

LABORATORY MEDICINE

Human immunodeficiency virus testing: Update

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Human immunodeficiency virus (HIV) types 1 and 2 have been associated with the acquired immunodeficiency syndrome (AIDS). The detection of HIV infections is based on the screening of serum samples for the presence of antibodies to HIV proteins. Serum samples that test positive on screening must be assayed by a confirmatory test to provide a definitive report on the presence of HIV infection. This article reviews the currently available screening and confirmatory testing procedures and their limitations.

(Key words: Human immunodeficiency virus, laboratory tests, screening tests, acquired immunodeficiency syndrome)

The human immunodeficiency virus (HIV) (Figure) selectively infects lymphocytes and macrophages, thereby causing immunosuppression. The immunosuppression allows the de-

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The authors have no commercial or proprietary interest in the assays discussed nor do they have any financial interest (as consultant, reviewer, or evaluator) in the assays. Furthermore, specific identification of assay manufacturers does not constitute endorsement by the authors.

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velopment of secondary opportunistic infections that are ultimately fatal to the host. During infection, gp120, a glycoprotein on the viral envelope, binds to the CD4 phenotypic marker found primarily on helper/inducer T lymphocytes (T4 lymphocytes). The specific binding of CD4 receptors by the gp120 glycoprotein accounts for the selective infectivity of this cell class, although other cells, such as macrophages, also possess the CD4 marker. The viral transmembrane glycoprotein gp41 is required for viral entry into the host cell.

Owing to the individual variability of hosts' abilities to produce antibodies, and because the cells of hosts' immune systems are specifically targeted, there is considerable variability in the time frame (window) in which HIV infections may be detected. During that window of time, the infected individual may be unwittingly spreading the virus.

Molecular biology of the HIV

The HIV is an RNA-containing retrovirus, of the *Lentivirinae* subfamily, that requires a living host for its survival. The HIV core carries a reverse transcriptase that catalyzes synthesis of complementary DNA (cDNA) from the viral RNA. The cDNA then integrates into the chromosomal DNA of the infected cell.

During early infection with the HIV, very few cells contain the proviral DNA. This paucity makes detecting the infection difficult when in vitro tissue culture methods are used. Successful detection of the HIV from viral culture ranges from 23% for plasma and up to 97% for peripheral blood mononuclear cells.¹

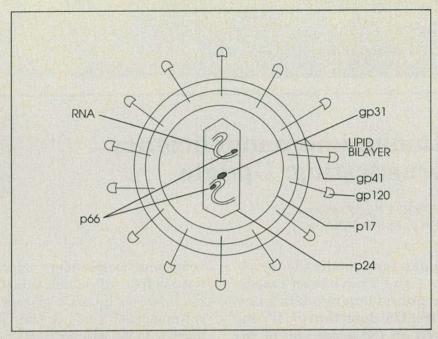


Figure. Human immunodeficiency virus.

Because of the difficulty of using tissue culture techniques to isolate the virus, HIV infection is currently detected by using immunochemical methods that detect specific host antibodies directed against viral proteins.

The HIV virus has a cylindric core surrounded by a lipid envelope derived mainly from the cell membrane of the infected cell. However, the envelope also has projections composed of two glycoproteins designated gp120 and gp41. The virus core consists of two strands of RNA and several proteins. The core proteins are identified by number based on their molecular weights. The core protein designated p24 is significant in that it is unique to the HIV. This protein induces antibody production in the host during early stages of infection and is therefore valuable in identifying HIV infection. The core also contains reverse transcriptase, which allows the viral RNA to produce proviral DNA to be incorporated into the host genome.

The HIV types 1 (HIV-1) and 2 (HIV-2) exhibit approximately 60% homology for the DNA sequences found in the gag and pol genes, and approximately 40% homology for other genes. Therefore, assays developed to detect HIV infections in a population infected primarily with HIV-1 may not produce conclu-

sive test results with individuals infected with the HIV-2.

A 1990 review by Smith² summarizes the pathobiology of HIV infection.

