SMDL #01-005
January 8, 2001

Dear State Medicaid Director:

This letter provides information about two relatively new laboratory tests for the management of Human Immunodeficiency Virus (HIV) disease to assist State Medicaid agencies in establishing policies regarding coverage, coding, and reasonable payment for these tests. The two tests are genotype human immunodeficiency virus type-1 (HIV-1) testing (mutation analysis) for drug resistance and phenotype HIV-1 drug susceptibility (commonly referred to as resistance) testing.

Because the technology to perform these tests has only recently become widely available, State Medicaid Agencies and other public and private health insurers are now faced with many complex issues concerning coverage, payment, and coding. Laboratories, manufacturers, community-based AIDS organizations, public health researchers, and health insurers have also asked HCFA for guidance and assistance regarding these tests.

Standards of Care

On January 19, 2000, a panel of experts convened by the U.S. Department of Health and Human Services and the Henry J. Kaiser Family Foundation updated their guidance on clinical practices for the treatment of HIV infection, entitled "Guidelines for the Use of Antiretroviral Agents in HIV Infected Adults and Adolescents." The Guidelines are generally accepted as the standard of care in the United States. With regard to drug resistance testing, the Guidelines state that both the genotype and phenotype drug resistance assays are recommended in certain circumstances.

The guidelines recommend resistance testing in two situations: (1) When the patient presents with virologic failure during Highly Active Antiretroviral Therapy (HAART), and (2) When the patient has suboptimal suppression of viral load after initiation of antiretroviral therapy. The Guidelines state that resistance testing is generally not recommended with chronic HIV infection prior to initiation of therapy, after discontinuation of drugs, and when the patient's plasma viral load is less than 1000 HIV RNA copies/mL. In the presence of acute HIV infection, the Guidelines state that the provider should consider resistance testing. Since the publication of the Guidelines in January, two additional studies have been completed that confirm the effectiveness of genotypic testing.

Coverage

While there has been concern that none of the available genotype and phenotype tests have received approval from the Food and Drug Administration (FDA), only "test kits" for interstate commerce require this approval. Currently, most genotype and all phenotype testing is being performed under the "homebrew" status and therefore is not subject to FDA approval. Some manufacturers are currently seeking FDA approval for genotype test kits. One manufacturer has a genotype kit that has received an FDA status of Investigational Device Exemption (IDE). The FDA regulates how these non-FDA approved laboratory tests can be used, marketed, and distributed.

While this information is important to States, HCFA and State Medicaid Agencies are not responsible under Federal regulations for knowing whether laboratories or manufacturers are complying with FDA requirements or for ensuring compliance with these requirements, nor is FDA approval of a test/procedure a prerequisite for Medicaid coverage. A State Medicaid agency can decide to cover an FDA-approved or non-FDA approved laboratory test if the agency determines the test to be medically necessary and if the test is provided by a qualified Medicaid laboratory that is certified in accordance with the Clinical Laboratory Improvement Act (CLIA) to perform such tests. In some States however, the Medicaid program is required by State law to cover only FDA-approved products and therefore, the State Medicaid agency must follow its own regulations.

If you have any questions that relate to FDA compliance requirements for HIV tests, you may contact the Food and Drug Administration, Center for Biologics Evaluation and Research, Office of Compliance & Biologics Quality, Division of Case Management, 1401 Rockville Pike, suite 400 South, HFM-610, Rockville, MD 20852, (301) 827-6201.

Cost

Reimbursement for the genotype assay test and phenotype assay test range from $250 to $500 and $625 to $900, respectively. State Medicaid agencies choosing to cover these tests should determine an adequate payment amount with the providers in their States to assure appropriate access to these tests. Payment should meet Federal requirements of economy and efficiency while assuring appropriate access to these services. Section 1903(i)(7) of the Social Security Act and section 6300 of the State Medicaid Manual provide that Medicaid payments cannot exceed what Medicare would pay for these tests (the 'Medicare upper limit') when Medicare establishes a national limitation amount (NLA). HCFA has set an NLA for the Medicare program for these two tests effective January 1, 2001. Instructions on the fee schedule, (Medicare Program Transmittal AB-00-109), can be found at http://www.hcfa.gov/pubforms/transmit/AB00109.pdf.

