Corporate Medical Policy

Plasma HIV-1 and HIV-2 RNA Quantification for HIV Infection AHS – M2116

File Name: plasma_HIV-1_and_HIV-2_RNA_quantification_for_HIV_infection
Origionation: 1/1/2019
Last CAP Review: 2/2020
Next CAP Review: 2/2021
Last Review: 4/2020

Description of Procedure or Service

Human immunodeficiency virus (HIV) is an RNA retrovirus that infects human immune cells, specifically CD4 cells, causing progressive deterioration of the immune system ultimately leading to acquired immune deficiency syndrome (AIDS) characterized by susceptibility to opportunistic infections and HIV-related cancers (CDC, 2014). HIV-1 is the dominant subtype of HIV infection, but another subtype, HIV-2, is a crucial subtype in certain areas of the world, such as Western Africa (Sax, 2019).

Related Policies

HIV Genotyping and Phenotyping
Diagnostic Testing of Sexually Transmitted Infections

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.

Policy

BCBSNC will provide coverage for Plasma HIV-1 and HIV-2 RNA Quantification for HIV Infection when it is determined the reimbursement guidelines below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Plasma HIV-1 and HIV-2 RNA Quantification for HIV Infection is covered

Reimbursement is allowed in clinical situations where risk of HIV infection is significant and initiation of therapy is anticipated, a baseline HIV quantification. These situations include:

A. Persistence of borderline or equivocal serologic reactivity in an at-risk individual.
B. Signs and symptoms of acute retroviral syndrome characterized by fever, malaise, lymphadenopathy and rash in an at-risk individual.

Reimbursement is allowed for plasma HIV-1 RNA quantification or plasma HIV-2 RNA quantification for use in monitoring disease progression in HIV-infected individuals.
Plasma HIV-1 and HIV-2 RNA Quantification for HIV Infection AHS – M2116

Reimbursement is allowed for plasma HIV-1 RNA quantification or plasma HIV-2 RNA quantification for monitoring response to antiretroviral therapy.

Reimbursement is allowed for plasma HIV-1 RNA quantification or plasma HIV-2 RNA quantification for infants younger than 18 months born to HIV positive mothers as antibody tests may be confounded by maternal antibodies in this time frame.

When Plasma HIV-1 and HIV-2 RNA Quantification for HIV Infection is not covered

Reimbursement is not allowed for plasma HIV-1 RNA quantification or HIV-2 RNA quantification for predicting maternal-fetal transmission of HIV-1.

Policy Guidelines

Policy Guidelines
Suggested frequency for HIV RNA measurement is:
1. At baseline: 2 measurements, 2 to 4 weeks apart
2. Every 3 to 4 months or in conjunction with CD4+ counts
3. Shorter intervals, as critical decision points are neared*
4. Three to 4 weeks after initiating/changing therapy*

* For prognosis including anti-retroviral therapy monitoring, regular, periodic measurements are appropriate. The frequency of viral load testing should be consistent with the most current Centers for Disease Control and Prevention guidelines for use of anti-retroviral agents in adults and adolescents or pediatrics.

Limitations

I. Viral quantification may be appropriate for prognostic use including baseline determination, periodic monitoring, and monitoring of response to therapy. Use as a diagnostic test method is not indicated, except as is noted in association with medically necessary indication 1 above

II. Because differences in absolute HIV copy number are known to occur using different assays, plasma HIV RNA levels should be measured by the same analytical method. A change in assay method may necessitate re-establishment of a baseline.

Background

HIV-1

Human immunodeficiency virus type 1 (HIV-1) RNA in blood can be measured using qualitative or quantitative techniques. Qualitative testing is used as a screening test to identify HIV-infected individuals whereas quantitative measurement of HIV-1 viral loads in the blood is used in management and monitoring of HIV-1 infected individuals. HIV-1 RNA levels may also be used to establish the diagnosis of HIV infection in specific situations where combination tests that detect HIV p24 antigen and HIV antibodies are not appropriate (neonatal or acute infection) (Caliendo, 2019).

