Title

HIV Testing
CD4 counts, Viral load testing and other HIV tests
Gamma interferon blood test
For lab testing for HIV Tropism, see policy #008

When services are covered for commercial products (excluding Medicare HMO Blue and Medicare PPO Blue)

We cover the following:

- **HIV tests** (including ELISA, Western Blot, and rapid HIV-1 Antibody) when HIV testing is done to diagnose HIV.
- **HIV testing during pregnancy**[3] (see billing guideline #255, obstetrical services)
- **FDA-approved viral load tests** for monitoring disease progression, for assessing response to therapy, and if clinically indicated. [1,4]
- **CD4 counts** for assessment of disease status and response to therapy
- **HIV genotyping or phenotyping** in patients failing a course of antiviral therapy or have suboptimal viral load reduction.[5, 8,11, 12]
- **HIV genotyping or phenotyping** in patients with acute or recent infection for guiding treatment decisions.[12] ***Coverage effective 3/09.***
- **HIV genotyping or phenotyping** in antiretroviral naïve patients entering treatment.[12] ***Coverage effective 3/09.***
- **Baseline HIV genotyping** is recommended for patients with acute HIV or recent infection.[9,10]

We cover **gamma interferon blood test to diagnose latent tuberculosis infection** in patients considered at high risk for latent tuberculosis infection, including but not limited to HIV-infected patients and intravenous drug users.[7]

When services are not covered for commercial products (excluding Medicare HMO Blue and Medicare PPO Blue)

We do not cover:

- **Viral load tests** not approved by the FDA.[4]

We do not cover **viral load testing** for predicting maternal-fetal transmission of HIV[1, 4] because it is considered investigational as it does not meet our Medical Technology Assessment Guidelines, #350.

We do not cover routine use of combined **HIV genotyping and phenotypic testing** [5, 11, 12], because it is considered investigational as it does not meet our Medical Technology Assessment Guidelines, #350.

We do not cover **drug susceptibility phenotype prediction using genotypic comparison to known genotypic/phenotypic database**[6, 11,12], because it is considered investigational as it does not meet our Medical Technology Assessment Guidelines, #350.

When services are covered for Medicare HMO Blue and Medicare PPO Blue

We cover **standard and FDA-approved diagnostic HIV testing** for our Medicare HMO Blue and Medicare PPO Blue members in accordance with CMS guidelines, when there is a strong clinical suspicion supported by **one or more** of the following clinical findings: [13]

1. The patient has a documented, otherwise unexplained, AIDS-defining or AIDS-associated opportunistic infection.
2. The patient has another documented sexually transmitted disease which identifies significant risk of exposure to HIV and the potential for an early or subclinical infection.
3. The patient has documented acute or chronic hepatitis B or C infection that identifies a significant risk of exposure to HIV and the potential for an early or subclinical infection.
4. The patient has a documented AIDS-defining or AIDS-associated neoplasm.
5. The patient has a documented AIDS-associated neurologic disorder or otherwise unexplained dementia.
6. The patient has another documented AIDS-defining clinical condition, or a history of other severe, recurrent, or persistent conditions which suggest an underlying immune deficiency (for example, cutaneous or mucosal disorders).
7. The patient has otherwise unexplained generalized signs and symptoms suggestive of a chronic process with an underlying immune deficiency (for example, fever, weight loss, malaise, fatigue, chronic diarrhea, failure to thrive, chronic cough, hemoptysis, shortness of breath, or lymphadenopathy).
8. The patient has otherwise unexplained laboratory evidence of a chronic disease process with an underlying immune deficiency (for example, anemia, leukopenia, pancytopenia, lymphopenia, or low CD4+ lymphocyte count).
9. The patient has signs and symptoms of acute retroviral syndrome with fever, malaise, lymphadenopathy, and skin rash.
10. The patient has documented exposure to blood or body fluids known to be capable of transmitting HIV (for example, needlesticks and other significant blood exposures) and antiviral therapy is initiated or anticipated to be initiated.
11. The patient is undergoing treatment for rape. (HIV testing is a part of the rape treatment protocol.)

