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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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Tenofovir: Gilead Applies for Approval; Expanded Access Liberalized

by Dave Gilden

Tenofovir, Gilead Sciences' candidate reverse transcriptase inhibitor, could be approved in about six months. In an unexpected move, the company announced May 1 that it had filed a New Drug Application with the FDA. After approval, tenofovir could be prescribed for any adult with HIV, according to the company's proposed labeling. Gilead will soon proceed with similar marketing applications in Europe.

Tenofovir, or PMPA, stops the infection of new cells by halting the gene-building activity of HIV's reverse transcriptase enzyme. The drug is similar to nucleoside analogs such as ddI but requires less intracellular processing to reach its active state. Tenofovir is distinguished by its long intracellular half-life, which allows once-a-day dosing. It also has a somewhat different resistance profile than the standard nucleoside analogs, so it may be active against many HIV isolates that have mutated to resist the approved nucleoside analogs. In trials so far, resistance to tenofovir has been slow to develop -- although it has been found.

Tenofovir's safety profile is considerably improved over adefovir, a closely related compound developed by Gilead. Adefovir was rejected by the FDA because of severe kidney toxicities coupled with modest efficacy.

Gilead's new drug may be helpful in a salvage regimen, but it does not represent any dramatic breakthrough. In a 189-person phase II treatment-intensification trial,¹ tenofovir was added to volunteers' previous regimens at doses of 0 mg (placebo), 75 mg, 150 mg or 300 mg per day. The trial participants had a mean 4.6 years prior anti-HIV therapy and a mean baseline viral load of 5,000. At study entry, 94% of the enrollees also had HIV with mutations conferring resistance to various nucleoside analogs, principally AZT and 3TC. HIV in more than half of the participants also had resistance to protease inhibitors. The trial participants on 300 mg/day -- the preferred dose -- recorded viral load reductions averaging about 0.6 log (75%) through both weeks 24 and 48. The presence or absence of AZT or 3TC resistance was not associated with a major difference in the response. The modest, stable viral load

reduction was not accompanied by any appreciable change in CD4 count, either.

Gilead scientists are reporting almost identical preliminary results from a similar 552-person phase III treatment-intensification trial. Both these trials make it clear that tenofovir requires concomitant active antiretrovirals from other drug classes to form a regimen that can successfully suppress HIV. This is true in treatment-naïve individuals, who appear to have a better response to tenofovir, as it is in those with a history of treatment failure. In its 600-person phase III trial for those without prior treatment, Gilead is comparing tenofovir directly to the nucleoside analog d4T, each combined with the nucleoside analog 3TC and the NNRTI efavirenz.

Expanded Access: Gilead Drops CD4, Viral Load Exclusions

Since last February, an expanded-access program has been open to people whose advanced disease state and treatment history mandate immediate use of new drugs to suppress their HIV (see *AIDS Treatment News* #360, February 23, 2001). Gilead always intended that this program would be very small. It at first restricted entry to persons with viral loads over 10,000 and CD4 counts under 100 – plus documented treatment failure with at least two protease inhibitors or one PI and one non-nucleoside reverse transcriptase inhibitor (NNRTI). (Those with a CD4 count between 100 and 200 could also apply if they had had an AIDS-defining opportunistic infection within the last 90 days.)

Expanded-access enrollment has been even slower than anticipated. Public dissatisfaction over the paltry enrollment figures led Gilead to abandon its viral load and CD4 count entry criteria. As to speeding up the enrollment process, Debbie Fletcher of Gilead said in an interview, “About 20% of the doctors have submitted incomplete registration materials and had their applications returned. The paper work can go back and forth and back and forth. Our field representatives will follow up with the physicians who don’t finish filling out the forms.”

One HIV specialist summed up his frustrating experience with Gilead: “Paperwork did go back and forth. It took them weeks to turn it around and tell you they needed something more. Then you would send that, and they would come up with something else.”