HIV tests

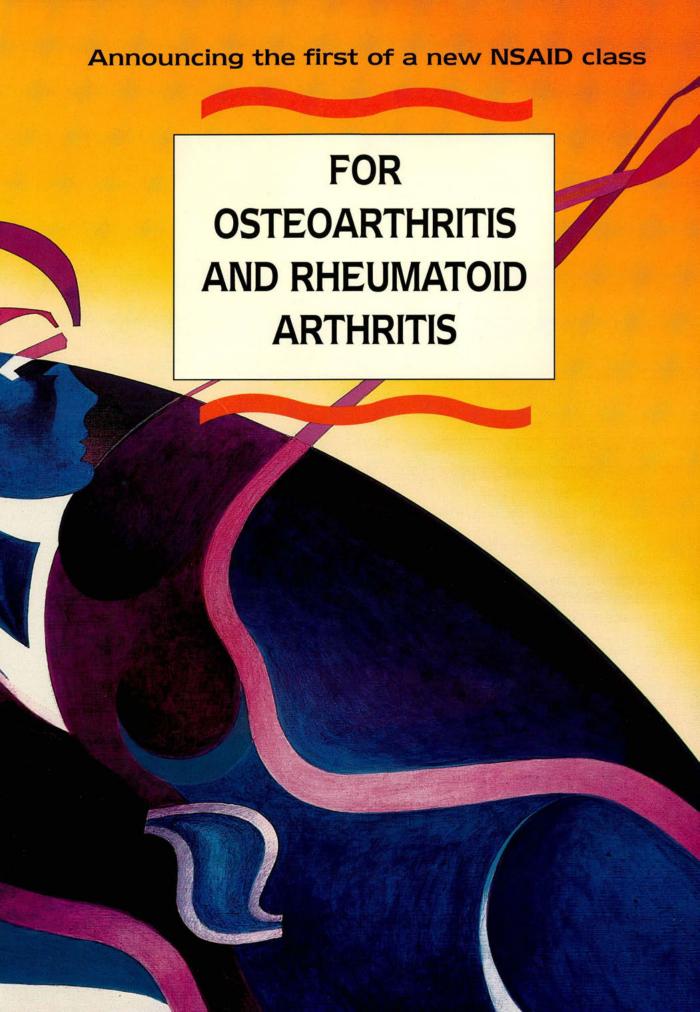
Cultural assays for the HIV in which the virus is grown in tissue culture are not currently feasible for use in the clinical laboratory. The common clinical laboratory tests for HIV can be classified into two groups: screening tests and confirmatory tests.

Screening tests

Screening tests are basically enzyme-linked immunosorbent assays (ELISAs) that use an enzyme-labeled immunoreactant (a mixture of HIV antigens in this case) and a solid support (beads, microtiter plate, test tube).

The ELISAs are currently widely used as screening tests to detect antibodies to the HIV. The specificity of most ELISAs exceeds 99.8%. However, the tests are used to screen populations that have a very low prevalence of HIV infection. Under these conditions, the positive predictive value of ELISA may be 10% or less. Therefore, a positive ELISA does not conclusively prove the presence of the HIV, and a negative ELISA does not rule out HIV expo-

(continued on page 496)



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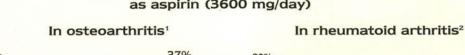
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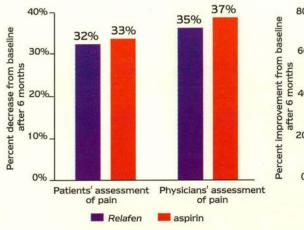


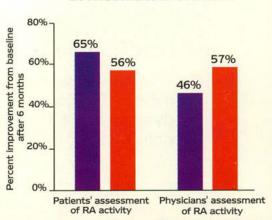
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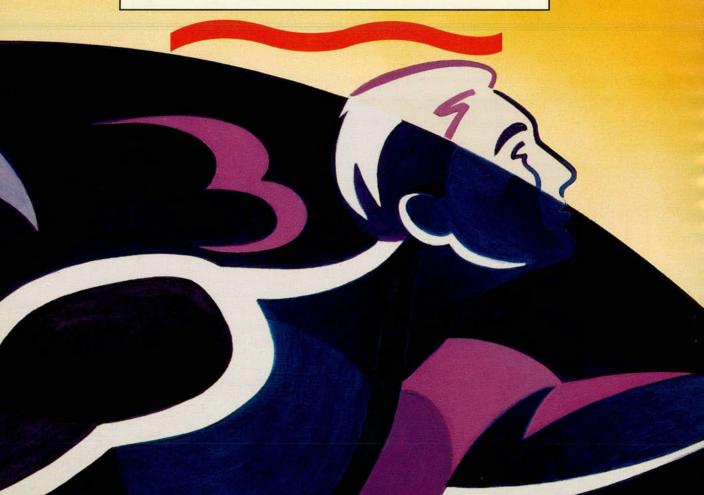
Arthritis treatment with a low incidence of peptic ulcers

