Maine AIDS Care

Maine Medical Center's AIDS Consultation Service Spring 1996

FDA Committee Recommends Approval of Viral Load Tests

Full FDA approval is expected soon on the use of quantitative HIV plasma viral load measurement for assessing prognosis in HIV infection and for monitoring the response to antiviral therapy.

Currently, HIV viral load or the concentration of HIV RNA strands in plasma is measured either by quantitative polymerase chain reaction (QT-PCR) or by a technique called branched DNA signal amplification (bDNA). A third means of measuring viral load nucleic acid sequence-based amplification (NASBA) is under study.

The value of HIV viral load determinations in predicting progression of HIV disease was demonstrated by Mellors et al using banked sera from the Multi-Center AIDS Cohort Trial. Patients with high CD4 counts had markedly variable rates of progression to AIDS and the rate of progression was predicted by the level of viral load. While CD4 count provides an indication of the overall status of the immune system, the viral load test provides an index of actual viral activity. Patients may have high or low CD4 counts and have any level of viral load. Those patients with HIV viral loads $>10^5$ HIV/RNA/ml of plasma had rapid progression, whereas those with levels of <10,000 had slower than average progression. Most clinicians believe that early treatment of the subset of patients at high risk for rapid progression may prove helpful.

Recent research trials also support the use of viral load in the assessment of an individual's response to antiviral therapy. O'Brien et al demonstrate the utility of a baseline level at the time of initiation of treatment followed by a second sample after 4 weeks of therapy. A drop in viral load of 0.5 log (three-fold) or greater is considered indicative of a good response to treatment. With the availability of this measure, it is hoped that patient's treatment can be individualized for maximum effectiveness.

Several caveats are in order when using viral loads. They should not be obtained during intercurrent viral infections or within one month of immunizations as viral load may be transiently elevated. Two baseline determinations are often recommended before starting antiviral therapy. In addition, for serial comparison, the same method (ie. quantitative PCR or bDNA) should be used each time for a patient. Viral load may vary within an individual by up to 0.3 log with repeat testing, so differences of <0.5 log are not considered reliable. EDTA rather than heparin anticoagulant tubes should be used for sample collection.

Viral load measurements should be obtained every 3-4 months to assess the continued effectiveness of antiviral therapy. A substantial rise in viral load during therapy suggests that antiviral resistance may be developing, and should lead to consideration of other therapeutic options.

Millers JW et al: Quantitation of HIV-1 RNA in plasma outcome after seroconversion
Ann Int Med 1995:573-579

O'Brien et al: Changes in plasma HIV-1 RNA and CD4 counts and risk of progression to AIDS.
NEJM 334: 426-432, 1996.

Research News

HIV Cofactor Discovered

A membrane protein that serves as a key cofactor necessary for the binding of HIV to CD4 cells has been isolated by a research team from the N.I.H. (Science 272: 809-810, 1996). This protein, called fusion, has been the object of a scientific search for over a decade. Researches believe that discovery of this co-factor will lead to new avenues of investigation of the pathogenesis of HIV, and may well lead to interventions that target virus-cell binding.

Maternal Viral Load

Several studies presented at the 3rd Conference on Retroviruses address the relationship of maternal viral load to vertical transmission of HIV. One study, recently published, found a clear relationship, with no maternal - fetal transmission at a viral load of 25,000. High viral loads were the best predictor of mother to child transmission. AZT treatment of the mother resulted in an eight-fold drop in viral load.

However, a second study was not so clear. In this report, most of the 151 pregnant woman received AZT treatment, but the medical vial load associated with transmission (~5,000 copies/ml) was only slightly higher than the median level among nontransmitters (2,000 copies). Secondly, reports from ACTG 076 revealed no substantial significant differences between viral load among transmitters and nontransmitters, although no transmission occurred among the women with undetectable levels of virus.

It was noted in this study that the effectiveness of AZT in pregnancy may be in large part due to the treatment of the infant after birth, as intrapartum exposure is thought to be of greater risk than the prepartum experience.