Three primary real-time reverse transcriptase polymerase chain reaction (RT-PCR) commercial tests are commonly used to quantify HIV-1 RNA from plasma. These tests are more sensitive (detecting 20 to 40 copies/mL of HIV RNA), have a broader linear range (detecting virus to at least 10 million copies/mL), and pose a lower risk of carry over contamination than prior PCR assays. The tests are “COBAS TaqMan HIV-1 Test version 2” by Roche Diagnostics, “RealTime HIV-1” by Abbott Molecular, and “Aptima HIV-1 Quant Dx Assay” by Hologic (Caliendo, 2019).
Plasma HIV-1 and HIV-2 RNA Quantification for HIV Infection AHS – M2116

Sources of variability between assays include differences in technology platform, plasma input volume, and ability to detect HIV-1 subtypes. Monitoring of individual patients should be performed on the same technology platform to ensure appropriate interpretation of changes in viral load (Sollis et al., 2014). An important difference between assays is the gene target; with the increasing use of integrase inhibitors, monitoring for resistance mutations in the integrase gene is essential to ensure that the primer and probe binding sites are not impacted (Caliendo, 2019).

Overall, studies of real-time RT-PCR tests have shown high concordance, high correlation values, and good agreement among all assays (Mor et al., 2015). However, their manufacturers have reported that variation and error tend to increase at the lower limits of quantitation of the assays (Swenson et al., 2014). The high variability around the threshold of detectability of the viral load assays should be noted since many patients have viral loads in this range. Agreement between these assays was improved using a 200-copies/ml threshold (Swenson et al., 2014) consistent with the current HIV treatment guidelines (Gunthard et al., 2016).

Furthermore, changes in HIV-1 RNA levels must exceed at least 0.5 log_{10} or threefold in magnitude to represent biologically relevant changes in viral replication (Hughes et al., 1997; Saag et al., 1996). Viral RNA levels can also transiently rise due to acute illness, herpes outbreak, or vaccination; however, values usually return to baseline within one month (Caliendo, 2019). CD4 cell counts are weakly correlated with viral RNA measurements. Viral RNA measurements, although, do not replace CD4 cell counts in the management of HIV-1-infected patients and should be used in parallel (Caliendo, 2019).

**HIV-2**

HIV-2 is another subtype of HIV. Compared to HIV-1, HIV-2 appears milder clinically; it is characterized by a longer asymptomatic stage, slower declines of CD4 cell counts, and lower levels of plasma viremia in chronically ill patients (Gottlieb, 2018). However, these numerical thresholds are not as well-defined as those of HIV-1 as there is currently not as much data available for HIV-2. Further, although quantification of HIV-2 RNA viral load may be useful, it is not widely commercially available, as the few labs that offer HIV-2 testing only offer qualitative testing and not quantitative (Gottlieb, 2019). This is particularly crucial as HIV-1 assays typically do not properly detect HIV-2 viral load (DHHS, 2019b). It is possible for commercially available HIV-1 diagnostic assays to cross-react with HIV-2, disrupting the results. A reactive HIV-1 Western Blot may not be indicative of a true HIV-1 infection. For example, a patient may have reactive HIV serology, but test negative on a confirmatory HIV-1 Western blot. This scenario may indicate an HIV-2 infection. Clinical manifestations of HIV-2 infection are generally similar to HIV-1 infection, but much remains to be discovered about the general course of HIV-2 infection (Gottlieb, 2019).

Despite HIV-2’s milder symptoms, certain clinical features may make an infection more difficult to manage; for example, HIV-2 is intrinsically resistant to non-nucleoside reverse transcriptase inhibitors, as well as enfuvirtide. Assessment of genotypic or phenotypic resistance is also unexplored, with no currently FDA-approved genotypic or phenotypic resistance assays available (DHHS, 2019b).