A low incidence of peptic ulcers in U.S. clinical studies of Relaten 1000 to 2000 mg/day

Time period	Cumulative incidence of peptic ulcers	95% confidence intervals	Number 1000 mg	er of pa	atients* 2000 mg
3 to 6 months	0.3%	(0.0%, 0.6%)	1064	712	84
up to 1 year	0.5%	(0.1%, 0.9%)	833	614	69
up to 2 years	0.8%	(0.3%, 1.3%)	540	513	46

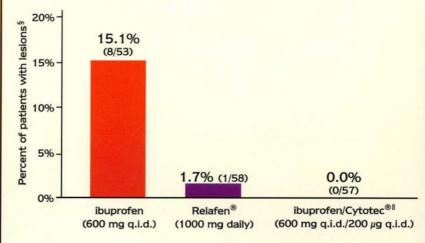
Other G.I. symptoms comparable to other NSAIDs, including diarrhea (14%), dyspepsia (13%) and abdominal pain (12%)

*Patients may have been treated at more than one dosage level.



Lower incidence of endoscopic lesions[†] than ibuprofen^{‡2}

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‡P=0.013.

§ Lesions defined as >5 mm.

|| Cytotec* (misoprostol), G.D. Searle & Co.

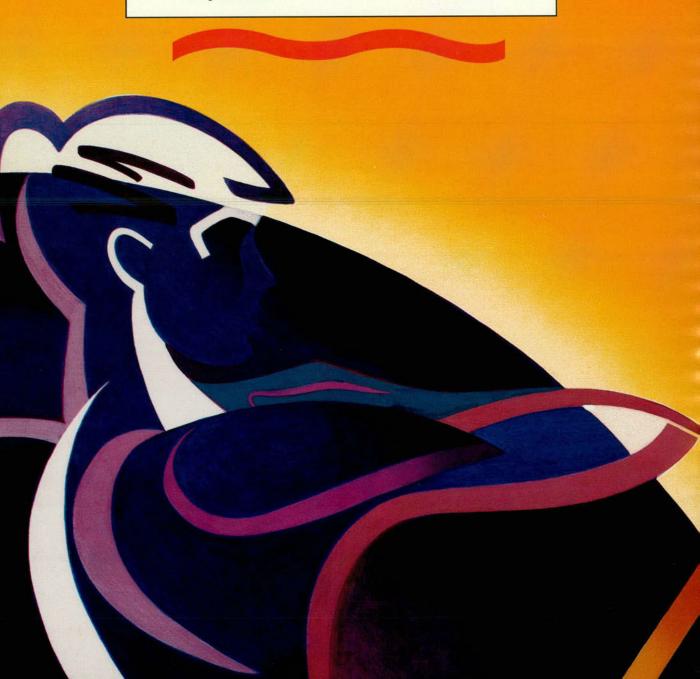
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- * Please-see dosage and administration section of accompanying brief summary of prescribing information.

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- Other G.I. symptoms comparable to other NSAIDs, including diarrhea (14%), dyspepsia (13%) and abdominal pain (12%)
- Convenient once-a-day dosing
- Starting dose 1000 mg/day given as two 500 mg tablets
- Can be titrated up to 2000 mg/day



Please see accompanying brief summary of prescribing information.



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See complete prescribing information in SmithKline Beecham Pharmaceuticals literature or *PDR*. The following is a brief summary.

CLINICAL PHARMACOLOGY: Relaten is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic and antipyretic properties in pharmacologic studies. As with other nonsteroidal anti-inflammatory agents, its mode of action is not known. However, the ability to inhibit prostaglandin synthesis may be involved in the anti-inflammatory effect. The parent compound is a prodrug, which undergoes hepatic biotransformation to the active component, 6-methoxy-2-naphthylacetic acid (6MNA), a potent inhibitor of prostaglandin synthesis.

