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## **1.0 Description of the Procedure, Product, or Service**

Human Immunodeficiency Virus (HIV) is a Ribonucleic Acid (RNA) virus characterized by a high replication rate throughout all stages of infection. The reverse transcription enzyme required for replication is "error-prone," resulting in a high rate of mutations, further leading to a swarm of related viruses (termed "quasi-species") within the host. In fact, it is estimated that every possible single point mutation occurs more than 10,000 times per day in infected individuals. While some of the mutations may be innocuous or render the virus unviable, others may confer resistance to antiviral drugs. It is likely that clones of drug-resistant viruses exist even prior to any anti-viral therapy, but due to an associated replication or competitive disadvantage compared to the wild type virus, the resistant clone only represents a small proportion of the total viral load. However, in the presence of anti-viral drugs that selectively eliminate the wild type virus, a resistant clone may rapidly emerge as the dominant quasi-species. Over time, this resistant clone may accumulate additional secondary mutations that overcome the original replication or competitive disadvantage. Virological treatment failure (i.e., increasing viral loads) may result.

Current recommendations for initial drug therapy suggest the use of combination therapy with antivirals with different mechanisms of action designed to reduce the viral load to as low a level as possible. (The four classes of antivirals available include nucleoside reverse transcription inhibitors [NRTI], non-nucleoside reverse transcription inhibitors [NNRTI], protease inhibitors [PR], and fusion inhibitors.) This therapeutic principle is based on the concept that cessation of detectable HIV replication decreases the opportunity for accumulation of mutations that may give rise to drug resistant viral variants. These regimens are referred to as HAART (highly active antiretroviral therapy). If initial drug therapy fails, as evidenced by rising HIV viral loads, it is likely that the emergent virus is drug resistant, unless failure is related to drug noncompliance. At this point, physicians must devise a salvage therapy, using drugs to which the virus likely remains sensitive. While drug resistance is most common in the setting of prior failed therapy; there have been reports of initial infection with drug resistant strains, particularly resistance to zidovudine, a drug that has been widely used since the 1980s.

**HIV genotyping (i.e., gene sequencing)** has revealed specific point mutations or combinations of mutations in the enzymes targeted by these drugs, i.e., viral protease and reverse transcriptase. These mutations may be associated with drug resistance. For example, a single point mutation in HIV can confer high level resistance to the antiviral lamivudine (a NRTI) and certain NNRTIs. In contrast, high level resistance to zidovudine (an NRTI) and certain protease inhibitors requires accumulation of 3 or more mutations. When only a single mutation is required for resistance, resistance may emerge within 1 month of treatment initiation. For this reason, these drugs are never used as monotherapy. In contrast, when multiple mutations are required, resistance may emerge only after months to years of therapy. Mutations that are common to several different drugs within a group will confer cross resistance. For example, cross resistance among the protease inhibitor drugs is common.

**HIV phenotyping** measures drug resistance by culturing infected cells in the presence of the tested drug to determine the drug concentration required to inhibit viral replication. In essence, phenotypic tests measure the ability of drugs to block viral replication in cell

culture, while genotypic tests determine the actual mutations. While phenotyping is a more direct measure of drug resistance compared to genotyping, the technique is labor intensive and technically challenging.

The evolving understanding of the clinical significance of drug resistance has created interest in both HIV genotyping and phenotyping to identify active drug regimens in the following clinical settings:

- a. To determine the most effective salvage therapy in recipients with drug resistance.
- b. To confirm that antiviral drug failure is due to drug resistance and not patient noncompliance.
- c. To determine viral resistance at initial diagnosis of HIV infection.

## **2.0 Eligible Recipients**

### **2.1 General Provisions**

To be eligible, NCHC recipients must be enrolled on the date of service.

## **3.0 When the Procedure, Product, or Service Is Covered**

### **3.1 General Criteria**

NCHC covers procedures, products, and services related to this policy when they are medically necessary and

- a. the procedure, product, or service is individualized, specific, and consistent with symptoms or confirmed diagnosis of the illness or injury under treatment, and not in excess of the recipient's needs;
- b. the procedure, product, or service can be safely furnished, and no equally effective and more conservative or less costly treatment is available; **AND**
- c. the procedure, product, or service is furnished in a manner not primarily intended for the convenience of the recipient, the recipient's caretaker, or the provider.

### **3.2 Specific Criteria**

HIV Genotyping and Phenotyping are covered by the NC Health Choice Program when it is determined to be medically necessary because the following medical criteria are met. HIV genotyping or phenotyping may be considered medically necessary:

- a. in recipients who have failed a course of antiviral therapy or who have suboptimal viral load reduction; or
- b. in recipients with acute or recent infection for guiding treatment decisions; or
- c. in antiretroviral naive recipients entering treatment.

