



# CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all plans administered by CIGNA Companies including plans administered by Great-West Healthcare, which is now a part of CIGNA.

**Subject Genotypic and Phenotypic Testing for HIV Drug Hypersensitivity and Resistance**

**Effective Date ..... 12/15/2010**  
**Next Review Date ..... 12/15/2011**  
**Coverage Policy Number ..... 0012**

## Table of Contents

Coverage Policy .....	1
General Background .....	2
Coding/Billing Information .....	6
References .....	7
Policy History.....	11

## Hyperlink to Related Coverage Policies

Pharmacogenetic Testing

### INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans as well as benefit plans formerly administered by Great-West Healthcare. Please note, the terms of a participant's particular benefit plan document [Group Service Agreement (GSA), Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a participant's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a participant's benefit plan document **always supercedes** the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable group benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. Proprietary information of CIGNA. Copyright ©2010 CIGNA

## Coverage Policy

**CIGNA covers genotype antiretroviral resistance testing (ART) assays as medically necessary for ANY of the following indications:**

- human immunodeficiency virus (HIV)-positive pregnant woman
- antiretroviral-naïve, chronically HIV-infected individual, prior to the initiation of treatment
- HIV-positive individual with failure or intolerance of the current drug regimen when a change in therapy is being considered
- newly diagnosed individual with acute HIV infection when the acquisition of a drug-resistant viral strain is suspected

**CIGNA covers phenotype ART assays as medically necessary for EITHER of the following indications:**

- HIV- positive individual with failure or intolerance of the current drug regimen when a change in therapy is being considered
- newly diagnosed individual with acute HIV infection when the acquisition of a drug-resistant viral strain is suspected

**CIGNA covers co-receptor tropism testing (i.e., Trofile™) as medically necessary for the determination of virus tropism prior to initiating a CCR5 antagonist (e.g., Maraviroc [Selzentry®]).**

**CIGNA covers HLA-B\*5701 haplotype testing as medically necessary in an HIV-positive individual prior to initiation of an abacavir-containing regimen (e.g. Ziagen<sup>®</sup>, Epzicom<sup>®</sup>, Trizivir<sup>®</sup>)**

**CIGNA does not cover antiretroviral resistance testing for any other indication, including but not limited to EITHER of the following, because such testing is considered experimental, investigational:**

- after the termination of antiretroviral treatment
- when viral load is maintained at an undetectable level on the current treatment regimen(s)

---

## **General Background**

The human immunodeficiency virus (HIV-1) replicates rapidly and demonstrates a high mutation rate with each replication cycle. Every mutation increases the potential for the development of drug-resistant virus strains. Additionally, human immunodeficiency virus persists within tissues throughout the body and likely sets off chain reactions of acute and chronic immune disturbances (Henry, 2006). Antiretroviral testing (ART) is utilized to determine the optimal initial antiretroviral regimen that can be used, or to determine if a patient may have a viral strain that is resistant to the current therapy regimen.

Pharmacotherapy selection and compliance are extremely important in the treatment of HIV-1. The optimal goal of antiretroviral therapy is to reduce plasma HIV-ribonucleic acid (RNA) to below detection by the most sensitive assay available (i.e., < 50 copies/ml) (Tsibris, 2009; Hammer, 2006). Sequential measurements of CD4 cell count and viral load at 4, 8–12, and 16–24 weeks, and regularly thereafter have been used to assess early response to antiretroviral therapy (Huffman, 2002; Hammer, 2006).

Resistance testing and HLA-B\*5701 typing are important laboratory tests that assist the clinician in designing the most effective and patient-specific antiretroviral regimen. When CCR5 antagonist therapy is being considered, co-receptor tropism testing is essential (Tsibris, 2009). Although viral suppression is the optimal goal of antiviral therapy, it may not be possible in perinatal infected infants and children. When it can be achieved there still exists the likelihood that genotypic (GT) or phenotypic (PT) resistance can emerge. Morbidity increases with known drug resistance.

### **Antiretroviral Resistance Testing (ART)**

Resistance to antiretroviral drugs remains an important limitation to successful HIV-1 therapy. Factors associated with the development of drug resistance include the use of serial monotherapy, suboptimal treatment regimens, lack of patient compliance, and initiation of therapy late in the course of HIV infection. Resistance testing can improve treatment outcomes for infected individuals (Hirsch, 2008). ART is of greatest value when performed before or within 4 weeks after drugs are discontinued. Because detectable resistant virus may persist in the plasma of some patients for longer periods of time, resistance testing beyond 4 to 6 weeks after discontinuation may still reveal mutations. However, the absence of detectable resistance in such patients must be interpreted with caution in designing subsequent antiretroviral regimens (U.S. Department of Health and Human Services [DHHS], 2009). Testing may include either a genotype or a phenotype measurement of the HIV-1 genome. These measurements are instrumental in establishing individually specific and effective drug treatment regimens based on the patient's specific viral load response. Both types of assays have been shown to provide reliable and reproducible measures of resistance, with certain caveats: accuracy depends on the experience of the interpreter and laboratory; results from the available tests are not interchangeable, and clinically relevant thresholds of resistance have not been fully defined (Demeter, 2001). Technical issues can sometimes prevent successful resistance testing when plasma HIV RNA levels are less than 500–1000 copies/mL (Tsibris, 2009). Despite these limitations, ART has become a standard of care in HIV medicine and its use for selected individuals with HIV-1 positivity is supported by several national and international professional societies/organizations.