INDICATIONS AND USAGE: Acute and chronic treatment of signs and symptoms of osteoarthritis and rheuma-

CONTRAINDICATIONS: Patients (1) who have previously exhibited hypersensitivity to it; (2) in whom Relaten, aspirin or other NSAIDs induce asthma, urticaria or other allergic-type reactions.

WARNINGS: Remain alert for ulceration and bleeding in patients treated chronically, even in the absence of

WARNINGS: Remain alert for ulceration and bleeding in patients treated chronically, even in the absence of previous G. I. tract symptoms. In controlled clinical trials involving 1,677 patients treated with *Relaten* (1,140 followed for one year and 927 for two years), the cumulative incidence of peptic ulcers was 0.3% at three to six months, 0.5% at one year and 0.8% at two years. Inform patients of the signs and symptoms of serious G.I. toxicity and what steps to take if they occur. In patients with active peptic ulcer, weigh the benefits of *Relaten* therapy against possible hazards, institute an appropriate ulcer treatment regimen and monitor the patients' progress carefully. In considering the use of relatively large doses (within the recommended dosage range), anticipate benefit sufficient to offset the potential increased risk of G.I. toxicity.

sufficient to offset the potential increased risk of G.I. toxicity.

PRECAUTIONS: Because nabumetone undergoes extensive hepatic metabolism, no adjustment of Relaten dosage is generally necessary in patients with renal insufficiency. However, as with all NSAIDs, monitor patients with impaired renal function more closely than patients with normal renal function, or in whom an abnormal liver test has occurred, for evidence of the development of a more severe hepatic reaction while on Relaten therapy. If abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), discontinue Relaten. Use Relaten cautiously in patients with severe hepatic impairment.

As with other NSAIDs, use Relaten cautiously in patients with a history of congestive heart failure, hypertension or other conditions predisposing to fluid retention.

Based on U.V. light photosensitivity testing, Relaten may be associated with more reactions to sun exposure than might be expected based on skin tanning types.

Physicians may wish to discuss with their patients the potential risks (see WARNINGS, PRECAUTIONS and ADVERSE REACTIONS) and likely benefits of NSAID treatment, particularly when the drugs are used for less serious conditions where treatment without NSAIDs may represent an acceptable alternative to both the patient and the physician.

and the physician.

and the physician.

Exercise caution when administering *Relaten* with warfarin since interactions have been seen with other NSAIDs. In two-year studies conducted in mice and rats, nabumetone had no statistically significant tumorigenic effect. Nabumetone did not show mutagenic potential in the Ames test and mouse micronucleus test *in vivo*. However, nabumetone—and 6MNA-treated hymphocytes in culture showed chromosomal aberrations at 80 mcg/mL and higher concentrations (equal to the average human exposure to *Relaten* at the maximum recommended dose). Nabumetone did not impair fertility of male of remale rats treated orally at doses of 320 m/g/kg/day before mating. Prepnancy Category C: Nabumetone did not cause any teratogenic effect in rats given up to 400 mg/kg and in rabbits up to 300 mg/kg orally. However, increased post-implantation loss was observed in rats at 100 mg/kg orally and at higher doses (equal to the average human exposure to 6MNA at the maximum recommended human dose). There are no adequate, well-controlled studies in pregnant women. Use the drug during pregnancy only if clearly needed. Because of the known effect of prostaglandin-synthesis-inhibiting drugs on the human fetal cardiovascular system (closure of ductus arteriosus), use of *Relaten* during the third trimester of pregnancy is not recommended.

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The effects of *Relafen* on labor and delivery in women are not known. As with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia and delayed parturition occurred in rats treated throughout pregnancy. It is not known whether nabumetone or its metabolites are excreted in human milk; however, 6MNA is excreted in the milk of lactating rats. Because of the possible adverse effects of prostaglandin-synthesis-inhibiting drugs on neonates, *Relafen* is not recommended for use in nursing mothers.

Safety and efficacy in children have not been established. Of the 1,677 patients in U.S. clinical studies who were treated with *Relafen*, 411 patients (24%) were 65 years of age or older. No overall differences in efficacy or safety were observed between these older patients and younger ones. Similar results were observed in a one-year, non-U.S. postmarketing surveillance study of 10,800 *Relafen* patients, of whom 4,577 patients (42%) were 65 years of age or older.