Coding

The American Medical Association (AMA) has developed three new Current Procedural Terminology (CPT) codes for the resistance tests. The effective date for these codes is January 1, 2001. Genotype testing has one CPT code (87901). Phenotype testing has two codes. The primary (87903) covers the first ten drugs that are tested. The second code (87904) is to be used for each additional drug, up to five drugs. The CPT manual specifies that code 87904 must be used in conjunction with 87903.

Conclusion

Based upon the information contained in this letter, the technical attachment, and the Guidelines regarding the recommended and optimal use of resistance testing, State Medicaid agencies should provide coverage of these tests under the specific clinical conditions outlined in the Guidelines and should determine what reimbursement is reasonable to assure appropriate access to care.

We have enclosed some technical information about these tests that we believe will be helpful to you and your State in establishing coverage and reimbursement. The Guidelines are available upon request by calling 1-800-448-0440 or may be downloaded from the Internet at http://www.hivatis.org/guidelines/adult/text/. We hope that this information proves useful in your implementation of this new laboratory test. If you have questions, please call Kurt Hartmann at (410) 786-0400.

Sincerely,

/s/
Timothy M. Westmoreland
Director

Enclosure

cc:

All HCFA Regional Administrators
All HCFA Associate Regional Administrators Division of Medicaid and State Operations
Lee Partridge, Director, Health Policy Unit - American Public Human Services Association
Brent Ewig, Senior Director, Access Policy - Association of State and Territorial Health Officers
Julie Scofield, Executive Director - National Alliance of State and Territorial AIDS Directors
Joy Wilson, Director, Health Committee - National Conference of State Legislatures
Matt Salo, Director of Health Legislation - National Governors' Association

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Resistance Testing
Technical Information

Why Resistance Testing

Since the discovery of HIV in 1983, an explosion of research has begun in the area of retroviral genes. HIV mutates frequently causing errors in the HIV genetic material (genome). These genetic mutations enable the virus to become resistant to previously effective antiretroviral drugs. Even with the development of HIV "drug cocktails" when three or more drugs designed to impede replication of the virus at different life-cycle stages are initially successful, the HIV virus mutates and eventually becomes resistant to these drug regimens. To date, over 140 HIV mutations have been identified which lead to drug resistance. The genotype and phenotype tests provide information to the clinician about the various mutations and the effectiveness of drugs on the virus. The U.S. Department of Health and Human Services/Kaiser Family Foundation HIV treatment guidelines state that HIV resistance testing is recommended to guide antiretroviral therapy in certain circumstances.

Genotypic Assay Test

Genotyping assays detect drug resistance mutations that are present in the patient's HIV viral genes (i.e. reverse transcriptase (RT) and protease). Some genotyping assays involve sequencing of the entire RT and protease genes, while others utilize probes to detect selected mutations that are known to confer drug resistance. Genotyping assays can be performed relatively rapidly, such that results can be reported within 1-2 weeks of sample collection. Knowing which drug resistance mutations are present may provide the clinician with valuable information when selecting or changing therapy for a particular individual. Genotypic testing has a number of advantages over phenotypic testing such as:

- it is faster and easier to perform,
- it can be performed at significantly lower cost,
- and it is more widely available throughout the United States.

Disadvantages include:

- lack of sensitivity for detecting drug resistant minor variants, and
- an imperfect relationship between resistance genotype, phenotype, and clinical outcome.

Interpretation of test results requires an appreciation of the range of mutations that are selected for various antiretroviral drugs, as well as the potential for cross-resistance to other drugs conferred by some of these mutations (see the http://hiv-web.lanl.gov web site). Consultation with an expert in HIV drug resistance is encouraged to facilitate interpretation of genotypic test results.