Genotypic and phenotypic assay results are complementary to each other, both being equally important. The processing of these assays should be conducted within certified laboratories and the interpretation of the data received from these tests should be conducted by an expert in the treatment and management of HIV-infected

patients (Sen, 2006). Recommendations by the U.S. Department of Health and Human Services regarding drug resistance testing are outlined in the Professional Societies/Organization section below.

**Genotype Assays:** These assays detect drug-resistant mutations that are present in the relevant viral genes. Genotypic assays involve sequencing of the reverse transcriptase and protease genes to detect mutations that are known to confer drug resistance. A genotypic assay that assesses mutations in the integrase gene is also available (DHHS, 2009). Genotypic resistance assays are generally preferred for antiretroviral-naïve patients. Currently available genotypic assays require a minimum viral load in the range of 500 to 2000 copies/mL, and generally require 2 weeks or less for results. Advantages include a rapid turn-around time and wide availability. Additionally, the appearance of resistant mutations may precede change in phenotype. Disadvantages: genotype may not correlate with phenotype, genotype assays may require “expert interpretation”, possible failure to detect minor species, and genotypes are unable to access mutational interactions. These assays are generally preferred for antiretroviral-naïve patients (Tsibris, 2009).

**Phenotype Assays:** These assays measure the ability of a virus to grow in different concentrations of antiretroviral drugs. Phenotypic assays report changes in sensitivities in the presence or absence of drugs and can be useful in the interpretation of more complex resistance patterns. Virtual phenotypic resistance assays make use of a library of known matched genotypes and empirically tested phenotypes to predict a patient's phenotype based on known genotype results (Tsibris, 2009). Phenotypic assays have a minimum viral load requirement of 500 to 1000 copies/mL, and generally require 3 to 5 weeks for results. Advantages include the direct measure of viral drug susceptibility, and the ability to assess net effect of mutational interactions and cross-resistance patterns. Disadvantages: cost, longer turn-around time, the possible failure to detect minor species, and the appropriate cut-offs are not defined for all drugs.

#### **U.S. Food and Drug Administration (FDA)**

Several assay tests are available that have been approved for use by the FDA. Genotype tests include the ABI Gene Sequencing; TrueGene™ HIV Genotyping GeneKit (Visible Genetics, Ontario, Canada); Murex LiPA HIV-1 RT; HIV-1 GeneSeek™ Test; ViroSeq HIV-1 Genotyping System (Applied Biosystems, Foster City, CA); and the Affymetric GeneChip® HIV PRT Assay. Examples of phenotype assay tests include: the PhenoSense™ HIV (ViroLogic, South San Francisco, CA) and Antivirogram (Virco, Mechlin, Belgium).

#### **Literature Review**

Evidence from several multi-center randomized prospective and cohort trials involving >8800 individuals with HIV-1 positivity suggest genotypic and phenotypic drug resistance assays may be used to enhance HIV treatment (Hales, 2006; NIH, 2006; Dunn, 2005; Foster, 2005; Ross, 2005; Watts, 2004; Durant, 2000). Treatment adjustments based on the results of antiretroviral resistance testing led to statistically significant improvements in patient outcomes and mortality. These studies support the use of phenotyping and genotyping to adjust antiretroviral treatment regimens in response to treatment failure or viral change.

**Co-receptor Tropism Testing:** Phenotypic assays predict which co-receptor the HIV virus uses to enter a cell (also known as tropism). The virus can enter through the CCR5 co-receptor, the CXCR4 co-receptor, or both (i.e., dual tropism). CCR5 is used almost exclusively for entry in early infection, but CXCR4-using viral populations emerge in approximately 50% of patients during the first 5 years of infection. The appearance of CXCR4-using virus is associated with a faster rate of CD4<sup>+</sup> T-cell loss, rapid disease progression, and increased rate of development of AIDS and death (Tsibis, 2009).

Predicting the tropism of the virus is important in the determination of an individual's response to the class of HIV drugs known as CCR5 antagonists (Braun and Weismann, 2007). Maraviroc (Selzentry®, Pfizer Labs, New York, NY), is a CCR5 co-receptor antagonist and is the only oral entry inhibitor indicated for use in combination with other antiretroviral drugs for the treatment of adults infected with only CCR5-trophic HIV-1. The safety and efficacy of Selzentry® have not been established in pediatric patients (Pfizer, 2010).