ADVERSE REACTIONS: Incidence ≥ 1%—Probably Causally Related—Diarrhea (14%), dyspepsia (13%), abdominal pain (12%), constipation", flatulence", nausea", positive stool gualac", dry mouth, gastritis, stomatitis, vomiting, dizziness", headache", fatigue, increased sweating, insomnia, nervousness, somnolence, pruritus", rash", tinnitus", deema".

*Incidence of reported reaction between 3% and 9%. Reactions occurring in 1% to 3% of the patients are unmarked.

unmarked ...

Incidence <1%—Probably Causally Related*—Anorexia, cholestatic jaundice, duodenal ulcer, dysphagia, pastric ulcer, gastroenteritis, gastrointestinal bleeding, increased appetite, liver function abnormalities, melena, asthenia, agitation, anxiety, confusion, depression, malaise, paresthesia, tremor, vertigo, vasculitis, weight gain, bullous eruptions, photosensitivity, urticaria, pseudoporphyria cutanea tarda, dyspnea, abnormal vision, albuminuria, interstitial nephritis, angioneurotic edema.

Incidence <1%—Causar Retalionabli Unknown*—Duodentitis, eructation, galistones, gingivitis, glossitis, pancreatitis, rectal bleeding, acne, alopecia, erythema multiforme, Stevens-Johnson Syndrome, asthma, cough, azotemia, bilirubinuria, dysuria, hematuria, impotence, renal stones, taste disorder, fever, chilis, angina, arrhythmia, hypertension, myocardia infarction, papitations, syncope, thrombophlebitis, anemia, leukopenia, granulocytopenia, thrombocytopenia, hyporalemia, hypokalemia, weight loss, nightmares.

†Adverse reactions reported only in worldwide postmarketing experience or in the literature are fatilicized.

DUEDNOSAGE Il acute ovardose occurs ampts the stomach by worpiting or layage and institute general sun-

OVERDOSAGE: If acute overdose occurs, empty the stomach by vomiting or lavage and institute general sup-portive measures as necessary. Activated charcoal, up to 60 grams, may effectively reduce nabumetone absorp-tion. Coadministration of nabumetone with charcoal to man has resulted in an 80% decrease in maximum plasma concentrations of the active metabolite.

One overdose occurred in a 17-year-old female patient who had a history of abdominal pain and was hospitalized for increased abdominal pain following ingestion of 30 Relaten tablets (15 grams total). Stools were negative for occult blood and there was no fall in serum hemoglobin concentration. The patient had no other symptoms. She was given an H₂-receptor antagonist and discharged from the hospital without sequelae.

DOSAGE AND ADMINISTRATION: Recommended starting dose; 1000 mg taken as a single dose with or without food. Some patients may obtain more symptomatic relief from 1500 mg to 2000 mg daily. Dosages over 2000 mg daily have not been studied. Use the lowest effective dose for chronic treatment.

HOW SUPPLIED: Tablets: Oval-shaped, film-coated: 500 mg — white, imprinted with the product name RELAFEN and 500, in bottles of 100 and 500, and in Single Unit Packages of 100 (intended for institutional use only); 750 mg — beige, imprinted with the product name RELAFEN and 750, in bottles of 100 and 500, and in Single Unit Packages of 100 (intended for institutional use only). Store at controlled room temperature (59° to 86°F) in well-closed container; dispense in light-resistant container.

500 mg 100's: NDC 0029-4851-20 500 mg 500's: NDC 0029-4851-25 500 mg SUP 100's: NDC 0029-4851-21

750 mg 100's: NDC 0029-4852-20 750 mg 500's: NDC 0029-4852-25 750 mg SUP 100's: NDC 0029-4852-21

BRS-RL:L2

C SmithKline Beecham, 1992

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2. Data on file, Medical Department, SmithKline Beecham Pharmaceuticals.

RL202

Coming in. . .

THE DO

The May issue of The DO will explore the nuts and bolts of setting up a medical practice. In addition to describing some of the surprises DOs have encountered when opening their first offices, the issue will offer advice on choosing professional business consultants, establishing billing and collection mechanisms, and hiring office staff.

