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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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Viral Load: Small Change by Sixth Day of Treatment Can Often Predict Poor Response

by John S. James

A U.S. National Institutes of Health study of 124 pediatric and adult patients taking protease inhibitors for the first time found that the change in viral load in the first six days of the treatment was able to predict many cases of poor response of the regimen by week 12. Therefore treatment could be changed quickly in these cases (instead of at 4 or 8 weeks, as recommended by current U.S. guidelines), reducing the development of drug resistance by minimizing the time on an ineffective therapy.

In this study, "reduction in plasma HIV-1 of less than 0.72 log by day 6 after initiation of therapy predicted poor long-term responses in more than 99% of the patients." For those with less than a 0.96 log reduction, the chance of poor response at 12 weeks was 95%. But while very good at predicting some cases of drug failure, 6-day viral load was not as good at assuring long-term success. This is because unpredictable events can occur after day six, such as new mutations that cause viral resistance.

In clinical practice, some patients will not get their blood drawn on exactly the sixth day. Presumably the cut-off value for counting drug failure should be adjusted if the second blood draw is at, for example, 7 days, although the paper did not discuss this. However, this study found that samples taken at day 13 or day 28 were not as predictive as those taken at day 6 -- probably because of the more complex factors affecting viral load after the initial period of rapid decline.

Prediction may be better if there is also a viral load test on day 3, 4, or 5 -- due to natural fluctuations of viral levels, and also due to the

variability of test results. The researchers did not seem to think that this extra test would be necessary in clinical practice.

This research team previously reported that the trough (lowest) drug concentration in blood plasma at the end of the first week, but not the dose, correlated with viral decline, and predicted long-term response. But it would be hard to measure blood levels of three or more drugs, or to know how sensitive the virus was to them. The authors suggest that the much simpler measurement of early viral load change is good enough.

Comment

Physicians might want to look at viral load decline by day six of certain new treatments -- in order to quickly change a clearly ineffective regimen. But the patients and treatments in this study were often not representative of what physicians see today. We hope the guidelines committees will study all the available information, and decide if a day-six viral load test should now be recommended for patients starting or changing antiretroviral therapy -- or if additional studies should be done first.

New Resistance Test Combines Phenotype and Genotype

by John S. James

On November 15 ViroLogic, Inc. announced a new testing service that combines phenotypic and genotypic resistance testing on a single report. The new test, named PhenoSense GT, is expected to be used especially for patients whose treatment is complicated by difficult or complex HIV resistance. The company expects to get test results back to physicians within 14 days.

Phenotypic resistance testing uses part of the

patient's virus to construct a new virus that is then grown in the lab and tested with varying concentrations of the approved anti-HIV drugs, using automated equipment (it would be difficult to grow the unchanged patient's virus in a laboratory). Genotypic testing looks for mutations known to be associated with resistance to the various drugs; it is usually less expensive than phenotypic testing, but more difficult to interpret. While the results are often similar, the two kinds of tests can give different information in some cases.

The PhenoSense GT assay includes resistance testing for the newly approved drug tenofovir.

The number to call for ordering this test is 1-800-777-0177. Unfortunately the price is \$1210.

New information on HIV resistance will be presented at the ICAAC conference in Chicago in mid December.

Comment

We believe that offering the two tests on one integrated report, by a single company that applies compatible standards and quality assurance throughout, opens opportunities to provide better information to physicians. How well it is accepted in practice remains to be seen.

As with other resistance testing, a major challenge will be giving physicians the help that they need to get the most out of the test. HIV physicians must keep up with many things, and cannot all be expected to be drug-resistance experts. At this time we do not know what information the company plans to provide to help physicians interpret the report.

What we would like to see eventually is a semi-automated system that would compare patterns in the reported data with a database of past experience, and add to the report any one or more of perhaps thousands of pre-written notes, calling the physician's attention to significant information that might otherwise be overlooked. Ideally, artificial-intelligence software would

make the first selection of these interpretive notes. Then an HIV-resistance expert or panel of experts would look at every report that was not clearly routine, changing the selection or text of the notes when there is a good reason to do so (these experts could work online from anywhere). Any improvements by the human expert(s) would go to the physician, and also be used to improve the software for the future.