Update : Provisional Public Health Service Recommendations for Chemoprophylaxis After Occupational Exposure to HIV

A Public Health Service (PHS) interagency working group (comprised of representatives of CDC, the Food and Drug Administration (FDA), the Health Resources and Services Administration, and the National Institutes of Health) has recently (MMWR, June 7, 1996) updated the PHS's recommendations on management of occupational exposure to HIV. Its findings and recommendations on postexposure prophylaxis (PEP) are as follows[1]:

Background Data Used:

ZDV - Postexposure prophylaxis (PEP) was associated with a decrease of approximately 79% in the risk for HIV seroconversion after percutaneous exposure to HIV-infected blood in a case-control study among health-care workers (HCW)[2]. In a prospective trial in which ZDV was administered to HIV-infected pregnant women and their infants, a direct effect of ZDV prophylaxis on the fetus and/or infant may have contributed to the observed 67% reduction in prenatal transmission[4].

The average risk for HIV infection from all types of reported percutaneous exposures to HIV-infected blood in 0.3%[3]. In the case-control study[2], risk was increased for exposures involving: 1- a deep injury to the HCW; 2- visible blood on the device causing the injury; 3- a device previously placed in the source patients vein or artery; or 4- a source patient who died as a result of AIDS within 60 days postexposure (and therefore was presumed to have a high titer of HIV)[2]. Identification of these risk factors suggests that the risk for HIV infection exceeds 0.3% for percutaneous exposures involving a larger blood volume and/or higher HIV titer in blood. The risks after volume and/or higher HIV titer in blood. The risks after mucus membrane and skin exposures to HIV-infected blood [on average, approximately 0.1% and <0.1%, respectively (7)], probably also depend on volume of blood and titer of HIV. The risk is probably higher for skin contact that is prolonged, involves an area that is extensive or in which the skin integrity is visibly compromised, and/or involves a higher titer.

Although information about the potency and toxicity of antiretroviral drugs is available from studies of HIV-infected patients, it is uncertain to what extent this information can be applied to uninfected persons receiving PEP. In HIV-infected patients, combination therapy with ZDV and 3TC has greater antiretroviral activity than AZT alone[8]. Adding a protease inhibitor provides even greater increases in antiretroviral activity; among protease inhibitors, Indinivir (IDV) is more potent than Saquinavir and appears to have fewer drug interactions and short-term adverse effects than Ritonavir[8]. Few data exists to assess possible long-term toxicity resulting from use of these drugs in persons not infected with HIV.

In currently recommended doses, ZDV PEP usually is tolerated well be health-care workers[3]. The toxicity of other antiretroviral drugs in persons not infected with HIV has not been well characterized.

Recommendations

The PHS recommendations are stated as provisional because they are based on limited data regarding efficacy and toxicity of PEP and risk for HIV infection after different types of exposure. The recommendations are prefaced with the following provisions:
Because most occupational exposures to HIV do not result in infection transmission; potential toxicity must be carefully considered when prescribing PEP. When possible, these recommendations should be implemented in consultation with persons have expertise in antiretroviral therapy and HIV transmission. Changes in drug regimens may be appropriate, based on factors such as the probable antiretroviral drug resistance profile of HIV from the source patient; local availability of drugs; and medical conditions, concurrent drug therapy, and drug toxicity in the exposed worker. These recommendations were not developed to address nonoccupational (eg. sexual) exposures.

1. Chemoprophylaxis should be recommended to exposed workers after occupational exposures associated with the highest risk for HIV transmission. For exposures with a lower, nonnegligible risk, PEP should be offered, balancing the lower risk against the use of drugs having uncertain efficacy and toxicity. For exposures with negligible risk, PEP is not justified (Table 1). Exposed workers should be informed that a)knowledge about the efficacy and toxicity of PEP is limited; b) for agents other than ZDV, data are limited regarding toxicity in persons without HIV infection or who are pregnant; and c) any or all drugs for PEP may be declined by the exposed worker.

2. At present, ZDV should be considered for all PEP regimens because ZDV is the only agent for which data support the efficacy of PEP in the clinical setting, 3TC should usually be added to ZDV for increased antiretroviral activity and activity against many ZDV-resistant strains. A protease inhibitor (preferably IDV because of the characteristics summarized in this report) should be added for exposures with the highest risk for HIV transmission (Table1). Adding a protease inhibitor also may be considered for lower risk exposures if ZDV-resistant strains are likely, although it is uncertain whether the potential additional toxicity of a third drug is justified for lower risk exposures. For HIV strains resistant to both ZDV and 3TC or resistant to a protease inhibitor, or if these drugs are contraindicated or poorly tolerated, the optimal PEP regimen is uncertain; expert consultation is advised.