The May issue also will feature an article on optical devices designed for patients with low vision. In addition, the issue will provide coverage of the annual convention of the American College of General Practitioners in Osteopathic Medicine and Surgery and the midwinter conference of the Colorado Society of Osteopathic Medicine.

Future issues of JAOA

- "Parietal bone mobility in the anesthetized cat"
- "A clinical study of the osteopathic management of children with neurological or medical problems at the Osteopathic Center for Children"
- "Training medical students in behavioral medicine"
- · "The physiologic role and clinical significance of reverse cholesterol transport"
- "The varied clinical presentations of meningococcal infection"
- "Autologous blood transfusion: Standard of care for the 1990s"
- "Helping patients reduce the risk of acquiring sexually transmitted disease"
- "Lyme disease: A review"
- "Suggestions for diagnosing avascular necrosis of the hip in the 1990s"
- "Recruiting residents: Attracting the best"
- "Male breast carcinoma: Suburban community experience"
- "Adult respiratory distress syndrome: A review for the clinician"

sure. Consequently, it is necessary for attending physicians to be sensitive to the patient's anxieties and present the patient with both pretest counseling, as well as posttest counseling. It is suggested that a positive ELISA test report not be given to the patient until a positive result has been obtained by a confirmatory test.

Similarly, negative test results should be followed by posttest counseling because screening tests have a limited potential for yielding false-negative results. Persons with negative results may be retested, based on physician judgment. Individuals who have indeterminate test results (either after screening or on confirmatory testing) should be retested within 3 to 6 months. Furthermore, the difficulty in detecting HIV in infected people is the fact that the virus infects a select cell population. Once the cells are infected, there are few proviral elements per cell; and, when the viral genome is incorporated into the host cell, there is a lengthy latency period. An individual who has consistently indeterminate confirmatory test results during a 6-month period and who has no known risk factors may be considered to be negative for HIV antibodies.

Confirmatory tests

The Western blot technique is most commonly used to verify the presence of HIV antibodies. The first stage of this procedure involves the growth and purification of the HIV. The virus is lysed, and the lysate is electrophoresed. After the proteins are separated by electrophoresis, the proteins, as bands, are transferred to nitrocellulose by placing the nitrocellulose over the electrophoresed proteins. Thereby, the proteins are transferred to the nitrocellulose in a pattern identical to their electrophoretic separation. The desired bands can then be cut from the nitrocellulose and can be used to detect the presence of antibodies to the particular HIV proteins. (This portion of the Western blot test is currently produced for users by commercial diagnostics manufacturers such as Du Pont, Wilmington, Del, and Electro-Nucleonics, Columbia, Md).

In the common clinical laboratory use of the Western blot technique, serum samples are in-

cubated with the nitrocellulose strips coated with HIV proteins. The strips are washed to remove nonadherent antibody. The strips are then incubated with horseradish peroxidase conjugated anti-IgG. After this incubation, the strips are washed again, and a substrate is added to allow visualization of the bands where antibody has attached to bound HIV proteins. The viral proteins that are detected by this method include the viral core gag proteins (p17, p24, p55), polymerase pol proteins (p31, p51, p66), and envelope env proteins (gp41, gp120, and gp160). This method is very sensitive and very specific for detecting antibodies to HIV. However, there is no consensus regarding the interpretation of results.

Western blot interpretation

Four major organizations have established similar, but different, criteria for the interpretation of Western blot test results (Table).4 Although agencies and organizations such as the Food and Drug Administration, the American Red Cross, and the Centers for Disease Control agree that the absence of bands on the blot indicates a negative test result, there is significant divergence of opinions as to what bands (complexes of antibody and viral protein) must be present for the test to be interpreted as positive. According to a report by O'Gorman and coworkers,5 interpretation of Western blot assay results using each organization's criteria, in addition to criteria developed by the University of North Carolina Hospitals-Chapel Hill, resulted in variable numbers of positive, negative, and indeterminate results.

Unusual Western blot patterns have been observed when non-HIV-1 retrovirus infections yield gag and pol gene products. In cases in which test results are indeterminate, every effort should be made to qualify the test results. Recommendations for resolution should include retesting the patient's serum sample within 6 weeks to 2 months.