Trofile™ (Monogram® Coreceptor Tropism, Monogram Biosciences, South San Francisco, CA) is currently the only commercially available diagnostic assay that can determine whether an individual patient's human immunodeficiency virus (HIV-1) infection is CCR5, CXCR4, or both. Testing is by polymerase chain reaction (PCR) amplification and viral culture (LabCorp, 2010). Viral load should be at least 1000 copies/ml to determine viral tropism (Monogram Biosciences, 2010).

## Literature Review

Whitcomb et al. (2007) conducted a validation study of the Trofile assay which included the assay's accuracy, reproducibility, specificity and sensitivity. Envelopes from 287 viruses were included in the study. In determining the accuracy of the assay, 38 HIV-1 representing six different subtypes were tested. All isolates had been previously documented as R5, X4, or dual tropic. The Trofile test matched 100% of the expected tropism assessments. Reproducibility was evaluated using the standard practice of pairwise comparison among multiple replicates. In the analysis, 100% of the 1,140 determinations were concordant. Amplification sensitivity rates were as follows: an amplification success rate of 90% was obtained at an average viral load of 680 copies/ml, 95% positive amplification was obtained at an average viral load of 1,430 copies/ml, and among all samples with a viral load greater than 1,000 copies/ml, 95% were successfully amplified. The sensitivity of the detection of minor variants was 100% detectable when present at a frequency of 10% and 85% when the frequency was 5%. No false-positives or false-negatives were reported. According to the authors, the test can be completed in two to three weeks. This study suggests that Trofile is an accurate measure of HIV-1 coreceptor tropism.

**HLA-B\*5701 Haplotype Testing:** Hypersensitivity reaction occurs in 5% to 8% of HIV-infected individuals who initiate therapy with abacavir (Ziagen<sup>®</sup>, Epzicom<sup>®</sup>, Trizivir<sup>®</sup>), which is a commonly prescribed nucleoside reverse-transcriptase inhibitor with potent antiviral activity against HIV (Mallal, 2002). This multi-system reaction, which can be life-threatening, has been strongly associated with the presence of the HLA-B\*5701 haplotype (i.e., gene allele). The incidence of hypersensitivity reaction varies among populations; about 6%–8% in Caucasians and 2%–3% in individuals of African ethnicity. In a double blind, randomized controlled trial of 1956 HIV-1 infected individuals, the prevalence of HLA-B\*5701 was 5.6% (n=109). Screening eliminated immunologically confirmed hypersensitivity reaction and had a negative predictive value of 100% and a positive predictive value of 47.9% (Mallal, 2008).

More than 90% of reactions occur within six weeks of initiating therapy (Mallal, 2002). In addition, rechallenge with abacavir-containing drug regimens after discontinuation of the drug can cause an immediate and potentially fatal reaction. According to prescribing information, and recommended by the U.S. Department of Health and Human Services all individuals being considered for an abacavir-containing regimen should first undergo HLA-B\*5701 testing (SmithGlaxoKline, 2010; DHHS, 2009). Individuals who test positive for this allele should not receive therapy with abacavir-containing treatment regimens, including Ziagen<sup>®</sup> (abacavir sulfate), Epzicom<sup>®</sup> (abacavir plus lamivudine), or Trizivir<sup>®</sup> (abacavir, lamivudine, and zidovudine). Polymerase chain reaction (PCR)/sequence-specific oligonucleotide probe methods are established methods for testing.

## Professional Societies/Organizations

**International Acquired Immune Deficiency Syndrome (AIDS) Society–U.S.A. Panel, (Hirsch, 2008):** The International AIDS Society-U.S.A. panel made the following recommendations for antiretroviral drug resistance testing:

Testing is recommended before initiation of therapy in primary (acute and early) infection, at first evaluation of chronic HIV-1 infection and with treatment initiation for chronic HIV-1 infection.

- Testing is recommended in antiretroviral-treated patients with treatment failure
- Testing is recommended before initiation of treatment in pregnancy.

The panel also recommended that samples to be tested for drug resistance should contain at least 500 HIV-1 RNA copies/ml and the sample should be obtained while the patient is receiving the failing regimen, if possible (Hirsch, 2008).

**U.S. Department of Health and Human Services (DHHS):** Resistance testing continues to be an important component of optimizing drug selection after treatment failure. Transmission of drug-resistant HIV strains has been well-documented and has been associated with suboptimal virologic response to initial antiretroviral therapy in some patients.

Recommendations for drug resistance testing for adults and adolescents (2009):

- HIV drug testing is recommended for persons with HIV infection when they enter into care regardless of whether therapy will be initiated immediately or deferred. If therapy is deferred, repeat testing at the time of antiretroviral therapy should be considered.
- Genotypic assays are preferred for antiretroviral-naïve persons.