Protease Inhibitors in Children: Combination Therapy Reduced Death by Two Thirds

by John S. James

A November 22 article in the *New England Journal of Medicine* reported on a cohort of 1028 HIV-infected children studied from 1996 through 1999¹. After statistical analysis to adjust for the fact that those starting treatment tended to be sicker, the study found that introduction of an antiretroviral regimen including a protease inhibitor was associated with a two-thirds reduction in risk of death (hazard ratio 0.33). The total reduction in death -- reflecting many treatment advances, not just antiretroviral therapy -- was more impressive: 5.3% mortality in 1996, 2.1% in 1997, 0.9% in 1998, and 0.7% in 1999. Both findings were highly statistically significant, $p < 0.001$.

This study could not compare combinations including a protease inhibitor with combinations including an NNRTI (efavirenz, nevirapine, or delavirdine) because too few of the children were on NNRTI combinations -- only 3% in the last year of the study, 1999 -- compared to 73% on protease-inhibitor combinations, and 24% receiving only nucleoside analogs. But an accompanying editorial² noted that combination therapy with NNRTI drugs can achieve the same result. All the children were on antiretroviral therapy of some kind by 1999.

African American and Hispanic children were found to start therapy later. After statistical adjustment for severity of illness, this effect became less, and was no longer statistically significant. However, the authors suggested continued vigilance to ensure equitable access to treatment.

The authors also urged continued vigilance about the long-term risks of today's antiretroviral drugs when started in childhood; serious metabolic and other side effects have been seen in children as well as adults. This cohort study (PACTG 219) is continuing, and will be able to provide more information about long-term outcome and risk vs. benefit.

The accompanying editorial looked at treatment in developing countries. In the United States, the rate of HIV transmission from infected pregnant women to their children went from 25% to 1.4% with standard antiretroviral therapy; in those children who do get infected, beginning treatment in the first three months of life can stop viral replication completely and preserve normal immune function, provided proper treatment is continued. However, infrastructure in the developing world is just beginning to be created -- the United Nations AIDS Summit this year set a goal of only a 20% reduction in mother-to-child transmission by 2005. "Our efforts must focus on devising simple, relatively inexpensive, triple-combination regimens for the treatment of all HIV-1-infected pregnant women and all HIV-1-infected children. Such a regimen could be provided for \$5 per day and would have a substantial effect on the prevention and treatment of HIV-1 disease in the developing world. These efforts would represent an important step toward changing the face of pediatric HIV-1 infection for the many millions who are affected by it around the world."²

References

1. Gortmaker SL, Hughes M, Cervia J, and others. Effect of combination therapy including

protease inhibitors on mortality among children and adolescents infected with HIV-1. *The New England Journal of Medicine*. November 22, 2001; volume 345, number 21, pages 1522-1528.

2. Sullivan JL and Luzuriaga K. The Changing Face of Pediatric HIV-1 Infection. *The New England Journal of Medicine*. November 22, 2001; volume 345, number 21, pages 1568-1569.

Note: The abstract is available online to anyone at:

<http://content.nejm.org/cgi/content/short/345/21/1522>

The abstract has links to the full text and the editorial -- but these are only available to subscribers to the *Journal*.

South Africa: Activists, Physicians Sue Government to Prevent Maternal Transmission, Ask International Support

by John S. James

On November 26 South Africa's Treatment Action Campaign (TAC), supported by about 200 doctors, sued the South African government, asking for wider use of nevirapine to prevent mother-to-infant transmission of HIV. About 70,000 infants every year are born with HIV in South Africa, and about half of these infections at birth could be prevented by a single tablet of nevirapine given to the mother, and a single dose to the infant. This lawsuit follows five years of lobbying by civil-society organizations.

The government is currently running a pilot program that offers testing, counseling, and nevirapine if needed to about 10% of pregnant women. It argues that it needs time to evaluate this program before expanding it; TAC says that the current program will not allow any expan-

sion beyond the 18 current sites until at least April 2003. The government also says that it cannot afford antiretrovirals, because it has only \$207 million a year to spend on public-sector medicines for the country of over 40 million people.

How you can support TAC in this case? At this time TAC is asking for letters to be sent to South Africa, and also for individuals and organizations to sign the Bredell Consensus Statement -- a statement on HIV treatment in South Africa, endorsed by participants of the Bredell Conference, which took place October 18 and 19. Since the situation will change over time, check their Web site, <http://www.tac.org.za>. This site also includes court papers and other background on the case.