The Coalition for Salvage Therapy has asked the company for a full and regular accounting of the

program’s enrollment. In a strongly worded letter, this national activist network said that applicants to the program “are not only patients with few or no remaining options for treatment, but also patients whose disease has been allowed to progress to the point where ‘waiting for things to get sorted out’ with the program is simply not an option.” The Coalition had long pressured Gilead for a much broader expanded-access distribution before finally settling for the present restricted effort.

For the expanded-access program, Gilead advises doctors to prescribe at least one new anti-HIV agent in addition to tenofovir. Tenofovir naturally substitutes for other nucleoside analogs, not for protease inhibitors or NNRTIs. Some treatment activists have argued that Gilead should abandon the requirement that enrollees have past failure with PIs or NNRTIs. The program should be open to anyone lacking new nucleoside analogs to create a viable treatment combination.

This is the way tenofovir expanded access works in France, where the drug is recommended for patients with nucleoside analog intolerance or with nucleoside analog-resistant HIV, as demonstrated by resistance assays. In the United Kingdom, tenofovir is available to any patient who, in the judgment of his or her doctor, could not otherwise construct an effective anti-HIV regimen. Regulations in both countries preclude strict entry criteria, including CD4 count or viral load limits.

When tenofovir is approved, the issues around expanded access will be largely academic. At least the program is growing. Enrollment has picked up dramatically in the U.S., where about 150 people are now signed up. Also, Gilead has asked Germany, Italy and Spain for permission to extend the program beyond the U.S., UK and France. Further information can be obtained from Gilead at 1-800-Gilead-5 in the US and 33-1-44-90-34-46 in Europe.

References

1. Miller MD et al. Baseline and Final Phenotypic Analysis of HIV-1 from Patients Adding Tenofovir Disoproxil Fumarate (TDF) Therapy to Background ART. 8th Conference on Retroviruses and Opportunistic Infections. February 4-8, 2001. Poster 441.

June 3 Demonstration in Washington to Mark 20th Year of AIDS

On June 3 over 100 organizations, including the NAMES Project AIDS Memorial Quilt, National Minority AIDS Council, National Association of People with AIDS, Project Inform, Gay Men's Health Crisis, and many ACT UP chapters will mark the 20th year of the AIDS crisis with a march on the Pharmaceutical Research and Manufacturers Association, Congress, and the White House. There will be a reading of all 80,000 names within the AIDS Memorial Quilt, although the Quilt itself will not be displayed.

The organizers are calling for youth and children to lead the march. Worldwide, over 4,000,000 children under 15 have been killed by AIDS, and over 13,000,000 children have been orphaned.

For more information, see <http://www.AIDSaction20.org>. Marchers are urged to make hotel arrangements soon. The march will begin at noon on June 3 in Washington D.C.

International AIDS Candlelight Memorial, May 20

On May 20 the annual International AIDS Candlelight Memorial is taking place at more than 500 communities around the world. More information, including local contacts, is at <http://www.candlelightmemorial.org>.

Updated Guidelines for Prevention of Mother-to- Infant Transmission

On May 4 the U.S. Public Health Service released an updated version of the official guidelines for use of antiretrovirals to reduce perinatal HIV transmission. The following sections have been changed:

* "Antiretroviral Clinical Scenarios" (beginning on page 17);

* "Recommendations for Monitoring of Women and

Their Infants" (beginning on page 39); and

* "Clinical Research Needs" (beginning on page 41).

You can obtain a copy of the guidelines without charge in any of three ways:

(1) <http://hivatis.org/trtgdlns.html>, the Web site of the HIV/AIDS Treatment Information Service;

(2) by calling 1-800-448-0440 or 301-519-0459, Monday through Friday 9-5 Eastern Time (TTY 888-480-3739); or

(3) by mailing a request to HIV/AIDS Treatment Information Service, P.O. Box 6303, Rockville, MD 20849-6903. It may take 7-10 days plus shipping time to receive the document.

Ask for the Perinatal Guidelines. (The full official title is *Public Health Service Task Force Recommendations for the Use of Antiretroviral Drugs in Pregnant HIV-1 Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States*.)