- HIV drug resistance testing should be performed to assist in the selection of active drugs when changing antiretroviral regimens in cases of virologic failure and HIV RNA levels >1000 copies/ml. In persons with >500 copies/ml but < 1000 copies/ml, testing may be unsuccessful but should be considered.
- Drug resistance testing should also be performed when managing suboptimal viral load reduction.
- When there is virologic failure, drug resistance testing should be performed while the patient is taking the antiretroviral drug or within four weeks of discontinuing therapy.
- Genotypic testing is recommended as the preferred resistance testing to guide therapy in antiretroviral naïve patients and in patients with suboptimal virologic responses or virologic failure while on first or second regimens.
- Addition of phenotypic testing to genotypic testing is generally preferred for persons with known or suspected complex drug resistance mutation patterns, particularly to protease inhibitors

Recommendations for co-receptor tropism testing:

- Co-receptor tropism assays should be used when considering the use of a CCR5 antagonist.
- Co-receptor tropism assays might also be considered for patients with virologic failure while receiving CCR5 antagonist.

Recommendations for HLA-B\*5701 testing:

- To reduce the risk of hypersensitivity reaction, the Panel recommends HLA-B\*5701 testing before starting patients on an abacavir-containing regimen.

Recommendations for drug resistance testing for children (2010):

- Antiretroviral drug resistance testing is recommended prior to initiation to therapy in all treatment-naïve children
- Antiretroviral drug resistance testing is recommended prior to changing therapy for treatment failure
- Resistance assays should be obtained when patients have a viral load of greater than 1000copies/ml and are still on the failing regimen or within four weeks of discontinuation of the regimen.
- The presence of viral resistance to a particular drug suggests the drug is unlikely to suppress viral replication.
- The absence of resistance to a drug does not ensure that its use will be successful, particularly if it shares cross-resistance with drugs previously used. Thus, the history of past use of antiretroviral agents as well as resistance testing is important in making decisions regarding the choice of new agents for patients with virologic failure.
- Consultation with a specialist in pediatric HIV infection is recommended for interpretation of resistance assays when considering starting or changing an antiretroviral regimen in a pediatric patient.

Recommendations for co-receptor tropism testing:

- Co-receptor tropism assays should be used when considering the use of a CCR5 antagonist.
- Co-receptor tropism assays might also be considered for patients with virologic failure while receiving CCR5 antagonist.

Recommendations for HLA-B\*5701 testing:

- HLA-B\*5701 testing should be performed prior to initiating abacavir-based therapy

Recommendations for drug resistance testing for pregnant women (2009):

- The goal of antiretroviral therapy in pregnant women is to reduce plasma HIV RNA to provide appropriate maternal therapy and to prevent mother-to-child transmission of HIV. Genotypic resistance testing is recommended for all pregnant women prior to initiation of therapy and for those entering pregnancy with detectable HIV RNA levels while on therapy. Optimal prevention of perinatal transmission may require initiation of antiretroviral therapy before results of resistance testing are available.
- Women who do not show an appropriate virologic response to their antiretroviral regimen require repeat antiretroviral drug resistance testing, as well as consultation with a clinician experienced in HIV treatment, to guide changes in antiretroviral therapy.
- Phenotypic testing may provide additional information in those found to have complex drug resistance mutation patterns, particularly to protease inhibitors

- Testing for HLA-B\*5701 should be done before starting abacavir-based therapy

Recommendations for drug resistance testing for the neonate (2008):

- The optimal prophylactic regimen for newborns of women with antiretroviral resistance is unknown. Therefore, antiretroviral prophylaxis for an infant born to a woman with known or suspected drug resistance should be determined in consultation with a pediatric HIV specialist, preferably before delivery.

The HHS guidelines do not recommend drug resistance testing when it has been > than four weeks after discontinuation of drugs or when the plasma viral load is <500 copies/ml.

**British HIV Association (BHIVA):** On behalf of the BHIVA (2008), Gazzard et al. noted that resistance testing should be performed for treatment-naïve patients. Following resistance testing at the time of diagnosis, repeat testing is not routinely recommended prior to starting therapy, although it should be considered in selected persons who may have experienced re-infection. Genotypic resistance tests are recommended in drug-naïve persons, as they are more sensitive and cost-effective than phenotypic tests for the detection of transmitted drug resistance. Resistance testing is recommended in all patients experiencing virological failure while on treatment and changes in therapy should be guided by the results of resistance testing in these patients. To be informative, resistance testing should be performed on samples taken while the patient is on therapy. Regarding tropism testing, Gerreti and Mackie (2009) note that genotypic testing is the preferred option. In drug-naïve patients, tropism testing may be considered prior to starting first-line highly active antiretroviral therapy (HAART). Detection of any CXCR4-using virus at any time should be considered long-lasting.