We cover both **standard and FDA-approved rapid HIV screening testing** in accordance with CMS guidelines for our Medicare HMO Blue and Medicare PPO members for the following indications: [14]

Effective 12/8/09

1. Annual voluntary HIV screening at increased risk for HIV infection per USPSTF guidelines:
   - Men who have had sex with men after 1975;
   - Men and women having unprotected sex with multiple (more than one) partners;
   - Past or present injection drug users;
   - Men and women who exchange sex for money or drugs, or have sex partners who do;
   - Individuals whose past or present sex partners were HIV-infected, bisexual or injection drug users;
   - Persons being treated for sexually transmitted diseases;
   - Persons with a history of blood transfusion between 1978 and 1985;
   - Persons who request an HIV test despite reporting no individual risk factors, since this group is likely to include individuals not willing to disclose high-risk behaviors; **and**
2. Voluntary HIV screening of pregnant Medicare HMO Blue and Medicare PPO Blue members when the diagnosis of pregnancy is known, during the third trimester, and at labor.

We cover the following:

- **HIV genotyping or phenotyping** in patients failing a course of antiviral therapy or have suboptimal viral load reduction.[5, 8,11, 12]
- **HIV genotyping or phenotyping** in patients with acute or recent infection for guiding treatment decisions.[12] ***Coverage effective 3/09.***
- **HIV genotyping or phenotyping** in antiretroviral naïve patients entering treatment.[12] ***Coverage effective 3/09.***

- **Baseline HIV genotyping** is recommended for patients with acute HIV or recent infection.[9,10]

We cover **gamma interferon blood test to diagnose latent tuberculosis infection** in patients considered at high risk for latent tuberculosis infection, including but not limited to HIV-infected patients and intravenous drug users.[7]

When services are not covered for Medicare HMO Blue and Medicare PPO Blue

We do not cover:

- **Viral load tests** not approved by the FDA[4]
- **HIV testing** not approved by the FDA**.**

We do not cover **standard and FDA-approved diagnostic HIV testing** if guidelines listed under when services are covered are not met, in accordance with CMS guidelines. [13]

We do not cover **standard and FDA-approved rapid HIV screening testing** if guidelines listed under when services are covered are not met, in accordance with CMS guidelines. [14]

We do not cover **viral load testing for predicting maternal-fetal transmission of HIV**[1, 4] because it is considered investigational as it does not meet our Medical Technology Assessment Guidelines, #350.

We do not cover **routine use of combined HIV genotyping and phenotypic testing** [5, 11, 12], because it is considered investigational as it does not meet our Medical Technology Assessment Guidelines, #350.

We do not cover **drug susceptibility phenotype prediction using genotypic comparison to known genotypic/phenotypic database**[6, 11,12], because it is considered investigational as it does not meet our Medical Technology Assessment Guidelines, #350.

Individual consideration

All our medical policies are written for the majority of people with a given condition. Each policy is based on medical science. For many of our medical policies, each individual's unique clinical circumstances may be considered in light of current scientific literature. For consideration of an individual patient, physicians may send relevant clinical information to:

For services already billed	Prior to performance of service
Blue Cross Blue Shield of Massachusetts Provider Appeals PO Box 986065 Boston, MA 02298	Blue Cross Blue Shield of Massachusetts Case Creation/Medical Policy One Enterprise Drive Quincy, MA 02171 Tel: 1-800-327-6716 Fax: 1-888-282-0780

Authorization Information

For Managed Care members:

- No authorizations are required for these services; *see **Managed Care Guidelines** for additional requirements*

For Indemnity and PPO members:

- No authorizations are required for these services; *see **Indemnity and PPO Guidelines** for additional requirements.*

Managed Care Guidelines

All authorization requirements are determined by the individual's subscriber certificate, explanation of coverage, or summary plan description; however,
For Medicare HMO Blue members:

- The service must meet the criteria for coverage noted in this policy, be medically necessary, prescribed by a plan physician and provided by a network provider.
- Referrals are required for all visits to a specialist.

For all other Managed Care plans:

- Any specialist visit requires a referral, except for visits performed by OB/GYN specialists.
- Authorization is required for an inpatient admission.

Indemnity and PPO Guidelines

All authorization requirements are determined by the individual's subscriber certificate, explanation of coverage, or summary plan description, however;

- Authorization is required for an inpatient admission.
- Authorizations are not required for most outpatient services as determined by the individual's subscriber certificate.
- Referrals to a specialist are not required.

Coding information

Procedure codes are from current CPT, HCPCS Level II, Revenue Code, and/or ICD-9-CM manuals, as recommended by the American Medical Association, Centers for Medicare and Medicaid Services and American Hospital Associations. Blue Cross Blue Shield Association national codes may be developed when appropriate.