3. PEP should be initiated promptly, preferably within 1-2 hours postexposure. Although animal studies suggest that PEP probably within 1-2 hours postexposure. Animal studies suggest that PEP probably is not effective when started later than 24-36 hours postexposure [6,7], the interval after which there is no benefit from PEP for humans is undefined. Initiating therapy after a longer interval (e.g., 1-2 weeks) may be considered for the highest risk exposures; even if infection is not prevented, early treatment of acute HIV infection may be beneficial[10]. The optimal duration of PEP is unknown; because 4 weeks of ZDV appeared protective[2], should probably be administered for 4 weeks, if tolerated.

4. If the source patient or the patient's HIV status is unknown, initiating PEP should be decided on a case-by-case basis, based on the exposure risk and likelihood of HIV infection in known or possible source patients. If additional information becomes available, decisions about PEP can be modified.

5. Workers with occupational exposures to HIV should receive follow-up counseling and medical evaluation, including HIV antibody

Continued on Page 3

Use of HIV RNA Viral Load Measures

Indications for use of viral load:

1. Determine prognosis in early disease
2. Assessment of adequacy of antiviral therapy

Currently Available Methods

	Quantitative PCR	Branched DNA Amplification
	(Roche)	(Chiron)
Advantages	High sensitivity (to <100 copies RNA / ml)	Higher reliability
Disadvantages	Labor - intensive	Lower sensitivity (to <10,000 copies RNA / ml)
Cost	Approx. $200.00	Approx. $200.00

Interpretative Use of Viral Load

1) For monitoring therapy, obtain 1-2 baseline levels and then repeat at approximately 1 month after initiation or change of therapy.

2) Consider a change every $\geq$ 0.5 log (three-fold) as significant.

3) Use same method for serial monitoring every 3-4 months.

4) Attempt to keep viral load as low as possible (ie. undetectable)

Table 1. Provisional Public Health Service recommendations for chemoprophylaxis after occupational exposure to HIV, by type of exposure and source material - 1996.

Type of Exposure	Source Material	Antiretroviral Prophylaxis	Antiretroviral Regimen
Percutaneous	Blood		
	Highest Risk	Recommended	ZDV plus 3TC plus IDV
	Increased Risk	Recommended	ZDV plus 3TC ± IDV
	No Increased Risk	Offer	ZDV plus 3TC
	Fluid containing visible blood, other potentially infectious fluid or tissue	Offer	ZDV plus 3TC
	Other body Fluid (e.g., urine)	Not Offer	
Mucous Membrane	Blood	Offer	ZDV plus 3TC ± IDV
	Fluid containing visible blood, other potentially infectious fluid or tissue	Offer	ZDV ± 3TC
	Other body Fluid (e.g., urine)	Not Offer	
Skin, increased risk	Blood	Offer	ZDV plus 3TC ± IDV
	Fluid containing visible blood, other potentially infectious fluid or tissue	Offer	ZDV ± 3TC
	Other body Fluid (e.g., urine)	Not Offer	

Corrected Maine AIDS Care, Winter 1996

Principles of Protease Inhibitor Use

1. Start with highest appropriate dose and avoid dose adjustment if possible.
2. Use in combination with other agents.
3. Be aware of drug interactions (see other side of insert).

New Antiviral Agents & Combinations

Class	Drug	Usual Dosage	Side Effects	Effective Regimens
RT Inhibitors				
Nucleoside	AZT (Zidovudine)	200 mg tid	Bone marrow suppression Myopathy GI symptoms	AZT AZT + DDI AZT + DDC AZT + 3TC *All regimens with or without a protease inhibitor.*
	DDI (didanosine)	200 mg bid	Pancreatitis GI intolerance Neuropathy	DDI DDI + AZT DDI + D4T (Z?) *All regimens with or without a protease inhibitor.*
	DDC (deoxycytidine)	0.75 mg tid	Pancreatitis (rare) Neuropathy Oral / esophageal ulcers	DDC DDC + AZT *All regimens with or without a protease inhibitor.*
	D4T (Stavudine)	40 mg bid	Neuropathy	D4T D4T + DDI (?)
	3TC (Lamivudine)	150 mg bid	GI intolerance Neutropenia (rare)	3TC + AZT AZT + 3TC + Protease Inhibitor
Non-Nucleoside	Delavirdine *(available through compassionate use only)*	400 mg tid	Rash GI intolerance	Delavirdine + AZT Delavirdine + DDI Delavirdine + AZT + DDI or DDC
Protease Inhibitors				
	Saquinavir	600 mg tid (*with food*)	GI intolerance Drug interactions	Saquinavir + 1 or 2 RT inhibitors
	Ritonavir	600 mg bid (*with food*)	GI intolerance Drug interactions	Ritonavir + 1 or 2 RT inhibitors
	Indinavir	800 mg q8hours (*without food*)	GI intolerance Nephrolithiasis (2-5%) Drug interactions	AZT + 3TC + Indinavir Indinavir + 1 or 2 RT inhibitors