**Infectious Disease Society of America:** The HIV Medicine Association of this Society (Aberg, 2009) noted the following:

- All HIV-infected patients should have a genotypic resistance test performed at baseline regardless of whether antiretroviral therapy will be initiated
- Because drug-resistant virus can be transmitted from one person to another, all patients should be assessed for transmitted drug resistance with an HIV genotype test upon initiation of care.
- If therapy is deferred, repeat testing at the time of antiretroviral therapy initiation should be considered because of the potential for superinfection.
- The results of a baseline resistance assay may be useful in guiding therapy, even if treatment is deferred for many years
- Resistance testing is also indicated for patients who are experiencing virologic failure, to guide modification of antiretroviral therapy
- Tropism testing should be performed prior to the initiation of a CCR5 antagonist antiretroviral drug
- HIV-infected infants should undergo HIV resistance testing
- The use of HIV resistance testing is recommended prior to initiating antiretroviral treatment in all treatment naive HIV-infected infants or children
- HLA-B\*5701 testing should be performed prior to initiating abacavir therapy to reduce the risk of a hypersensitivity reaction

## Summary

Antiretroviral resistance testing (ART) using genotype and phenotype assays has been shown to be an effective way of detecting drug-resistant strains of the human immunodeficiency virus (HIV-1) and is considered a standard of care for selected individuals. These assays allow for individualized treatment plans to be determined. When treatment failure occurs and/or viral resistance is suspected, the use of ART can also assist in determining which subsequent medications may be effective in treating patients with HIV-1. Co-receptor tropism testing is also considered a standard of care to predict the co-receptor of the HIV-1 virus. All individuals for whom treatment with an abacavir-containing regimen is considered should undergo HLA-B\*5701 haplotype testing.

---

## Coding/Billing Information

**Note:** This list of codes may not be all-inclusive.

**Covered when medically necessary:**

<b>CPT<sup>®*</sup> Codes</b>	<b>Description</b>
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 regions
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)
87906	Infectious agent genotype analysis by nucleic acid (DNA or RNA); HIV-1, other region (eg, integrase, fusion) (Code effective 01/01/2011)
87999 <sup>†</sup>	Unlisted microbiology procedure

<sup>†</sup>**Note:** Covered when medically necessary and when used to report co-receptor tropism testing (i.e., Trofile<sup>™</sup>).

<b>ICD-9-CM Diagnosis Codes</b>	<b>Description</b>
042	Human immunodeficiency virus [HIV] disease
079.53	Human immunodeficiency virus, type 2 [HIV-2], in conditions classified elsewhere and of unspecified site
795.71	Nonspecific serologic evidence of human immunodeficiency virus [HIV] inconclusive human immunodeficiency virus [HIV] test (adult) (infant)
V08	Asymptomatic human immunodeficiency virus (HIV) infection status

**\*Current Procedural Terminology (CPT<sup>®</sup>) © 2010 American Medical Association: Chicago, IL.**

---

## References

1. Aberg JA, Kaplan JE, Libman H, Emmanuel P, Anderson JR, Stone VE, et al. Primary care guidelines for the management of persons infected with immunodeficiency virus: 2009 update by the HIV medicine Association of the Infectious Diseases Society of America. Clin Infect Dis. 2009 Sep 1;49(5):651-81.
2. Anastos K, Barren Y, Cohen MH, Greenblatt RM, Minkoff H, Levine A, et al., The prognostic importance of changes in CD4+ cell count and HIV-1 RNA level in women after initiating highly active antiretroviral therapy. Ann Intern Med. 2004 Feb;140(4):256-64.
3. Baxter JD, Mayers DL, Wentworth DN, Neaton JD, Hoover ML, Winters MA, et al. A randomized study of antiretroviral management based on plasma genotypic antiretroviral resistance testing in patients failing therapy. CPCRA 046 study team for the Terry Beinr community programs for clinical research on AIDS. AIDS. 2000;14(9):F83-93.
4. Braun P, Weismann F. Phenotypic assays for the determination of coreceptor tropism in HIV-1 Infected individuals. Eur J Med Res, 2007 Oct 15;12(9):463-72.
5. British HIV Association. Published and approved guidelines. Accessed Oct 2010. Available at URL address: <http://www.bhiva.org/PublishedandApproved.aspx>
6. Centers for Disease Control and Prevention (CDC). Estimates of new HIV infections in the United States. Aug 2008. Accessed Oct 2010. Available at URL address: <http://www.cdc.gov/hiv/topics/surveillance/resources/factsheets/incidence.htm>