The following codes are included below for informational purposes. Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member. A draft of future ICD-10 Coding related to this document, as it might look today, is included below for your reference.

HIV (Antibody Testing, T Cells, Antigen Detection, Viral Load and Genotyping & Phenotyping)
CPT codes:

- **82397:** chemiluminsecent assay
- **83890:** nuclear molecular diagnostics; molecular isolation or extraction, each nucleic acid type (i.e., DNA or RNA)
- **83896:** nuclear molecular diagnostics; nucleic acid probe, each
- **83898:** nuclear molecular diagnostics; nucleic acid probe with amplification
- **86359:** T cells; total count
- **86360:** T cells; absolute CD4 and CD8 count, including ratio
- **86361:** T cells; absolute CD4 count
- **86481:** Tuberculosis test, cell mediated immunity antigen response measurement; enumeration of gamma interferon-producing T-cells in cell suspension
- **86689:** antibody; HTLV or HIV antibody, confirmatory test (eg, Western Blot)
- **86701:** antibody; HIV-1
- **86702:** antibody; HIV-2
- **86703:** antibody; HIV-1 and HIV-2, single assay
- **87390:** infectious agent antigen detection by enzyme immunoassay technique, qualitative or semiquantitative, multiple step method; HIV-1

- **87391:** infectious agent antigen detection by enzyme immunoassay technique, qualitative or semiquantitative, multiple step method; HIV-2
- **87534:** infectious agent detection by nucleic acid (DNA or RNA); HIV-1, direct probe technique
- **87535:** Infectious agent detection by nucleic acid (DNA or RNA); HIV-1, amplified probe technique, includes reverse transcription when performed
- **87536:** Infectious agent detection by nucleic acid (DNA or RNA); HIV-1, quantification, includes reverse transcription when performed
- **87537:** infectious agent detection by nucleic acid (DNA or RNA); HIV-2, direct probe technique
- **87538:** Infectious agent detection by nucleic acid (DNA or RNA); HIV-2, amplified probe technique, includes reverse transcription when performed
- **87539:** Infectious agent detection by nucleic acid (DNA or RNA); HIV-2, quantification, includes reverse transcription when performed
- **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)

Note: Indemnity contracts do not cover screening in the absence of symptoms. However, if HIV testing is done in a pregnant patient for determining changes in management, be sure to put the diagnosis of **pregnancy** *(ICD-9-CM V22.0-V22.2, V23.8 or V23.9)*

ICD-9 Diagnosis Codes

ICD-9-CM diagnosis codes:	**Code Description**
V22.0	Supervision of normal first pregnancy
V22.1	Supervision of other normal pregnancy
V22.2	Pregnant state, incidental
V23.9	Supervision of unspecified high-risk pregnancy
V23.8	Supervision of other high-risk pregnancy

ICD-10 Diagnosis Codes

ICD-10-CM diagnosis codes:	**Code Description**
Z34.00	Encounter for supervision of normal first pregnancy, unspecified trimester
Z34.01	Encounter for supervision of normal first pregnancy, first trimester
Z34.02	Encounter for supervision of normal first pregnancy, second trimester
Z34.03	Encounter for supervision of normal first pregnancy, third trimester
Z34.80	Encounter for supervision of other normal pregnancy, unspecified trimester
Z34.81	Encounter for supervision of other normal pregnancy, first trimester
Z34.82	Encounter for supervision of other normal pregnancy, second trimester
Z34.83	Encounter for supervision of other normal pregnancy, third trimester
Z34.90	Encounter for supervision of normal pregnancy, unspecified, unspecified trimester
Z34.91	Encounter for supervision of normal pregnancy, unspecified, first trimester
Z34.92	Encounter for supervision of normal pregnancy, unspecified, second trimester
Z34.93	Encounter for supervision of normal pregnancy, unspecified, third trimester

Z33.1	Pregnant state, incidental
O09.90	Supervision of high risk pregnancy, unspecified, unspecified trimester
O09.91	Supervision of high risk pregnancy, unspecified, first trimester
O09.92	Supervision of high risk pregnancy, unspecified, second trimester
O09.93	Supervision of high risk pregnancy, unspecified, third trimester

HCPCS codes:

- **G0432:** Infectious agent antigen detection by enzyme immunoassay (EIA) technique, qualitative or semi-quantitative, multiple-step method, HIV-1 or HIV-2, screening ***(Implemented 4/5/10, effective for dates of service on and after 12/8/09)***
- **G0433:** Infectious agent antigen detection by enzyme-linked immunosorbent assay (ELISA) technique, antibody, HIV-1 or HIV-2, screening ***(Implemented 4/5/10, effective for dates of service on and after 12/8/09)***
- **G0435:** Infectious agent antigen detection by rapid antibody test of oral mucosa transudate, HIV-1 or HIV-2, screening ***(Implemented 4/5/10, effective for dates of service on and after 12/8/09)***

Gamma Interferon
CPT code:

- **86480:** tuberculosis test, cell mediated immunity measurement of gamma interferon antigen response

Modifier:

- **26:** professional component

The procedure noted below will reject as non-covered, ***for commercial products and for Medicare HMO Blue and Medicare PPO Blue products,*** leaving **no** patient balance because this procedure does not meet our Medical Technology Assessment Guidelines.

- **87900:** infectious agent drug susceptibility phenotype prediction using regularly updated genotypic bioinformatics

Other information

- For our Medical Technology Assessment Guidelines, see document #350.

Clinical trials for Cancer Mandate
As required by law, we provide coverage for services and supplies received as part of a qualified clinical trial (for treatment of cancer) when the member is enrolled in that trial. This coverage is provided for services and supplies that are consistent with the study protocol and with the standard of care for someone with the patients' diagnosis and that would be covered if the patient did not participate in the trials. This coverage may also be provided for investigational drugs and devices that have been approved for use as part of the trial. Coverage for services and supplies that are received as part of a qualified clinical trial is provided to the same extent as it would have been provided if the patient did not participate in the trial.
However, no coverage is provided for:

- Investigational drugs and devices that have not been approved for use in the trial.
- Investigational drugs and devices that are paid for by the manufacturer, distributor or provider of the drug or device, whether or not the drug or device has been approved for use in the trial.
- Non-covered services under the member's contract.
- Costs associated with managing the research for the trial.
- Items, services or costs that are reimbursed or otherwise furnished by the sponsor of the trial.
- Costs of services that are inconsistent with widely accepted and established national and regional standards of care.
- Costs of clinical trials that are not "qualified trials."

Policy update history

Policy issued 8/96. Updated 10/96 to include coverage for viral load testing for HIV, based on a 9/96 TEC assessment. Updated 11/97 to include 1998 CPT codes under billing and reimbursement and routine and high risk pregnancy diags. Reviewed 8/98; no changes in coverage were made. Reviewed 8/99; no changes in coverage were made. Updated 8/00 to emphasize coverage for HIV testing during pregnancy. Updated 10/01 to include coverage for HIV genotyping and phenotyping in patients failing a course of antiviral therapy, and to exclude coverage for other applications of HIV genotyping and phenotyping. Updated 1/02 to exclude coverage for drug susceptibility phenotype prediction using genotypic comparison to known genotypic/phenotypic database. Updated 8/02 to include coverage for gamma interferon blood test for diagnosis of latent tuberculosis. Reviewed 9/03 MPG hematology/oncology, no changes in coverage were made. Updated 9/04 MPG Hematology/Oncology, to include coverage of HIV genotyping or phenotyping in patients with suboptimal viral load reduction, and for baseline HIV genotyping for patients with acute HIV or recent infection. Coverage clarified for HIV testing. Reviewed 5/05 BCBSA National policy with policy statement unchanged relating to HIV Genotyping and Phenotyping, added rationale and references. Reviewed 9/05 MPG Hematology/Oncology, no changes in coverage were made. Updated 3/06 after review of BCBSA National policy issued 12/05 with policy statement unchanged related to HIV Genotyping and Phenotyping, and billing information updated with 2006 CPT codes. Updated 4/06 after review of BCBSA National policy issued 1:2005 with policy statement unchanged related to gamma interferon blood test for diagnosis of latent tuberculosis. Updated 10/06 to clarify coverage of Rapid HIV-1 Antibody test. Reviewed 9/06 MPG Hematology/Oncology, no changes in coverage were made. Reviewed 10/06 MPG – Obstetrics and Gynecology, no changes in coverage were made. Updated 1/07 Billing Information now Coding Information. Updated 6/07 after review of BCBSA policy HIV Genotyping and Phenotyping issued 4/07 with no change in policy statements; additional references added under footnote 11. Reviewed 9/07 MPG Hematology/Oncology, no changes in coverage were made. Reviewed 10/07 MPG – Obstetrics and Gynecology, no changes in coverage were made. Updated 3/08 after review of BCBSA new medical policy Laboratory Testing for HIV Tropism issued 12/07, to add one coverage statement and four non coverage statements related to HIV tropism testing, effective 2/08; added rationale and references under footnote 12. Updated 5/08 to remove information on lab testing for HIV Tropism, as this is now separately addressed under Medical Policy #008. Reviewed 10/08 MPG-obstetrics/gynecology, no changes in coverage were made. Updated 2/09 after review of BCBSA policy specific to HIV Genotyping and Phenotyping issued 6/08, references 22-28 added to newly created footnote 12; added coverage of HIV genotyping and phenotyping in patients with acute or recent infection for guiding treatment decisions and also in antiretroviral naïve patients entering treatment, effective 3/09. Reviewed 9/2009 MPG-Hematology and Oncology, no changes in coverage were made. Reviewed 10/2009 MPG-Obstetrics and Gynecology, no changes in coverage were made. Updated 12/09 to clarify coverage of standard and FDA-approved rapid HIV screening testing for our Medicare HMO Blue and Medicare PPO Blue products to align with CMS NCD and Decision Memorandum, effective 12/8/09. Updated 3/10 to add HCPCS Level II codes G0432, G0433 and G0435 reporting HIV screening lab testing to Coding Information section; the noted HCPCS Level II G codes are to be implemented 4/5/10, for dates of service on and after 12/8/09. Reviewed 9/2010 MPG-Hematology and Oncology, no changes in coverage were made. Reviewed 10/2010 MPG Obstetrics and Gynecology, no changes in coverage were made. Updated 12/10 to add new CPT code 86481 effective 1/1/2011. Reviewed 7/2011 MPG – Hematology and Oncology, no changes in coverage were made. Reviewed 9/2011 MPG – Urology, Obstetrics and Gynecology, no changes in coverage were made. Revised 8/1/2012 to reflect Affordable Care Act requirements. Updated 12/2012 to remove code 83912. Updated 7/2014 coding section with ICD10 procedure and diagnosis codes, effective 10/2015.