Note: For information in English, Spanish, or Portuguese about federally approved treatment for HIV and AIDS, you can contact health information specialists at the HIV/AIDS Treatment Information Service, Monday through Friday 9-5 at the phone numbers, email, or mailing address above.

Syringe Prescription Study Unexpected Bonus: Helping Long-Time Users Quit Drugs

by John S. James

A pilot study in Rhode Island, allowing physicians to prescribe syringes in order to reduce that state's exceptionally high rate of HIV infection among injection drug users, not only reduced needle sharing as hoped, but also helped some patients get into drug treatment programs and quit their drug abuse entirely. These people had been injecting drugs for a median of 10 years. A description of the project appeared in May issue of the *American Journal of Public Health*¹.

On May 4 we spoke to principal investigator Josiah D. Rich, M.D., M.P.H., an infectious-disease specialist. He explained that until recently Rhode Island had one of the harshest syringe laws in the

nation. Possession of each syringe was a felony punishable by up to five years in prison, and the average sentence for possession of syringes alone was 11 months. As a result drug users often did not carry syringes but re-used those available where they bought their drugs, and Rhode Island is one of only four states where more than 50% of AIDS cases are due to injecting drugs. And the state spent was spending over a million of dollars a year arresting, trying, and imprisoning people for syringes.

A coalition of medical organizations and others worked to change the law, and they won a partial victory in 1998; possession of syringes was reduced to a misdemeanor, but they remained illegal (until 2000) and drug users had difficulty getting sterile syringes. Lobbyists said it would take at least two years to change the law again. Evaluation of the law revealed that doctors could prescribe syringes if approved by the state Department of Health; a drug user could have a prescription and buy and possess syringes legally, like a diabetic. So a study, the Rhode Island Blood Borne Pathogen Harm Reduction Program, was designed to see if prescribing syringes would help to reduce sharing and HIV transmission.

The program began when the director of the Rhode Island Department of Health, with the support of many medical organizations, wrote to all licensed physicians in the state, inviting them to join the program under certain conditions. At this time the program employs four physicians at two locations in Providence, Rhode Island and has enrolled 350 drug users and prescribed 50,000 syringes. The published report is preliminary, as data are still coming in, but it appears that needle re-use has dropped dramatically and that the syringes are being disposed of properly.

The surprise for researchers was the great interest among these hard-core users not only in obtaining the syringes, but also in getting into drug treatment. There was an overwhelming response, despite the fact that those who approached the program were very high risk, with most of them having injected illegal drugs for at least 10 years. Half were homeless. A large majority had hepatitis C, and many had hepatitis B as well.

"What is most remarkable is that these long-time users were very interested in drug treatment -- half said did want treatment to help them stop using drugs. We do not ask immediately. We take a medical history, do a physical, and discuss the findings. We tell them that their behavior is very dangerous because of the risk of infectious diseases, overdose, and other lifestyle problems. I recommend, as their doctor, that

we work together to try to get them to stop.

"But if they are not able or willing to stop at this time, I teach them sterile technique that doctors use for injection -- including the use of a sterile syringe.

"They come to us to ask for syringes. So they have to admit that they inject drugs, and here there are no negative consequences to admitting that they are injecting drugs. Who else can have this discussion with them? Usually the people they talk to about their drug use -- their dealer, pimp, or peers -- have a vested interest in them continuing to use drugs.

"This program has a unique window into peoples' lives. We can ask them, if you decide to stop, what would you do? Would you go to detox? What was your experience in detox last time? What if there are no beds now -- would you just give up?

"It is most rewarding when patients come in and say they do not need syringes -- that they have looked at their lives and stopped their drug use because they are tired of what it is doing to them. We see that as doctors, we can really help these people."

This is the first time that a physician syringe prescription program has ever been tried (although a few physicians have prescribed syringes to individual patients). The May 2001 article¹ includes recommendations for those who want to try such a program elsewhere -- starting with knowing the local legal situation.²

From the article:¹

"Because of the illicit nature of drug use, a tremendous amount of mistrust and fear often leads to poor interaction with the medical establishment. Prescription of syringes by a physician can serve as a tool for reaching out to a high-risk and often out-of-treatment population of drug users. It is a way for the health care community to tap into drug-using networks and bring those populations into a medical care system..."