7. Centers for Medicare & Medicaid Services (CMS). SMDL #01-005: Letter to state Medicaid directors. Jan 2001. Accessed Oct 2010. Available at URL address: <http://www.cms.hhs.gov/smdl/downloads/smdl010801.pdf>
8. Chessman D, Kostenko L, Lethborg T, Purcell AW, Williamson NA, Chen Z, et al. Human leukocyte antigen class I-restricted activation of CD8+ T cells provides the immunogenetic basis of systemic drug hypersensitivity. *Immunity*. 2008 Jun;28(6):822-32.
9. Coffey S, Bacon O, Volberding P, editors. HIV InSite knowledge base. Accessed Oct 14, 2010. Available at URL address: <http://hivinsite.ucsf.edu/InSite?page=KB>
10. Cohen CJ, Hunt S, Sension M, Farthing C, Conant M, Jacobson S, et al. A randomized trial assessing the impact of phenotypic resistance testing of antiretroviral therapy. *AIDS*. 2002;16(4):579-88.
11. D'Aquila RT, Johnson VA, Welles SL, Japour AJ, Kuritzkes DR, DeGruttola V, et al. Zidovudine resistance and HIV-1 disease progression during antiretroviral therapy. *Ann Intern Med*. 1995;122:401-8.
12. Deeks SG, Hellman NS, Grant RM, Parkin NT, Petropoulos CJ, Becker M, et al. Novel four-drug salvage treatment regimens after failure of a human immunodeficiency virus type 1 protease inhibitor-containing regimen: antiviral activity and correlation of baseline phenotypic drug susceptibility with virologic outcome. *J Infect Dis*. 1999;179:1375-81(June 179 (6)).
13. del Rio C. Current concepts in antiretroviral therapy failure. *Top HIV Med*. 2006;14(3):102-6.
14. Demeter L, Haubrich R. Phenotype and genotype resistance assays: methodology, reliability and interpretations. *J Acquir Immune Defic Syndr*. 2001 Mar 1;26 Suppl 1:S3-9.
15. Descamps D, Flandre P, Calez V, Peytavin G, Meiffredy V, Collin G, et al. Mechanisms of virologic failure in previously untreated HIV- infected patients from a trial of induction-maintenance therapy. *JAMA*. 2000;283(2):205-11.
16. Dunn DT, Green H, Loveday C, Rinehart A, Pillay D, Fisher M, et al. A randomized controlled trial of the value of phenotypic testing in addition to genotypic testing for HIV drug resistance. *J Acquir Immune Defic Syndr*. 2005 Apr 15;38(5):553-9.
17. ECRI Institute. Human immunodeficiency virus (HIV) drug-resistance testing to guide choice of antiretroviral regimen. Plymouth Meeting (PA): ECRI Institute Health Technology Assessment Information Service;2004 July. 60 p. (Evidence Report: no. 111). Available at URL address: <http://www.ecri.org>.
18. ECRI Institute. Hotline Response [database online]. Plymouth Meeting (PA): ECRI Institute;2008 Jan 29. Human immunodeficiency virus drug resistance testing to guide choice of antiretroviral regimen,2008 Jan 29. Available at URL address: <http://www.ecri.org>.
19. Foster C, Lyall EGH. Children with HIV: improved mortality and morbidity with combination antiretroviral therapy. *Curr Opin Infect Dis*. 2005 Jun;18(3):253-9.
20. Gallant JE. Antiretroviral drug resistance and resistance testing. *Top HIV Med*. 2005;13(5):138-42.
21. GlaxoSmithKline. Prescribing Information: Epzicom<sup>®</sup> (abacavir sulfate plus lamivudine). Research Triangle Park, NC: GlaxoSmithKline, 2004. Accessed Oct 2010. Available at URL address: <http://www.epzicom.com/>
22. GlaxoSmithKline. Prescribing Information: Ziagen<sup>®</sup> (abacavir sulfate). Research Triangle Park, NC: GlaxoSmithKline, 2004. Accessed Oct 2010. available at URL address: [http://us.gsk.com/products/assets/us\\_ziagen.pdf](http://us.gsk.com/products/assets/us_ziagen.pdf)