Scientific background, Rationale and References

[1] Based upon a 9/96 TEC (Technology Evaluation Center) assessment of medical literature from 1980 to 9/96 on plasma RNA. At the time of this assessment, one plasma HIV-1 RNA assay had received FDA approval (Amplicor^{R} HIV-1 Monitor, Roche Molecular systems, Inc. The approval acknowledged ongoing evaluation of the assay's use in monitoring response to anti-viral therapy. The CDC is currently evaluating the characteristics of the various available assays. bDNA and NASBA assays can detect a true change in RNA of < 0.3 $\log_{10}$ from baseline (95% confidence). For the Roche RT-PCR assay, to achieve 95% confidence, a 5

fold or more change (0.7 log units) is required (depends on baseline value). ACTG quality assurance program is evaluating standard deviations in these assays.

Concept: While lymphoid organs are the biological reservoir of continued cellular infection and viral reproduction, it is theorized that virions released into the circulation are reflective of tissue viral activity. With progressive disease, lymphoid organs are increasingly unable to limit and control viral production, and increased levels are detectable in plasma. CD_4 cell counts are not reflective of the sometimes dramatic CD_4 cell turnover, and the count does not always accurately reflect perturbations in the infectious process.

Evidence: RNA levels are somewhat stable in long-term non-progressors. Several studies have suggested plasma RNA is a strong independent predictor of disease progression (Mellors, 1996, O'Brien 1996, Henrad 1995, Katzenstien 1996, Phillips 1996). Plasma RNA appears to decrease in response to therapy, and larger decreases are noted with combination therapy. Treatment failure is associated with increased levels, presumably reflecting high levels of virion production. Shafer (1995) suggests that patients with only transient suppression of viral load during therapy, are more likely to develop resistant strains.