"That the physician-patient interaction is based on the acknowledgement of injecting behaviors engenders trust and seems to open the door for discussion of a whole host of injecting-related activities, including commercial sex, participation in the underground economy, violence, and abuse. The participants seem to be open and honest about their drug use.

They understand that physicians are trying to help them in a non-judgmental way and are quite appreciative of the efforts. Participants are extremely willing to participate in health care including hepatitis B vaccination; testing for hepatitis, HIV, and other

sexually transmitted diseases; and followup."

This study was funded in part by the American Foundation for AIDS Research (AmFAR).

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1. Rich JD, Macalino GE, McKenzie M, Taylor LE, and Burris S. Syringe prescription to prevent HIV infection in Rhode Island: A case study. *American Journal of Public Health*. May 2001; volume 91, number 5, pages 1-2.

2. Burris S, Lurie P, Abrahamson D, and Rich JD. Physician prescribing of sterile injection equipment to prevent HIV infection: Time for action. *Annals of Internal Medicine*. August 1, 2000; volume 133, number 3, pages 218-226.

TAG Seeks Policy Director

The Treatment Action Group (TAG), a New York-based nonprofit organization focusing on AIDS research and treatment policy, is hiring a policy director. From the announcement:

"The Policy Director will have a broad-based background incorporating an understanding of science, government, and policy, and ideally would have experience managing highly-qualified people working in policy roles. The Policy Director will be the key staff person responsible for setting and implementing and coordinating the overall policy agenda for TAG -- in conjunction with the executive director -- and thus for oversight, facilitation, and supervision of the policy and program work of the agency..."

For years TAG has been one of the most important AIDS treatment advocacy organization. It has been called a "think tank without walls," as it provides computer and communication equipment to staff who work from home offices. It also has a small central office. Staff travel frequently to research and treatment meetings and conferences. Its Web site is <http://www.treatmentactiongroup.org>.

"Interested candidates should send a letter expressing their qualifications and interest in the position with a resume/CV and three references with contact information by 31 May 2001 to: Policy Director Search, c/o Regina Gillis, Treatment Action Group, 350 Seventh Ave., Suite 1603, New York, NY 10001, phone 212-971-9022, fax 212-971-9019, email tagnyc@msn.com

South Africa Court Case -- Documents on the Web

Documents in the lawsuit by 39 pharmaceutical companies against Nelson Mandela and the government of South Africa, dropped April 19 after becoming a public-relations disaster for the companies, are available on the TAC (Treatment Action Campaign) Web site, <http://www.tac.org.za>.

From the other side, the International Association of Pharmaceutical Manufacturers Associations has the one-page "Joint Statement of Understanding between the Republic of South Africa and the Applicants, and a press release, at its Web site, <http://www.ifpma.org/> (select News).

In our view the real significance of this case was not so much the legal issues, but rather in showing that world public opinion will no longer allow lifesaving medicines to be priced out of reach of millions of people in poor countries in order to avoid the risk of disturbing lucrative markets in rich countries. Three years ago when the case was filed, very few people were aware of this issue. Now millions are aware, and millions are demanding access to treatment. Industry is welcome to help in developing systems that work, rules everyone can live with. When industry fails to provide viable leadership, the work will be done without them.

AIDS Treatment News Publication Schedule: No Issues Dated April 2001

Because we have been more than a month behind our twice-monthly publication schedule, we will not publish any issues dated April 2001. All subscriptions will be extended a month to compensate, so subscribers will receive the same number of issues.

Our previous issue, #363, was dated March 30. This issue, #364, is dated May 11.



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Questions about HIV Causing AIDS?

Viral Load and T-Cell (CD4) Counts: Why They Really Matter

If you are being treated for HIV or AIDS, your doctor uses a number of blood tests to check how you're doing. One of the most important tests measures *viral load*, the amount of HIV in your blood. Another very important test counts your *CD4 cells*, sometimes called *T-cells*. CD4 cells are a key part of your body's disease-fighting defenses, called the immune system.