23. GlaxoSmithKline. Prescribing Information: Trizivir® (abacavir sulfate, lamivudine, and zidovudine). Research Triangle Park, NC GlaxoSmithKline. Accessed Oct 2010. Available at URL address: [http://us.gsk.com/products/assets/us\\_trizivir.pdf](http://us.gsk.com/products/assets/us_trizivir.pdf)
24. Green H, Gibb DM, Compagnucci A, Giacomet V, de Rossi A, Harper L, et al. A randomized controlled trial of genotypic HIV drug resistance testing in HIV-1-infected children: the PERA (PENTA 8) trial. *Antivir Ther.* 2006;11(7):857-67.
25. Hales G, Birch C, Crowe S, Workman C, Hoy JF, Law MG, et al. A randomized trial comparing genotypic and virtual phenotypic interpretation of HIV drug resistance: The CREST Study. *PLoS Clin Trials.* 2006;1(3):e18. Accessed Nov 18, 2009. Available at URL address: <http://clinicaltrials.plosjournals.org/perlserv/?request=get-document&doi=10.1371/journal.pctr.0010018>
26. Hammer SM, Saag MS, Schechter M, Montaner JSG, Schooley RT, Jacobsen DM, et al. Treatment for adult HIV infection. *JAMA.* 2006;296(7):827-43.
27. Hammer SM, Eron JJ, Reiss P, Schooley RT, Thompson MA, Walmsley S, et al. Antiretroviral treatment of adult HIV infection: 2008 recommendations of the International AIDS Society-USA panel. *JAMA.* 2008 Aug 6;300(5):555-70.
28. Haubrich RH, Kemper CA, Hellmann NS, Keiser PH, Witt MD, Tilles JG et al. A randomized, prospective study of phenotype susceptibility testing versus standard of care to manage antiretroviral therapy: CCTG 575. *AIDS.* 2005;19:295-302.
29. Henry WK, Tebas P, Lane HC. Explaining, predicting, and treating HIV-associated CD4 cell loss after 25 years still a puzzle. *JAMA.*2006;296(12):1523-5.
30. Hirsch HH, Drechsler H, Holbro A, Hamy F, Sendi P, Petrovic K, et al. Genotypic and phenotypic resistance testing of HIV-1 in routine clinical care. *Eur J Clin Microbiol Infect Dis.*2005;24:733-8.
31. Hirsch MS, Gunthard HF, Schapiro JM, Brun-Vezinet F, Clotet B, Hammer SM, et al. Antiretroviral drug resistance testing in adult HIV-1 infection: 2008 recommendations of an International AIDS Society-USA panel. *Clin Infect Dis.* 2008 Jul 15;47(2):266-85.
32. Lawrence J, Mayers DL, Hullsiek KH, Collins G, Abrams DI, Reisler RB, et al. Structured treatment interruption in patients with multidrug-resistant human immunodeficiency virus. *NEJM.* 2003 Aug;349(9):837-46.
33. Little SJ, Holte S, Routy J-P, Daar ES, Markowitz M, Collier AC, et al. Antiretroviral-drug resistance among patients recently infected with HIV. *N Engl J Med.* 2002 Aug;347(6):385-9.
34. Lyons FE, Coughlan S, Byrne CM, Hopkins SM, Hall WW, Mulcahy FM. Emergence of antiretroviral resistance in HIV-positive women receiving combination antiretroviral therapy in pregnancy. *AIDS.* 2005;19:63-7.
35. Mallal S, Nolan D, Witt C, Masal G, Martin AM, Moore C, et al. Association between presence of HLA-B\*5701, HLA-DR7, and HLA-DQ3 and hypersensitivity to HIV-1 reverse transcriptase inhibitor abacavir. *Lancet.* 2001 Mar 2;359(9308):727-32.
36. Mallal S, Phillips E, Carosi G, Molina JM, Workman C, Tomazic J, et al. HLA-B\*5701 screening for hypersensitivity to abacavir. *N Eng J Med.* 2008 Feb 7;358(6):568-79.
37. Monogram Biosciences. Trofile™ co-receptor tropism assay sets the standard for identifying tropism. Accessed Oct 2010. Available at URL address: <http://www.trofileassay.com/>
38. Mylonakis E, Paliou M, Rich JD. Plasma viral load testing in the management of HIV infection. *Am Fam Physician.* 2001;63:483-90,495-6.