Potential Drug Interactions - Ritonavir
(Data on Indinavir Not Available)

	Avoid	Alternative Treatment
Analgesic	meperidine (Demoral) piroxicam (Feldene) propoxyphene (Darvon)	acetaminophen (Tylenol) aspirin oxycodone (Percodan)
Cardiovascular (Antiarrhythmic)	amiodarone (Cordarone) encainide (Enkaid) flecainide (Tambocor) propafenone (Rythmol) quinidine	
Antimycobacterial	rifabutin (Mycobutin)	clarithromycin (Biaxin) ethambutol (Myambutol)
Cardiovascular (calcium channel blocker)	bepridil (Vascor)	
Cold & Allergy (antihistamine)	astemizole (Hismanal) terfenadine (Seldane)	loratadine (Claritin)
Gastrointestinal	cisapride (Propulsid)	
Psychotropic (antidepressant)	bupropion (Wellbutrin)	fluoxetine (Prozac) desipramine (Norpramin)
Psychotropic (sedative/hypnotic)	alprazolam (Xanax) clorazepate (Tranxene) diazepam (Valium) estazolam (Prosam) fluroepam (Dalmane) midazolam (Versed) triazolam (Halcion) zolpidem (Ambien)	temazepam (Restoril) lorazepam (Ativan)

If you have questions regarding the use or side effects of Protease Inhibitors call the AIDS Consultation Service Treatment Information Line @ 1-800-871-2701

Viral Load: A Patients Perspective

by Michael Martin

For over eight years, the amount of time I've known I'm HIV-positive, I've depended on the results of CD4 counts to assess where I stand with my HIV infection. The actual number of CD4 cells and their percentages have been and still are my markers for evaluating how my immune system is doing. If the numbers went up, and they often did, then I could be self-satisfied that the virus was being held at bay. If the numbers went down, and they often did, then I could convince myself that I was having a bad day, maybe I had a cold or was overly tired, and the next test would be better. Or if they dropped, I could say that the drop was really statistically insignificant and safely assuage myself until the next count. In other words, I had a handle, intellectually and emotionally, on whatever results I got.

So along comes the new viral load test which monitors actual viral amounts and activity. A test that some think actually predicts future health. To say that I was resistant to this new test, at first, is a bit of an understatement. Without being able to say why, my initial reaction (for a couple of months) was that I didn't want to take this test. When I figured out my resistance, it really amounted to this, a viral load is significantly different medically and psychologically from getting a CD4 count. A CD4 count is an indirect way of trying to tell how the virus is working in my body. A CD4 count is about the strength of my immune system and its ability to fight infections. If my CD4 count drops and my immune system is therefore weakened, then I will be more open to opportunistic infections. I have had years to get comfortable with CD4 counts. A viral load measures actual amounts of virus in the blood, a direct look at my HIV virus, a direct indicator of how much virus I have at any given time. One more reality step closer to the nasty HIV virus. In other words, another layer between me and my virus is being exposed and I wasn't too thrilled about it.

Still, I relented and finally got a viral load test done and, lo and behold, the world did not end, the sky did not fall, and neither did my arches. On the other hand, my viral load count was significantly higher than my doctor liked, (normally he's so easy to please!), and although, at the very same time I got significantly good news about a jump in my CD4 count, the mixed results managed to ruin about half a day. On any other day, a jump from 340-500 in my CD4 count would have left me feeling very happy, even cocky. But the higher viral load count of 36,600 was my headache that day. In the end I reminded myself that it was a first count, a new experience for me and that like CD4 counts at the beginning of my infection, I would get a better handle on viral loads with experience. That I will understand and withstand the results of viral loads better in the future. And, right now, a count of 36,600 is not devastating news. It could be better or it could be a lot worse.

