

Is AIDS A Treatable Illness?

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In March 1996 there was a symposium in California on HIV/AIDS therapy. This annual meeting discusses the current status of new treatments. The previous six meetings have presented promising new agents that never quite met earlier expectations. The reasons for these previous failures has become clearer as a greater knowledge of HIV natural history has developed.

Our present understanding of the life cycle of HIV is that this virus replicates from the time of infection until the time of death of the host. This contrasts sharply with the early research that suggested a very indolent process where the virus remained dormant for a period as long as ten years, with only intermittent viral replication. If the new research is correct the virus produces from one to ten billion copies a day, every day.

The net result of this level of replication is that a large number of molecular variants of HIV are present in each infected person. The great genetic diversity of the virus is due to two factors. Factor one is that the RNA reverse transcriptase that reproduces the viral DNA makes a mistake about every ten thousand to one hundred thousand nucleotides that it incorporates into the viral genetic structure. The second key is that the virus is very actively replicating itself, therefore providing a great number of chances for those mistakes to occur. The result is about ten thousand mutant virus being produced per day. Many of these will be defected to the point that they are replication incompetent and cannot reproduce themselves. However a great number will be infectious and will continue to replicate along with the wild type virus. Wild type virus refers to the first type of the virus discovered and is also the most prevalent in a particular location. This constitutes the normal *in situ* genetic background of this virus, with a very diverse group of HIV siblings.

Historically, when AIDS patients have been treated with a new drug, the first trials have been with monotherapy. While this approach has been useful to establish efficacy for various antiviral drugs in the past, it was doomed to failure due to the high level of preexisting HIV mutants. In practice, when a new drug was tried it simply selected for the mutant form that was insensitive to the agent. The result being that the mutant now replaces the wild type as the most prevalent form. While monotherapies are necessary to study potential drug toxicity, they are uniformly inappropriate for treatment efficacy.

At this year's meeting, data was presented for a new combination treatment. The drugs were AZT, 3TC, and a new protease inhibitor, Indinavir. This combination of drugs reduced the level of circulating virus by about 2 to 2.5 logs; a factor of one hundred to five hundred fold. The good news is that the level of reduction has now been maintained for nine months for 24 of 26 patients. While the virus is no longer detected in the blood of these patients, this may not mean that they are "cured". Recall that the bulk of virus replication is in tissues other than blood.

AZT and 3TC are reverse transcriptase (RTase) inhibitors. AZT is a nucleotide analog that prematurely terminates the HIV RNA translation into DNA, while 3TC is a non-nucleotide drug that blocks the correct folding to form active RTase. In AIDS patients, if resistance develops to AZT the patient remains sensitive to 3TC. In similar manner, if the patient develops resistance to 3TC, he or she remains sensitive to AZT. The probability of resistance is further reduced by the incorporation of Indinavir, a protease inhibitor. For HIV to replicate would require three independent mutations in two different genes to circumvent three independently acting agents. This type of simultaneous mutation is a very low probability.

In this cohort of treated patients, CD4 cells increased on the average 100 per microliter, range 20 to 400. Accompanying the increase in CD4 count is a return of skin sensitivity for mumps and tuberculin antigens. Initial data suggests that the increase is by division of existing CD4 cells, not new differentiation of stem cells. The full extent of immune system recovery is yet to be determined.

The report of the response of 24 of 26 patients is extremely encouraging. If this treatment does permanently reduce the replication of HIV, the AIDS patient at last has hope of a normal life expectancy. Only time will tell if this therapy is effective long term. Only company policy will determine how this treatment will affect the underwriting of HIV positive applicants.

How Does This New Treatment Affect My Company?

The issue has become somewhat more complicated with FDA approval of home collection of samples for HIV testing. At first glance, there might appear to be no clear relationship between these two events. However, if the home test kit manufacturer is correct, there may be a very important connection. The Federal Government through local departments of Public Health provides free testing for HIV. A recent report by the Harvard School of Public Health on the effectiveness of federally funded testing presented a number of surprises. First was that after ten years of free testing, 60% of high risk individuals are untested. The number is 80% for individuals that report themselves to be at moderate risk. Why have so few been tested through these free programs? The two most common reasons for refusing an HIV test are the fear of disclosure of their possible HIV status and no effective treatment. The approval of home HIV testing and the development of an effective HIV therapy may drastically alter that decision process.

The two approved home collection test kits will provide for true confidential testing. The patient will no longer be concerned about what the nurse or doctor will suspect if he or she asks for an HIV test. Neither will the patient be concerned about bumping into an acquaintance at the Free Health Clinic. With the home test, there will be no way to couple the test result or that a test was even done for a patient or applicant. Both companies, Home Access Health Corporation and Access Medical, are marketing their respective products nationwide.

The current home collected sample is a dried blood spot (DBS), but Epitepe and Smith-Klein will soon submit an application to use saliva as the sample. The introduction of home testing and the advances in HIV treatments may provide a new set of reasons to review the current testing limits for your company.

New and Old HIV Medications

David Ho, one of the speakers at the UCLA Meeting suggested that patients may be cured with these new triple drug therapies. He suggests that after three years at least half of these patients will stop therapy to determine if the virus is gone.

DRUG	COMPANY
Epivir (3TC, Lamivudine)	Glaxo Wellcome
Crixivan (Indinavir)	Merck
Invirase (Saquinavir)	Hoffmann-La Roche
Retrovir (AZT)	Glaxo Wellcome
Zerit (Stavudine, d4T)	Bristol-Myers Squibb
Viramune (Nevirapine)	Boehringer Ingelheim
Norvir (Ritonavir)	Abbott
Viracept (Nelfinavir)	Agouron

References:

Emilio A. Emini, Jon H. Condra, William A. Schleif, Ferdinand E. Massari, Randi Y. Leavitt, Paul J. Deutsch and Jeffrey A. Chodakewitz. Merck Research Laboratories, West Point, PA. *Clinical and Virological Evaluation of the HIV Protease Inhibitor CRIXIVAN® (Indinavir)*. Presented at 1996 Palm Springs Symposium on HIV/AIDS "Frontiers of HIV Therapy." March 7-10, 1996.