39. National Institutes of Health (NIH). Clinical Alert: International HIV/AIDS trial finds continuous antiretroviral therapy superior to episodic therapy. Updated January 2006. Accessed Oct 14, 2010. Available at URL address: [http://www.nlm.nih.gov/databases/alerts/aids\\_smart.html](http://www.nlm.nih.gov/databases/alerts/aids_smart.html)
40. Nettles RE, Kieffer TL, Kwon P, Monie D, Han Y, Parsons T, et al. Intermittent HIV-1 viremia (blips) and drug resistance in patients receiving HAART. *JAMA*. 2005;293(7):817-29.
41. New York State Department of Health AIDS Institute's Clinical Guidelines Development Program. HIV Clinical Resource. © New York State Department of Health AIDS Institute, 2000-2010. Accessed Nov 5, 2010. Available at URL address: <http://www.hivguidelines.org/>
42. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. December 1, 2009; 1-161. Available at <http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>. Accessed Oct 14, 2010.
43. Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children. Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection. August 16, 2010; pp 1-219. Available at <http://aidsinfo.nih.gov/ContentFiles/PediatricGuidelines.pdf>. Accessed Oct 14, 2010.
44. Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States. May 24, 2010; pp 1-117. Available at <http://aidsinfo.nih.gov/ContentFiles/PerinatalGL.pdf>. Accessed Oct 14, 2010.
45. Panidou ET, Trikalinos TA, Ioannidis JPA. Limited benefit of antiretroviral resistance testing in treatment-experienced patients: a meta-analysis. *AIDS*. 2004;18:2153-61.
46. Pfizer Labs. Prescribing Information: Selzentry® (maraviroc). New York, NY. Pfizer labs. Accessed Oct 2010. Available at URL address: <http://selzentry.com>
47. Russ L, Boulme' R, Fusco G, Scarsella A, Florance A. Comparison of HIV Type-1 protease inhibitor susceptibility results in viral samples analyzed by phenotypic drug resistance assays and by six resistance algorithms: an analysis of a subpopulation of the CHORUS Cohort. *AIDS Res Hum Retroviruses*. 2005 Aug;21(8):696-701.
48. Sen S, Tripathy SP, Paranjape RS. Antiretroviral drug resistance testing. *J Postgrad Med*. 2006;52:187-3.
49. Tsibris AMN, Hirsch MS. Antiretroviral therapy for human immunodeficiency virus infection. In: Mandell GL, Bennett JE, Dolin R, editors. *Mandell, Douglas & Bennett's Principles and practices of infectious diseases*, 7<sup>th</sup> ed. Philadelphia, PA: Churchill Livingstone, 2009.
50. U.S. Department of Health and Human Service. HIV basics. Accessed Oct 14, 2010. Available at URL address: [www.aids.gov](http://www.aids.gov)
51. U.S. Food and Drug Administration. Center for Biologics Evaluation and Research. Devices. Accessed Oct 14, 2010. Available at URL address: <http://www.fda.gov/cber/devices.htm>
52. Volberding. Cohorts, trials and evidence: expanding our confidence in guidelines for antiretroviral testing. *Ann Intern Med*. 2009 Jul 21;151(2): 135-6.
53. Watts DH, Balasubramanian R, Maupin RT, Delke I, Dorenbaum A, Fiore S, et al. Maternal toxicity and pregnancy complications in human immunodeficiency virus-infected women receiving antiretroviral therapy: PACTG 316. *Am J Obstet Gynecol*. 2004 Feb;190(2):506-16.

54. Whitcomb, JM, Huang W, Fransen S, Limoli K, Toma J, Wrin T, et al. Development and characterization of a novel single-cycle recombinant-virus assay to determine human immunodeficiency virus type 1 coreceptor tropism. *Antimicrob Agents Chemother.* 2007 Feb;51(2):566-75.
55. Yeni PG, Hammer SM, Carpenter CCJ, Scott M, Cooper D, Charles CJ, et al. Antiretroviral treatment for adult HIV infection in 2002, updated recommendations of the International AIDS Society–USA Panel. *JAMA.* 2002;288:222-35.
56. Zhang J, Rhee S-Y, Taylor J, Shafer RW. Comparison of the precision and sensitivity of the Antivirogram and PhenoSense HIV drug susceptibility assays. *J Acquir Immune Defic Syndr.* 2005;38:439-44.
57. Zolopa AR, Lazzeroni LC, Rinehart A, Vezinet FB, Clavel F, Collier A, et al. Accuracy, precision, and consistency of expert HIV Type 1 genotype interpretation: an international comparison (The GUESS Study). *Clin Infect Dis.* 2005 Jul 1;41(1):92-9. Epub 2005 May 24.

---

## Policy History

<b>Pre-Merger Organizations</b>	<b>Last Review Date</b>	<b>Policy Number</b>	<b>Title</b>
CIGNA HealthCare	1/15/2008	0012	Genotypic and Phenotypic Testing for HIV Drug Resistance

“CIGNA” and the “Tree of Life” logo are registered service marks of CIGNA Intellectual Property, Inc., licensed for use by CIGNA Corporation and its operating subsidiaries. All products and services are provided exclusively by such operating subsidiaries and not by CIGNA Corporation. Such operating subsidiaries include Connecticut General Life Insurance Company, CIGNA Behavioral Health, Inc., Intracorp, and HMO or service company subsidiaries of CIGNA Health Corporation and CIGNA Dental Health, Inc. In Arizona, HMO plans are offered by CIGNA HealthCare of Arizona, Inc. In California, HMO plans are offered by CIGNA HealthCare of California, Inc. and Great-West Healthcare of California, Inc. In Connecticut, HMO plans are offered by CIGNA HealthCare of Connecticut, Inc. In North Carolina, HMO plans are offered by CIGNA HealthCare of North Carolina, Inc. In Virginia, HMO plans are offered by CIGNA HealthCare Mid-Atlantic, Inc. All other medical plans in these states are insured or administered by Connecticut General Life Insurance Company.

Connecticut General Life Insurance Company has acquired the business of Great-West Healthcare from Great-West Life & Annuity Insurance Company (GWLA). Certain products continue to be provided by GWLA (Life, Accident and Disability, and Excess Loss). GWLA is not licensed to do business in New York. In New York, these products are sold by GWLA’s subsidiary, First Great-West Life & Annuity Insurance Company, White Plains, N.Y.