Although HIV-2 is endemic to West Africa (Senegal, Gambia, Guinea-Bissau, et al) the epidemiological trends may be shifting; the CDC only reported 166 cases of HIV-2 from 1987 to 2009 but this may be underestimated as HIV-2 is often asymptomatic. 62 cases of HIV-2 have been identified in New York City alone since 2000 and as much as 5% of HIV cases are thought to be HIV-2 (Gottlieb, 2018; Quinn, 2019).

Clinical Validity and Utility
Plasma HIV-1 and HIV-2 RNA Quantification for HIV Infection AHS – M2116

Hopkins et al performed a study comparing the three main RT-PCR tests available, Aptima, COBAS TaqMan (CTM), and Abbott RealTime. The assays were evaluated based on plasma samples from 191 HIV positive patients as well as WHO International Standards (12-500 copies/mL). Aptima detected 141/191 (74%) of the HIV samples, CTM detected 145/191 (76%), and Abbott RealTime detected 119/191 (62%). The authors noted that precision decreased as the viral load got closer to the lower limit of quantification of 50 copies/mL (Hopkins et al., 2015).

Sempa et al evaluated the utility of HIV-1 viral load as a prognostic indicator. A total of 489 patients were evaluated, and the viral load curves were evaluated on a linear scale and a logarithmic scale. The authors found that the viral load curve on the logarithmic scale was a statistically significant predictor of mortality, noting that each log10 increase in viral load corresponded to a 1.63 times higher risk of mortality. However, the authors stress that the choice of variables and statistical model influences the predictive power of this metric (Sempa et al., 2016).

Lindman et al investigated the test performance of the Bio-Rad Geenius HIV-1/2 confirmatory assay against INNO-LIA HIV 1/2 Score and ImmunoComb HIV 1/2 BiSpot. The Geenius test is purported to differentiate between HIV-1 and HIV-2 infections. 131 samples from ART naïve HIV infected patients in Guinea-Bissau were evaluated. The Geenius test identified 62 samples as “HIV-1 reactive”, 37 as “HIV-2 reactive” and 32 as “HIV-1/2 dually reactive”. INNO-LIA identified 63 as HIV-1 reactive, 36 as HIV-2 reactive, and 32 as HIV-1/2 dually reactive. The agreement between Geenius compared to INNO-LIA and Immunocomb was 92.4% and 84% respectively.

Abana et al evaluated the viral load and drug resistance mutations in HIV-2 mutations in patients (n = 16) from Ghana. The authors identified viral loads in 9 of 16 patients, with 3 patients having viral loads below the limit of quantification. Sequences were generated for 7 samples, and 1 patient was found to have HIV-2 drug resistance mutations (Abana et al., 2019).

State and Federal Regulations, as applicable

All three of the primary RT-PCR tests for HIV-1 have been approved by the FDA.

In May 2007, the FDA approved the Abbott RealTime HIV-1 Amplification Reagent Kit. From the FDA website: “The Abbott RealTime HIV-1 assay is an in vitro reverse transcription-polymerase chain reaction (RT-PCR) assay for the quantitation of Human Immunodeficiency Virus type 1 (HIV-1) on the automated m2000 System in human plasma from HIV-1 infected individuals over the range of 40 to 10,000,000 copies/mL”. (FDA, 2007a)

On May 11, 2007, the FDA approved the COBAS® AmpliPrep/COBAS® TaqMan® HIV-1 Test. From the FDA website: “The COBAS AmpliPrep/COBAS TaqMan HIV-1 is an in vitro nucleic acid amplification test for the quantitation of Human Immunodeficiency Virus (HIV-1) nucleic acid in human plasma, using the COBAS AmpliPrep Instrument for automated sample preparation and the COBAS TaqMan Analyzer or COBAS TaqMan 48 Analyzer for automated amplification and detection. This test is intended for use in conjunction with clinical presentation and other laboratory markers of disease progress for the clinical management of HIV-1 infected patients”(FDA, 2007b).

In 2016, the FDA approved the Aptima® HIV-1 Quant Assay. From the FDA website: “The Aptima HIV-1 Quant assay is an in vitro nucleic acid amplification test (NAAT) for the quantitation of human immunodeficiency virus type 1 (HIV-1) RNA in human plasma from HIV-1 infected individuals on the fully automated Panther® system. The Aptima HIV-1 Quant assay quantitates HIV-1 RNA groups M, N, and O over the range of 30 to 10,000,000 copies/mL” (FDA, 2016).