Phenotypic Assay Test

Phenotyping assays measure the ability of the patient's HIV viruses to grow in various concentrations of antiretroviral drugs. Automated, recombinant phenotyping assays have recently become commercially available with turn-around times of 2-3 weeks, but generally turn-around time is 6 to 12 weeks. In addition, the phenotype assays are significantly more costly to perform than genotypic assays. Recombinant phenotyping assays involve insertion of the RT and protease gene sequences derived from patient plasma HIV RNA into the backbone of a laboratory clone of HIV either by cloning or in vitro recombination. Replication of the recombinant virus at various drug concentrations is monitored by expression of a reporter gene and is compared with replication of a reference strain of HIV. The concentrations of drugs that inhibit 50 percent and 90 percent of viral replication (i.e. the IC50 and IC90) are calculated, and the ratio of the IC50s of the test and reference viruses is reported as the fold increase in IC50, or fold resistance. To date researchers and clinicians have identified a number of problems with phenotype testing to include:

- A national database has not been sufficiently developed to benchmark the specific level of resistance (fold increase in IC50) that is associated with failure of different drugs;

- the reporting time is considerably delayed due to the culture growth stage;
- insensitivity to minor viral species (less than 20 percent of the circulating population);
- the minimum blood level of drug needed to suppress replication in vivo is not known for any drug;
- and the test is relatively expensive.

Interpretation of phenotyping assay results is complicated by the paucity of data on the specific level of resistance (fold increase in IC50) that is associated with failure of different drugs; again, consultation with an expert may be helpful for interpretation of test results.

Further Limitations

Both genotyping and phenotyping assays currently lack uniform quality assurance standards for performing assays, are done at relatively high cost, and are not sensitive to minor viral species (i.e., if drug-resistant viruses are present but constitute less than 10-20 percent of the circulating virus population, they will likely not be detected by current assays). This latter limitation is of particular importance when interpreting data about susceptibility to drugs that the patient has taken in the past but are not parts of the current antiretroviral regimen. If drug resistance had developed to a drug that was subsequently discontinued, the drug-resistant virus can become a minor species because its growth advantage is lost. Consequently, resistance assays should be performed while the patient is taking his/her antiretroviral regimen, and data suggesting the absence of resistance should be interpreted carefully in relation to the prior treatment history.

DHHS/Henry J. Kaiser Family Foundation Guidelines--Recommendations Regarding Drug Resistance Assays

Resistance assays may be useful in the setting of virologic failure on antiretroviral therapy and in acute HIV infection. Recent prospective data supporting the use of resistance testing in clinical practice come from trials in which the utility of resistance tests were assessed in the setting of virologic failure. Thus, resistance testing appears to be a useful tool in selecting active drugs when changing antiretroviral regimens in the setting of virologic failure. There are currently no prospective data to support the use of one type of resistance assay over the other (i.e. genotyping vs. phenotyping) in different clinical situations. Only one type of assay is generally recommended per sample; however, in the setting of a complex prior treatment history, both assays may provide important and complementary information.

Treatment of acute HIV infection is associated with improved immunological outcome and optimization of the initial antiretroviral regimen through the use of resistance testing is a reasonable albeit untested strategy. Because of its more rapid turn-around time, the use of a genotypic assay may be preferred in this setting. However, the treatment guidelines state that therapy should not be withheld while awaiting the results of resistance testing. The use of resistance testing prior to initiation of antiretroviral therapy in chronic HIV infection is not generally recommended because of uncertainty about the prevalence of resistance in treatment-naive individuals and the fact that currently available resistance assays may fail to detect drug resistant

species that were transmitted at the time of primary infection but became a minor species in the absence of selective drug pressure. The currently favored approach would be to reserve resistance testing for cases in which viral load suppression was suboptimal after initiation of therapy. Although this may change as more information becomes available on the prevalence of resistant virus in antiretroviral-naïve individuals.

In general, recommendations for resistance testing in pregnancy should be the same as for non-pregnant patients: acute HIV infection, virologic failure on an antiretroviral regimen, or suboptimal viral load suppression after initiation of antiretroviral therapy are all appropriate indications for resistance testing.

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