Comment

It is widely believed that the real issue for the government is not the cost of the nevirapine for preventing maternal-infant transmission (which the drug's manufacturer Boehringer Ingelheim has offered free, although the cost of so little nevirapine would not be a barrier in any case), but that once the government provides the drug routinely to HIV-positive pregnant women, there will certainly be more pressure to also treat the mothers, fathers, and others. Antiretrovirals are heavily patented and expensive in South Africa. While generic nevirapine is available from India, which has different patent laws, the South African government is afraid to use compulsory licensing or other means to override patents and obtain drugs it can afford, due to fear of economic retaliation. While South Africa is considered a middle-income country, so much of its population is infected that it could not pay for widespread access at the high prices set by the manufacturers.

A related problem is that South Africa's President Mbeki personally has a hard time backing down from a position once he has taken it. In this case, he picked up conspiracy theories over a year ago from AIDS denialists who

argued that antiretrovirals are inappropriate because HIV does not cause AIDS -- or because AIDS in Africa does not exist, and the deaths are due to other illnesses and to poverty instead. So officials under him are constrained in what they can do.

The result is that South Africa is not successfully making the plans, building the infrastructure, and getting the experience to deal with one of the highest rates of HIV infection in the world.

HIV Testing 101 (Part 1 of 2)

by Bruce Mirken

[Note: On November 9, 2001, the U.S. Centers for Disease Control and Prevention issued two revised guidelines encouraging health care providers to routinely offer HIV testing more often. The goal is to increase the number of people who know their HIV status. These guidelines are available at: <http://www.cdc.gov/hiv/ctr>, or by calling 1-800-458-5231.

[We had asked previously asked Bruce Mirken to write an introduction to HIV testing, including reliability of the tests today, oral HIV tests, rapid HIV tests, anonymous testing, the home test kit (which makes anonymous testing available in all states), and viral load testing to detect HIV in the "window period" before the immune system has produced antibodies, which standard HIV tests detect. JSJ]

* * * * *

HIV antibody testing has been with us since 1985. Testing technology has evolved considerably over the years, with a variety of new and improved tests coming into use, both in research and daily practice. Since determining one's HIV status is the first step in treatment decisions, it is important to understand the tests being used today, including their limitations.

The Basic Testing Procedure

"The primary purpose of the test in 1985 was to screen the blood supply," recalls Steve Morin, director of the University of California San Francisco's AIDS Policy Research Center. At the time there were no treatments available for HIV infection, and no one knew how likely it was that an HIV-infected person would get AIDS or how quickly it might happen. The only medical interventions available dealt with the opportunistic diseases that appeared once the immune system was weakened, so there was no pressing need for people to find out their HIV status.

Still, it was clear that some who believed themselves at risk would want to know.

And that, Morin notes, led to "a fear that people who wanted to know whether they were infected or not would go to donate blood in order to find out." To head off this possible threat to the blood supply, federal and state governments set up alternative test sites, where people could be tested without giving blood. Back then, the main public health value of HIV testing was "as a prevention tool," Morin says, "to counsel people... about not transmitting the virus to anyone else."

That changed with the advent of antiretroviral therapy and prophylaxis (preventive treatment) aimed at preventing opportunistic infections. Over time, HIV testing became a gateway to treatment, as well as a prevention tool.

Although there have been technological changes, HIV testing in the U.S. still follows the same basic testing procedure as in 1985: HIV infection is only considered confirmed after two tests have been done, a screening test and a confirmatory test. In a recent article for the University of California San Francisco's HIV InSite (<http://hivinsite.ucsf.edu>), University of Maryland researcher Niel Constantine explains that "screening tests possess a high degree of sensitivity, whereas confirmatory assays have a

high specificity. Tests with high sensitivity produce few false-negative results, whereas tests with high specificity produce few false-positive results.” Because the screening tests can produce false positives, a second screening test is typically run on the same sample - in duplicate - with the confirmatory tests only run on samples that are repeatedly positive (“reactive” in lab parlance).

The combination of the two types of tests produces results that are “highly accurate,” Constantine notes, but technical errors are possible, and biological factors can occasionally produce problems.

The most common screening test is the enzyme-linked immunosorbent assay (ELISA), sometimes called enzyme immunoassay (EIA). The most often used confirmatory test is the Western blot. Identical technology is used in tests for numerous illnesses, including Lyme disease, Constantine explains. Indeed, the immunological methods underlying these tests are so fundamental that Sally Liska, head of the city of San Francisco’s Public Health Laboratory, calls it “serology 101.”

The ELISA is used for initial screening because of both its high sensitivity and its practical advantages, Liska adds: “It’s a lot easier to do many specimens on an ELISA. It’s smaller volume, it’s less handling, it’s more automated.”