Of course, I took counsel from my doctor, my favorite nurse, and Project Inform and I understand that viral loads are a new and significant tool in deciding treatment strategies and will become as routine as CD4 counts in the future. They also respond more rapidly than CD4 counts to changes in the body. With my new drug study regimen of U90, AZT, and 3TC, the next viral load should show a drop. That's my hope, anyway. It also helps that I have good health insurance and am involved in a drug study that provides my medications for free. I try to count my blessings, and keeping a handle on the spiralling costs of even routine HIV care is important.

In the meantime, I can only do what I can do, which is to take my medicines faithfully, get plenty of rest, watch out for undue stress, and enjoy the fact that I've not had any opportunistic infections associated with HIV. And to remember to enjoy life. Every day fretting over this or that not-as-perfect-as-I-would-like test result is time lost enjoying mild weather, the company of friends and family, the satisfaction of freshly mowed grass, and the joy of four cats named Fanny, George, Sandy, and Tigger. In short, I can worry or I can be content. As long as I can, I'll take contentment.

I remember the words of Abraham Lincoln when he said, " Most people are about as happy as they want to be."

Continued from page 2

tests at baseline and periodically for at least 6 months postexposure (e.g., 8 weeks, 12 weeks, and 6 months), and should observe precautions to prevent possible secondar transmission [1]. If PEP is used, drug toxicity monitoring should include a complete blood count and renal and hepatic chemical function tests at baseline and 2 weeks after starting PEP. If subjective or objective toxicity is noted, dose reduction or drug substitution should be considered with expert consultation, and further diagnostic studies may be indicated. Health-care workers who become infected with HIV should receive appropriate medical care.

6. Beginning July 15, 1996, health care providers in the United States ar encouraged to enroll all workers who receive PEP in an anonymous registr being developed by CDC, Glaxo Wellcome Inc., and Merck & Co., Inc., to assess toxicity (telephone [888]737-4448). Unusual or severe toxicity from antiretroviral drugs should be reported to the manufacturer and/or the Food and Drug Administration (telephone [800] 332-1088). Updated information about HIV PEP will be available beginning in early 1997 from the Internet at CDC home page (http://www.cdc.gov.); CDC's fax information service, telephone (404)332-4565 (Hospital Infections Program Directory); the National AIDS Clearinghouse, telephone (800)458-5231; and the HIV/AIDS Treatment Information Service, telephone (800)448-0440.

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Maine AIDS Plan

by Martha Piscuskas

A recently published resource synthesizes much of what Maine's response to HIV looks like, and points the way to the future. The *Maine AIDS Plan: A Blueprint for Action*, a product of the Maine AIDS Alliance, is an accessible reference and action guide created by and for Maine people.

Says Sandy Putnam, Maine Medical Center's AIDS Consultation Service Nurse Coordinator and a *Plan* founder, "Since this disease truly effects all of us, right from the start our intent was to create a very accessible, user-friendly document. I believe we've succeeded". And users all over the state confirm that this is "an excellent resource".

One section was specifically developed my and for Maine health care providers, with some surprising findings. Recommendations are interspersed throughout the chapter, and several pages are devoted to local and national resources specifically for physicians and other health care providers and consumers.

This is not a small book, though its 270 pages are bound in a 3-ring binder for easy photocopying (which is encouraged), and tabs make it easy to flip through and find specific sections. Fact sheets and brief chapters are designed for quick reading. Photos, sidebar interviews, and graphics also contribute to its utility for the general public.

Over 200 individuals, including people with HIV, providers, advocates, educators, employers, and policy makers contributed. "This is not a top-down plan," explains Martha Piscuskas, director of the project, which was funded through CDC prevention monies and private donations. "The research and recommendations came directly from the experience of people in the field".

The ***Maine AIDS Plan*** is free to non-profits, one per agency; all AIDS Service Organizations, and many schools and libraries throughout the state have copies. Individuals may also purchase copies for a minimal fee. For more information, contact the Maine AIDS Plan, 112 State Street, Augusta, ME 04330 Telephone (208)622-2962.

AIDS Cases

World AIDS Cases	*4,500,000**
U.S. AIDS Cases	*513,486*
U.S. AIDS Deaths	*319,849*

Reported through 12/31/96 by CDC

Maine AIDS Cases	*720*
Maine AIDS Deaths	*347*

Reported through March 31, 1996

Videos of the AIDS Consultation Service's HIV/AIDS Symposium 1996 are available by contacting the AIDS Consultation Service at (207)871-2099.

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