Data from the XI International AIDS Conference (Vancouver, July, 1996) were also considered. Results of the ACTG 175 Trial showed that for every $\log_{10}$ increase in plasma RNA (Katzenstein 1996), there was nearly a 6-fold increase in risk of AIDS or death; CD_4 count was not a significant predictor of risk. O'Brien (1996) reports a relative risk of AIDS of 0.44 for every $0.6\log_{10}$ decrement in plasma RNA ($p=0.009$) during treatment, and a relative risk of 0.48 for every 10% increase in CD_4 count ($p=0.007$). In O'Brien's study, 59% of the treatment effect was explained by a decrease of >=75% in plasma RNA, and 79% of the total treatment effect was explained by a combination of plasma RNA and CD_4 counts . NUCA30001 and NUCA 3002 trials showed both RNA levels and CD_4 counts to be significant predictors. Only one report (Read 1996) with very small sample size, suggested that only CD_4 counts were predictive. A step-wise logistic regression of data from Mellors (1995) estimates the odds ratio for AIDS to be 10.8 ($p=0.01$) when $\log_{10}$ RNA was >=5. A Cox proportional hazards model estimates the relative hazard of AIDS to be 1.77 for each $\log_{10}$ increase in $\log_{10}$ RNA (Henrard 1995). Also significant was the hazard of AIDS for every 5% decrease in CD_4 counts ($p<0.05$). Plasma RNA may be a better predictor earlier after seroconversion than later (O'Brien, Mellors).

Statistical analysis of clinical trial data show plasma RNA to be a superior predictor of disease progression and response to therapy than is CD_4 counts. For response to treatment, plasma RNA accounts for a greater share of the response than does CD_4 counts. Therefore, HIV-1 RNA quantification for monitoring disease and assessing response to therapy meet TEC criteria. The International AIDS Society-USA have published a statement (Carpenter 1996) emphasizing the importance of plasma RNA measurements for predicting disease progressions, based upon reports that combination therapy trials have associated reduced plasma RNA with increased survival and decreased progression to AIDS. Specific guidelines for management were not given.

Ongoing Trials:
The California Collaborative Treatment Group (CCTG) 570 is a blinded prospective analysis of MD's use of RNA viral load results, employing guidelines by Sagg and others (1996). The Community Programs for Clinical Research on AIDS (CPCRA) will follow RNA levels on all patients, but reveal results only to the physicians of the experimental arm. No specific guidelines will be used to guide therapy. These trials are not expected to show results for about 3 years. Snow (1996) (n=100) has initiated a short-term (24-week) unblinded pilot.

Maternal-fetal transmission: HIV-1 transmission occurs in 15-40%, depending upon disease status and infant exposure. AZT reduces this risk by 2/3 in asymptomatic women without previous exposure to AZT, prompting US Public Health Service to recommend AZT to all pregnant women (CDC 1994). Dickerson (1996) compared mean RNA levels for transmitters and non-transmitters, and found that mean RNA differed according to AZT use. They suggest that at levels of 4.70 $\log_{10}$ RNA copies/ml, transmission was highly likely; below 4.30 $\log_{10}$ copies, transmission was unlikely. However, there was considerable overlap in levels between transmitters and non-transmitters. Hence, if viral loads are low, this test cannot be confidently used to

withhold therapy. The US Public Health Service guideline should be followed until more definitive evidence is available.

[2] See *Perinatally Acquired HIV/AIDS-United States 1997*, in the CDC (Centers for Disease Control) Morbidity and Mortality Weekly Report November 21, 1997/ vol. 46 / no.46, pg 1086. 1994 clinical trials demonstrated a two-thirds reduction in the risk for perinatal transmission associated with treatment of HIV-infected pregnant women and their infants, with zidovudine therapy. The US Public Health Service issued recommendations (CDC MMR July 7, 1995, vol. 44, no. RR-7) on the use of AZT in pregnant women. The Service recommended routine HIV counseling and voluntary testing for all pregnant women. For women who have HIV infection, appropriate therapy and timely interventions may improve the health of the the mother, and decrease the risk of perinatal transmission to the infant.

The 1997 report noted that the implementation of those recommendations has been temporally associated with a substantial and geographically widespread decline in perinatally acquired AIDS in the IS among all racial/ ethnic groups in both urban and rural areas. The findings from states that conduct HIV surveillance indicate that most HIV-infected mothers were tested for HIV before their child's birth, and confirm the effectiveness of current PHS guidelines for routine HIV counseling and voluntary testing of pregnant women. Previous assessments also have demonstrated high acceptance levels following counseling by informed providers. Documentation of the increasing use of ZDV therapy among mothers following publication of PHS guidelines is consistent with other assessments noting the increased use of ZDV by pregnant HIV-infected women and their newborns that was associated with reduced rates of peri-natal transmission.

[3] Medical Policy Group, August 2000.

[4] Based on the 1998 Blue Cross Blue Shield Association national policy 2.01.22, issued 1/30/98.