### **3.3 Other Medical Policy Guidelines**

U.S. Department of Health and Human Services (DHHS) treatment guidelines currently recommend resistance testing with acute onset of infection, regardless of whether therapy will be initiated, in order to ascertain whether or not drug-resistant virus was transmitted.

This recommendation is based, in part, on the consideration that transmitted drug resistance is thought to be fundamentally different from drug resistance acquired during treatment, both in its fitness (capacity to infect and replicate) and its persistence (does not revert to a minority species).

Areas with a relatively high prevalence of drug-resistant disease at diagnosis and at the time of initial treatment may find resistance testing helpful given that transmitted drug resistance is associated with a higher likelihood of virologic failure. The prevalence of transmitted drug resistance may be important in guiding treatment decisions. Several studies have estimated the prevalence of infection with virus resistant to at least one class of antiretroviral therapy among treatment naive patients enrolled in U.S.-based studies from 2000-2004 at 10-16%. In addition, prevalences as high as 24% in U.S. populations have been reported.

Because infection with drug-resistant virus may be fundamentally different in its course, and knowledge of the initial resistance pattern may decrease the incidence of virologic failure, the use of genotype or phenotype testing may be considered medically necessary in recent onset infection or, if a patient is entering care years after infection occurred, at the start of treatment.

## **4.0 When the Procedure, Product, or Service Is Not Covered**

### **4.1 General Criteria**

Procedures, products, and services related to this policy are not covered when

- a. the recipient does not meet the eligibility requirements listed in **Section 2.0**;
- b. the recipient does not meet the medical necessity criteria listed in **Section 3.0**;
- c. the procedure, product, or service unnecessarily duplicates another provider's procedure, product, or service; or
- d. the procedure, product, or service is experimental or investigational.

### **4.2 Specific Criteria**

HIV Genotyping and Phenotyping is not covered in the following situations:

- a. Drug susceptibility phenotype prediction using genotypic comparison to known genotypic/phenotypic database is considered investigational.
- b. Routine use of combined genotyping and phenotyping is considered investigational.

## **5.0 Requirements for and Limitations on Coverage**

### **5.1 Prior Approval**

Prior Approval Prior approval is not required for HIV Genotyping and Phenotyping.

## 6.0 Providers Eligible to Bill for the Procedure, Product, or Service

To be eligible to bill for procedures, products, and services related to this policy, providers shall

- a. meet NCHC qualifications for participation;
- b. be currently enrolled with NCHC; **AND**
- c. bill only for procedures, products, and services that are within the scope of their clinical practice, as defined by the appropriate licensing entity.

## 7.0 Additional Requirements

### 7.1 Compliance

Providers must comply with all applicable federal, state, and local laws and regulations, including the Health Insurance Portability and Accountability Act (HIPAA) and record retention requirements.

## 8.0 Policy Implementation/Revision Information

**Original Effective Date:** July 1, 2010

**Revision Information:**

Date	Section Revised	Change
July 1, 2010		Policy Conversion: Implementation of Session Law 2009-451, <b>Section 10.32 “NC HEALTH CHOICE/PROCEDURES FOR CHANGING MEDICAL POLICY.”</b>

## Attachment A: Claims-Related Information

Reimbursement requires compliance with all NCHC guidelines.

### A. Claim Type

Professional (CMS-1500/837P transaction)

Institutional (UB-04/837I transaction)

### B. Diagnosis Codes

Providers must bill the ICD-9-CM diagnosis codes(s) to the highest level of specificity that supports medical necessity.

### C. Procedure Code(s)

CPT Code(s)	Description
87900	Infectious agent drug susceptibility phenotype prediction using regularly updated genotypic bioinformatics
87901	Infectious agent genotype analysis by nucleic acid (DNA or RNA); HIV-1, reverse transcriptase and protease
87903	Infectious agent phenotype analysis by nucleic acid (DNA or RNA) with drug resistance tissue culture analysis, HIV-1; first through 10 drugs tested
+87904	Infectious agent phenotype analysis by nucleic acid (DNA or RNA) with drug resistance tissue culture analysis, HIV-1; each additional drug tested (List separately in addition to code for primary procedure)

### D. Modifiers

Providers are required to follow applicable modifier guidelines.

### E. Billing Units

The appropriate procedure code(s) used determines the billing unit(s).

### F. Place of Service

Inpatient Hospital, Outpatient Hospital and Office

### G. Co-payments

Co-payment(s) may apply to covered prescription drugs and services.

### H. Reimbursement

Providers must bill their usual and customary charges.