The following screening antibody tests are FDA-approved to differentiate HIV-1 from HIV-2.
On August 26, 2019, the FDA approved the Geenius HIV-1/2 Supplemental Assay. From the FDA Website: “The Geenius™ HIV 1/2 Supplemental Assay is a single-use immunochromatographic assay for the confirmation and differentiation of individual antibodies to Human Immunodeficiency Virus Types 1 and 2 (HIV-1 and HIV-2) in serum or plasma samples (EDTA, lithium heparin, sodium citrate, and CPD) from blood donors. The Geenius™ HIV 1/2 Supplemental Assay is intended for use as an additional, more specific test for human serum and plasma samples with repeatedly reactive results by an FDA licensed blood donor screening test for antibodies to HIV-1/HIV-2. The results of the Geenius™ HIV 1/2 Supplemental Assay are read and interpreted only with the Geenius™ Reader with dedicated software.” 200 known HIV-2 positive samples were classified by Geenius, with 77 interpreted as only HIV-2 positive, 108 with HIV-2 with HIV-1 cross reactivity, 12 as undifferentiated, and 3 as HIV-2 indeterminate (FDA, 2019).

On July 23, 2015, the FDA approved the BioPlex 2200 HIV Ag-Ab Assay. From the FDA Website: “The BioPlex 2200 HIV Ag-Ab assay is a multiplex flow immunoassay intended for the simultaneous qualitative detection and differentiation of the individual analytes HIV-1 p24 antigen, HIV-1 (groups M and O) antibodies, and HIV-2 antibodies in human serum or plasma (fresh or frozen K2 EDTA, K3 EDTA, lithium heparin, sodium heparin; fresh citrate). This assay is intended as an aid in the diagnosis of infection with HIV-1 and/or HIV-2, including acute (primary) HIV-1 infection. The assay may also be used as an aid in the diagnosis of infection with HIV-1 and/or HIV-2 in pediatric subjects as young as two years of age, and pregnant women.” The test was found to differentiate all 1363 HIV-1 samples correctly and 188 of 200 HIV-2 samples correctly (with 12 “undifferentiated”) (FDA, 2015).

Additionally, many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA ’88). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

A. Guidelines and Recommendations

**Department of Health and Human Services (DHHS)**

DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents updated the guidelines on use of antiretroviral drugs in 2019. The panel states “viral load is the most important indicator of initial and sustained response to ART (AI) and should be measured in all HIV-infected patients at entry into care (AIII), at initiation of therapy (AIIII), and on a regular basis thereafter. Pre-treatment viral load level is also an important factor in the selection of an initial ARV regimen because several currently approved ARV drugs or regimens have been associated with poorer responses in patients with high baseline viral load” (DHHS, 2019a).

The panel’s recommendations on the frequency of viral load monitoring are summarized below (DHHS, 2019b):

- “After initiation of ART or modification of therapy because of virologic failure: Plasma viral load should be measured before initiation of ART and within 2 to 4 weeks but no later than 8 weeks after treatment initiation or modification (AIII). Repeat viral load measurement should be performed at 4- to 8-week intervals until the level falls below the assay’s limit of detection (BIII).”
- “In virologically suppressed patients in whom ART was modified because of drug toxicity or for regimen simplification: Viral load measurement should be performed within 4 to 8 weeks after changing therapy (AIII). The purpose of viral load monitoring at this point is to confirm the effectiveness of the new regimen.”
Plasma HIV-1 and HIV-2 RNA Quantification for HIV Infection AHS – M2116

- “In patients on a stable, suppressive ARV regimen: Viral load should be repeated every 3 to 4 months (AIII) or as clinically indicated to confirm continuous viral suppression. Clinicians may extend the interval to 6 months for adherent patients whose viral load has been suppressed for more than 2 years and whose clinical and immunologic status is stable (AIII).”
- “In patients with suboptimal response: The frequency of viral load monitoring will depend on clinical circumstances, such as adherence and availability of further treatment options. In addition to viral load monitoring, a number of additional factors, such as patient adherence to prescribed medications, suboptimal drug exposure, or drug interactions, should be assessed. Patients who fail to achieve viral suppression should undergo resistance testing to aid in the selection of an alternative regimen”.