HIVAGEN, a proprietary, second-generation, ELISA-based confirmatory assay for HIV antibodies is available from SmithKline Beecham Clinical Laboratories (SKBL). It is the contention of SKBL that because the HIV

	Table	
Criteria for Int	rpretation of Western Blot Assays3*	

	Interpretive criteria			
Organization	Positive	Negative	Indeterminate	
American Red Cross	Minimum of 3 bands: 1 each of env, gag, pol	No bands	Failure to meet positive test criteria	
Centers for Disease Control	Minimum of 2 of the p24, gp41, or gp160/120	No bands	Failure to meet positive test criteria	
Food and Drug Administration	p24, p31, and gp41 and/or gp120/160	No bands	Failure to meet positive test criteria	
Consortium for Retrovirus Serology Standardization	p24 or p31 and gp41 or gp160/120	No bands	Failure to meet positive test criteria	

*Adapted from Centers for Disease Control: Interpretation and use of the Western blot assay for serodiagnosis of human immunodeficiency virus type 1 infections. MMWR 1989; 38(suppl 7):1-7.

used in ELISA screening tests and Western blot procedures is grown in human tissue cultures, the virus extracts contain significant amounts of human cell material. Furthermore, because ELISA-based screening assays have been adjusted to maximum sensitivity, specificity is decreased and false-positive reactions can occur. SmithKline Beecham Clinical Laboratories further notes that false-positive reactions are caused when non-HIV antibodies react with the contaminating human cell material or cross-react with HIV protein. The Western blot assay, according to some estimates based on proficiency testing, may have a falsenegative rate of up to 10% and a false-positive rate of up to 5%.6 Also, SKBL contends that the Western blot assay has other limitations. including:

- Many laboratories do not use standardized reagents or procedures when performing the Western blot technique.
- Variable reporting and interpretive data are used for positive, negative, and indeterminate test results.
- Technical accuracy is dependent on the skill of the person performing the test.
- Interpretation of test strip reactions is subjective.

HIVAGEN consists of a six-panel ELISA assay. The HIV antigens used to bind patient antibodies are purified peptides produced by

recombinant DNA technology. This assay uses two recombinant antigens (Kp24 and Kp55) to detect antibodies to the viral core, or gag gene product; three recombinant antigens (Kp41, Kp120N, Kp120CC) to detect antibodies to envelope, or env, products; and one antigen (Kp66/31) to detect antibodies to pol polymerase/enolase gene products. According to information provided by SKBL, HIVAGEN has not shown any false-positive or false-negative results. However, according to the same data, HIVAGEN demonstrated a 4% indeterminate rate, albeit significantly lower than that demonstrated by Western blot technique.

HIV detection by use of polymerase chain reaction

The HIV infects a select cell population, providing a limited number of proviral particles, with a lengthy latency before the expression of viral proteins. Investigators^{1,7} have developed an in vitro DNA amplification technique called *polymerase chain reaction* (PCR) in an attempt to improve diagnosis by eliminating false-negative or indeterminate test results.

The technique uses two synthetic oligonucleotide primers that are complementary to DNA sequences that border a section of viral cDNA of interest. A DNA probe, complementary to the viral cDNA under investigation, is incorporated with the oligonucleotides. One

oligonucleotide is complementary to the negative DNA strand, while the other is complementary to the positive DNA strand. By lysing the infected cell, viral cDNA may be opened (the complementary strands of DNA separate), and the primers anneal to the proviral DNA. A polymerase extends the length of primers in the presence of deoxynucleoside triphosphates. Polymerase cycling amplifies the proviral sequence under investigation to the point that millions of copies of the DNA fragment may be produced. By amplification, the possibility for detecting specific HIV cDNA is significantly enhanced. The PCR is a difficult procedure to perform and, to date, there have been no significant developments in reagents or instrumentation that make widescale use feasible.

Comment

Despite the rapid technologic advances in the detection and identification of HIV infections, there is currently no single assay with a 100% predictive value that is inexpensive and easy to perform. For the time being, it appears that the testing sequence for HIV diagnosis will con-

tinue to rely on screening with subsequent confirmatory testing. Because of the nature of the infection, even negative test results cannot be considered to correctly indicate that the individual is not infected. Therefore, physicians must be judicious in the interpretation of test results.

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