But some people claim that HIV doesn't really cause AIDS. These people, known as "AIDS deniers," "denialists" or "AIDS dissidents," also say that viral load and CD4 tests are meaningless. They claim these tests don't really tell anything about your health, and that they might even hurt you by frightening you for no reason.

What Do Viral Load and CD4 Tests Really Tell Us?

What are CD4 Cells?

CD4 cells help to organize your body's defenses against disease. Doctors can take a sample of your blood and count the number of CD4 cells. Healthy adults and teenagers usually have a CD4 count of at least 800 cells per *cubic millimeter* of blood (a cubic millimeter is a very small amount, roughly one small drop).

What does HIV do to CD4 counts?

HIV attacks CD4 cells, and as time goes by people with HIV often see their CD4 counts drop. The lower your CD4 count, the greater your chances of getting a number of very serious diseases. When your CD4 count is below 200, the risk of illness becomes severe.

I've heard that you can have a low CD4 count and still be healthy. Is that true?

While there have been a few medical reports of people who seemed healthy even though they had very low CD4 counts, these cases are rare. Research overwhelmingly shows that people with low CD4 counts are much more likely to get sick than people who have a normal amount of CD4 cells.

The AIDS denialists who claim that CD4 counts are meaningless often point to a study of AIDS patients called the Concorde study, in which people who had a small increase in CD4 counts did not live longer than those whose CD4 counts stayed the same. But that study was done nearly 10 years

ago, before modern combination therapy, and the CD4 increases were very small. Newer studies with more potent treatments show that a big boost in CD4 cells almost always lowers the risk of getting seriously ill.

For example, the deadly pneumonia called PCP occurs much more often in people with very low CD4 counts. In one study with over 1,000 patients, almost everyone who got PCP had a CD4 count below 200. Study after study has shown the same thing: The lower your CD4 count, the greater your chance of getting PCP or other serious infections.

The AIDS denialists leave out these important facts.

Why are viral load tests used?

CD4 counts give you and your doctor a good idea of how much damage HIV has done to your immune system. But you also need to know how fast that damage is happening. Viral load tests, which tell the doctor how much HIV is in your blood, are a very important clue to how quickly HIV is doing harm.

These tests go by several different names, like *PCR* (*polymerase chain reaction*) or *bdNA* (*branched DNA*), but they all work roughly the same way. They count HIV's genetic material--the building blocks of the virus

What does viral load tell us?

People with a high viral load are much more likely to get sick or die of AIDS than people with a low viral load.

The AIDS denialists sometimes suggest reasons why these tests might give a wrong answer. They point to a few old reports, from when viral load tests were new and still experimental, as evidence that they don't work. But there is a huge pile of newer evidence showing that viral load tests work extremely well. Many studies have shown that people with high viral loads are more likely to get sick or die from AIDS-related illnesses than people whose viral load is lower.

For example, one very important study has followed thousands of gay men since 1984. A few years ago researchers did viral load tests on the very earliest blood samples from that study and then looked at how many of those patients were still alive. The men with the highest viral loads were 77 times more likely to have died of AIDS than those with the lowest viral loads. Other studies in the U.S. and Europe have shown the same thing: A higher viral load almost always means a higher risk of sickness and death.

What happens when treatment reduces my viral load?

Studies have shown that when treatment reduces your viral load, it also reduces your chance of getting an AIDS-related infection or dying. Recently, a group of expert scientists reviewed 18 studies of anti-HIV drugs, which involved over 5,000 patients. Over and over again they found the same thing: The more viral load was reduced, the healthier the patients stayed.

The Bottom Line

No medical test is perfect, and mistakes or misunderstandings sometimes happen. You should always go over your test results carefully with your doctor to make sure you understand them.

But the people who claim that viral load and CD4 tests are useless are not telling the truth. These tests give you and your doctor important information that can help you make the best treatment choices.