The guideline also comments on HIV-2. Although the optimal treatment strategy has not been defined, the guideline does recommend (with a strong level A recommendation) that quantitative plasma HIV-2 RNA viral load testing should be performed before initiating ART. HIV-2 RNA should also be used to assess treatment response. The guideline also notes that the “Geenius HIV 1/2 Supplemental Assay (Bio-Rad Laboratories)” is FDA-approved to differentiate HIV-1 infection from HIV-2 infection (DHHS, 2019b).

**International Antiviral Society (2016)**

International Antiviral Society-USA Panel includes the following recommendations on HIV-1 RNA testing (Gunthard et al., 2016):

- “As close to the time of HIV diagnosis as possible and prior to beginning ART, CD4 cell count, plasma HIV RNA, serologies for hepatitis A, B, and C, serum chemistries, estimated creatinine clearance, complete blood cell count, and urine glucose and protein should be measured (evidence rating AIII). Genotypic resistance assays for reverse transcriptase and protease should be ordered for all patients (evidence rating AIIa).”
- “HIV RNA level should be monitored every 4 to 6 weeks after treatment is initiated or changed until it is undetectable, generally below 20 to 50 copies/mL (evidence rating AIA). Virologic suppression should occur within 24 weeks of ART initiation even when initiated during acute infection. Failure to achieve suppression by 24 weeks should prompt evaluation for virologic failure. After suppression is achieved, HIV RNA should be monitored every 3 months until suppression has been sustained for 1 year and at least every 6 months thereafter for adherent patients who remain clinically stable (evidence rating AIII).”

**HIV Medicine Association (2016)**

The HIV Medicine Association as part of the Choosing Wisely initiative of the ABIM Foundation states that quarterly viral load testing of patients with durable viral suppression is to be avoided unless clinically indicated. The Association notes “Viral load testing should be conducted before initiation of treatment, two to eight weeks after initiation or modification of therapy, and then every three to four months to confirm continuous viral suppression” (HIVMA, 2016).

**Infectious Diseases Society of America (IDSA, 2013)**

The IDSA recommends that “A quantitative HIV RNA (viral load) level should be obtained upon initiation of care (strong recommendation, high quality evidence).”

The IDSA also notes that viral load is generally monitored every 3-4 months in untreated patients and patients on stable antiretroviral therapy (ART), 6 months for “adherent patients whose viral load has been suppressed for 2-3 years”, and more frequently after initiation or change in ART (IDSA recommends within 2-4 weeks of initiation or change but not more than 8 weeks) (IDSA, 2013).
Plasma HIV-1 and HIV-2 RNA Quantification for HIV Infection AHS – M2116

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 87536, 87539

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources


Plasma HIV-1 and HIV-2 RNA Quantification for HIV Infection AHS – M2116


Plasma HIV-1 and HIV-2 RNA Quantification for HIV Infection AHS – M2116


**Policy Implementation/Update Information**

1/1/19  New policy developed. BCBSNC will provide coverage for Plasma HIV-1 RNA Quantification for HIV-1 Infection when it is determined to be medically necessary because the medical criteria and guidelines are met. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (sk)


10/1/19  Policy statement revised to read: BCBSNC will provide coverage for Plasma HIV-1 RNA Quantification for HIV-1 Infection when it is determined the reimbursement guidelines below are met. Wording revised in When Covered section. “Medically Necessary” changed to “Reimbursement is allowed…” Wording revised in the Not Covered section “Investigational” changed to read “Reimbursement is not allowed…” Deleted coding grid. Notification given 10/1/2019 for effective date 12/2/2019. (an)


Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.