac.org/nataf/2001/scholarship/scholarship.htm

Note:

Project Inform included the following to it's Treatment Action Network (tan@projectinform.org) "While many of the questions on the scholarship form ask about your agency, applications are especially encouraged from individuals not association with an agency or organization. Put "N/A" on the agency questions and focus on the personal statement section."