FDA approval status: *Amplicor® HIV-1 Monitor HIV-plasma RNA quantification manufactured by Roche Molecular System, has received FDA approval for monitoring disease progression. The FDA approval also acknowledged the use of this assay in monitoring response to antiretroviral therapy.*

[5] Based on the 2001 Blue Cross Blue Shield Association national policy 2.04.18, issued 8/15/01.

Assays that are available include: ABI Gene Sequencing, TroGene,™ HIV-I Genotyping Assay, HIV-1GeneSeek™ Test, Affymetric GeneChip® HIV PRT Assay, PhenoSense™ assay, and Antivirogram.

Randomized trials done by VIRADAPT (n=108) to evaluate the contribution of genotyping in patient management, patients in the genotyping group had significant decrease in viral load. This benefit was still apparent at 12 months. In a randomized trial done by GART (n=153), there was a noted change in viral load after 8 weeks; 50% of the patients had undetectable levels of HIV, compared to only 23% in the control group. In a study to evaluate the contribution of phenotyping in patient management, VIRA300 1(n=271), the overall affect was that 58% of patients utilizing this regime had undetectable viral loads after 4 months, compared with only 22% in the control group. In addition to the studies above, the International AIDS Society USA and the Department of Health and Human Services (DHHS) support the use of either HIV genotyping or phenotyping in patients who have failed antiviral regimes. DHHS guidelines also state that they do not support the use of this testing in patients prior to initiation of treatment.

There are no data that support the use of combined HIV genotyping and phenotyping.

[6] Based on the 2001 Blue Cross Blue Shield Association national policy 2.04.18, issued 11/20/01.

Phenotype Prediction from Genotype

Results of genotypes have been used to predict the phenotype by identifying genotypes from a large database of other HIV genotypes for, which there are known phenotypes (Virtual Phenotype™). Clinical efficacy of this

approach depends on the database. Comparison between actual and virtual phenotype will be weaker for new drugs, due to minimal data, and weaker when complex genotypes are present. The clinical use of this method requires validation in clinical studies.

[7] Based on Blue Cross Blue Shield Association National policy 2.04.28, issued 5/15/02. QuantiFERON-TB® assay is FDA-approved for the following indication: QuantiFERON-TB test is intended as an aid in the detection of latent *Mycobacterium tuberculosis* infection."

Results of large clinical trials using the QuantiFERON-TB GOLD diagnostic test (see Description section) have not been published in the peer-reviewed literature, but are available on the manufacturer's Web site. (6) The specificity of this test was assessed in a population of over 300 patients considered to be at low risk of TB; 80% of them had undergone previous vaccination with BCG. The specificity was estimated at 98.7%; in contrast, more than 30% of the BCG-vaccinated subjects had positive skin tests (i.e., a false positive result). The sensitivity was evaluated in untreated patients with active TB; in this population the sensitivity was approximately 90%. As noted above, the test is indicated in patients with suspected latent TB. However, it is difficult to study this population due to the lack of a readily available gold standard diagnostic tests. However, QuantiFERON-TB GOLD was performed in contact investigations and in a large healthcare work study. In all cases, positive results were significantly related to well known risk factors for TB, such as length of exposure of a contact, past history of working with TB patients, etc. Mori and colleagues reported on the sensitivity and specificity of an interferon gamma assay using the same antigens CFP-10 and ESAT-6 in BCG immunized patients (i.e., low risk) and in patients with newly diagnosed active infection. (7) The specificity was estimated at 98.1%, and the sensitivity was 89.0%.

References:

1. Streeton JA, Desem N, Jones SL. Sensitivity and specificity of a gamma interferon blood test for tuberculosis infection. Int J Tuberc Lung Dis 1998; 2(6):443-50.
2. Converse PJ, Jones SL, Astemborski J et al. Comparison of a tuberculin interferon-gamma assay with the tuberculin skin test in high-risk adults: effect of human immunodeficiency virus infection. J Infect Dis 1997; 176(1):144-50.
3. Chaisson RE, Keruly JC, McAvinue S et al. Effects of an incentive and education program on return rates for PPD test reading in patients with HIV infection. J Acquir Immune Defic Syndr Hum Retrovirol 1996; 11(5):455-9.
4. FDA Summary of Safety and Effectiveness: www.fda.gov/ohrms/dockets/ac/01/briefing/3795b2 01.pdf
5. Mazurek GH, LoBue PA, Daley CL et al.Comparison of a whole-blood interferon gamma assay with tuberculin skin testing for detecting latent *Mycobacterium tuberculosis* infection. JAMA 2001; 286(14):1740-7.
6. Clinician's Guide to QuantiFERON-TB GOLD. www.cellestis.com
7. Mori T, Sakatani M, Yamagishi F et al. Am J Respir Crit Care Med 2004; 170:59-64.