Over 40 different ELISA HIV test kits are available from various manufacturers, though only a fraction of these are licensed by the FDA - a requirement if they are to be used in the U.S. (a few tests are approved for research only). These tests use artificial HIV proteins that are able to capture antibodies to the virus. Once those antibodies are caught, Constantine explains, they “can be detected using other reagents that are usually coupled to an indicator such as a dye or enzyme that can produce color.” The change in color is read by a machine.

The Western blot is somewhat similar, but uses an electrical field that separates out the various components by their molecular weight. This allows identification of antibodies to specific viral antigens, which show up as identifiable “bands” on a strip of test paper.

The Western blot, Liska says, “is a little more complicated to do... It’s more hands-on.” Because it is less sensitive, she adds, it “should never be run by itself.”

Although the Western blot is the most common confirmatory test, others are sometime used, including the indirect fluorescent antibody assay (IFA) and the radioimmunoprecipitation assay (RIPA). “If performed and interpreted correctly, these extremely specific tests should not produce biologic false-positive results,” Constantine writes.

The "Window" Period Just After Infection

One major drawback of antibody tests is the “window” period: the time it takes the body to produce antibodies after infection has begun. The standard tests for HIV do not detect the virus itself, but the antibodies that the body produces in response. During the period before the antibodies are produced, a person can be infected with HIV and can infect others, but still test negative on the HIV antibody test.

For the first tests licensed, this window period ranged from six to 12 weeks, but improved technology has allowed the detection of lower levels of antibodies, making it possible to identify them earlier. “Currently used tests can detect HIV infection between three and five weeks in most individuals,” Constantine says. “This is true of just about all of the ELISAs and the rapid tests [discussed further below]. Some tests are a little more consistent in detecting at the three week period, but in general they are all equivalent.” To some degree, he explains, “it also depends on the individual (who may not produce antibodies as fast as another).”

Oral HIV Testing

All of the early tests were done on blood. More recently developed tests look for antibodies in oral fluid or urine.

The oral test, which follows the same screening/confirmatory protocol as blood tests, has the advantage of being a noninvasive procedure that can be done in settings where blood draws would be impractical or unsafe. Presently just one brand of oral test, called OraSure, is FDA-approved. It is not a saliva test, but instead uses a small pad to draw fluid from within the gums. These fluids are in fact derived from blood, Constantine explains. "Therefore they include the same fluid (plasma) that is used for testing with serum-based tests."

"We're not taking fluid that's already available" in the mouth, Liska notes. "It's not saliva or spit."

The pad used to draw the fluid is attached to a small handle resembling a toothbrush. It is placed against the gum, where it must remain for at least two full minutes to collect a proper sample.

Because the saliva present in the mouth dilutes the antibodies obtained, oral tests must be able to detect weaker concentrations of antibodies than blood tests. In general oral tests have been found to be just as accurate, but Liska believes "the oral fluid test may not be as sensitive for early seroconverters as the blood test."

Urine HIV Testing

Urine tests exist as well, but have not been as popular as the oral fluid test. This may be because the FDA has not yet approved a confirmatory urine test, so anyone with a positive urine test must return for a confirmatory test .

Rapid HIV Testing

Another innovation has been the development of rapid tests. In conventional tests the sample is collected and sent to a central laboratory for processing, a procedure that usually requires the patient to return a week or more later for the results. Rapid tests (which come in both blood and oral versions) are done on-site and give a reading within half an hour. As with the ELISA, a positive reading on a rapid test requires a second, confirmatory assay such as a Western blot.

An advantage of rapid tests is that they eliminate the problem of testers who don't return for their results. Non-return rates are fairly low in doctors' offices and anonymous test sites, but can be quite high in other settings, including STD clinics, whereas many as one third of patients never come back to get their results.

According to Constantine, rapid tests have "proved to be as accurate as the ELISA when performed carefully by experienced personnel. Technical errors are common with these assays, however, because users become careless with these simple procedures." To deal with this problem, many rapid tests now include a built-in control that indicates whether or not the test was done properly. At present, the FDA has licensed one rapid test, made by Murex Diagnostics.

* * *

[Part II will include viral load testing for acute (primary) HIV infection, the "detuned ELISA," accuracy of HIV tests today and answers to "denialist" claims they are unreliable, anonymous testing, home testing anonymously, informed consent for testing, and counseling.]