[8] Based on Blue Cross Blue Shield Association National Policy 2.04.18 issued 10/9/03.

[9] Based on recommendation of local HIV experts through Electric Blue Review. Medical Policy Group, September, 2004.

[10] Based on IAS (Internation AIDS Society) recommendations as well as abstract no. ThPeB7210 submitted for the XIV International AIDS Conference, 2002.

[11] Based on Blue Cross Blue Shield Association National policy 2.04.18 issued 3/05.

Summary: Randomized trials have suggested that genotype directed and, to a lesser extent, phenotype directed therapy may result in improved short-term virologic outcomes in patients failing or having a suboptimal response to antiretroviral therapy. While guidelines suggest that either type of assay may be recommended in treatment-naïve patients with acute infection, particularly in geographic areas in which there

is a high prevalence of resistant virus, this strategy has not been tested in controlled studies and therefore remains investigational. No randomized studies have used combined genotype and phenotype directed therapy; therefore this indication remains investigational. However, the Department of Health and Human Services notes that there may be individual cases of such complexity that combined resistance testing may be helpful. Finally, no randomized studies have compared genotype alone with predicted phenotype (i.e., "virtual phenotype").

2004 Update: A literature search was performed for the period of 2003 through November of 2004, with a particular focus on genotype predicted phenotype ("virtual phenotype") and the role of genotyping or phenotyping in treatment naïve patients. No additional studies were identified that would prompt reconsideration of the policy statement; therefore, the policy is unchanged.

Based on Blue Cross Blue Shield National Policy 2.04.18 issued 12/05.

2005 Update: A literature search was performed for the period of 2003 through October 2005, with a particular focus on genotype predicted phenotype ("virtual phenotype") and the role of genotyping or phenotyping in treatment naïve patients. No additional studies were identified that would prompt reconsideration of the policy statement; therefore, the policy is unchanged.

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2006-2007 Update: Based upon BCBSA national policy 2.04.18, HIV Genotyping and Phenotyping, issued 4/07. The policy was updated with literature review; with no change in policy statement. References numbers 17-21 added. Reference number 6 updated to reflect publication.

A literature search was performed for the period of October 2005 through February 2007. None of the articles identified would alter the policy conclusions. DeLuca and colleagues reported that the benefit of genotype-guided treatment decisions continued over time in patients who failed antiviral therapy. (17) Hirsch and colleagues noted no differences between genotyping and phenotyping in a series of 102 patients, but cautioned that the numbers of tests may not have been sufficient to detect differences. (18) Dunn reported on a randomized trial that did not demonstrate added value of phenotypic resistance in conjunction with genotypic testing in patients with virologic failure. (19) A review article by Zolopa mentions potential problems caused by discordant results between genotyping and phenotyping and also mentions replication capacity as having potential prognostic value. (20) While some modeling studies suggest that resistance testing could have value in treatment-naïve patients, trials are needed to demonstrate the clinical impact. Updated guidelines recommend drug resistance testing (generally genotyping) in treatment-naïve patients; however, this recommendation is based on expert opinion. (21) This guideline notes that resistance testing in those who have failed antiviral therapy is supported by data from clinical trials. Thus, the policy statements are unchanged.

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[12] Based upon Blue Cross Blue Shield Association National policy 2.04.18 issued 6/08. The national policy with updated with a literature review through May 2008, references 22-28 were added. The national policy statements were changed to consider resistance testing with recent onset of infection and at the start of treatment medically necessary.

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[13] Based upon CMS National Coverage Determination for Human Immunodeficiency Virus (HIV) Testing (Diagnosis) (1090.14), ***effective 6/16/06*** and can be found at the following web address: http://www.cms.hhs.gov/mcd/viewncd.asp?ncd_id=190.14&ncd_version=2&basket=ncd%3A190%2E14%3A2%3AHuman+Immunodeficiency+Virus+%28HIV%29+Testing+%28Diagnosis%29

[14] Based upon CMS Decision Memo for Screening for the Human Immunodeficiency Virus (HIV) Infection (CAG-00409N) ***effective 12/8/09*** and can be found at the following web address: http://www.cms.hhs.gov/mcd/viewdecisionmemo.asp?from2=viewdecisionmemo.asp&id=229&