Plasma HIV-1 and HIV-2 RNA Quantification for HIV Infection

Policy Number: AHS – M2116 – Plasma HIV-1 and HIV-2 RNA Quantification for HIV Infection	Prior Policy Name and Number, as applicable:
Original Effective Date: 5/15/2022 Current Effective Date: 5/15/2022	

I. Policy Description

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).

II. Related Policies

Policy Number	Policy Title
AHS-M2093	HIV Genotyping and Phenotyping
AHS-G2035	Prenatal Screening
AHS-G2157	Diagnostic Testing of Common Sexually Transmitted Infections

III. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request

1. In clinical situations where risk of HIV infection is significant, and initiation of therapy is anticipated, a baseline HIV quantification **MEETS COVERAGE CRITERIA**. 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.

2. Plasma HIV-1 RNA quantification or plasma HIV-2 RNA quantification **MEETS COVERAGE CRITERIA** for use in monitoring disease progression in HIV-infected individuals.

3. Plasma HIV-1 RNA quantification or plasma HIV-2 RNA quantification **MEETS COVERAGE CRITERIA** for monitoring response to antiretroviral therapy.

4. Plasma HIV-1 RNA quantification or plasma HIV-2 RNA quantification **MEETS COVERAGE CRITERIA** for infants younger than 18 months born to HIV-positive mothers as antibody tests may be confounded by maternal antibodies in this time frame.

5. Plasma HIV-1 RNA quantification or plasma HIV-2 RNA quantification **MEETS COVERAGE CRITERIA** for predicting maternal-fetal transmission of HIV-1 or HIV-2.

Policy Guidelines

The Department of Health and Human Services (DHHS) recommend the following frequencies for HIV RNA measurement:

1. At entry into care
2. After initiation of treatment, within 2-4 weeks but not later than 8 weeks post-initiation
3. For first two years of antiretroviral treatment (ART), every 3-4 months
4. After two years of ART, every 6 months
5. After modification of ART due to drug toxicity, 4-8 weeks after modification
6. Every 3 months if there is a change in clinical status or detectable viremia while on ART

** 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 DHHS guidelines for use of anti-retroviral agents in adults and adolescents or pediatrics (DHHS, 2019).*

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 MNC 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.

IV. Scientific 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). The Aptima assay recently received FDA approval to aid in diagnosis, in addition to its original use of quantitation (BusinessWire, 2020; FDA, 2020).

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' definition of virological failure (Michael S. Saag et al., 2020).

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; M. S. 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, 2020). 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, 2019). 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, 2019).

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, 2020; Quinn, 2019).

Clinical Validity and Utility

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).

Avram et al. compared the cost-effectiveness of measuring viral load to guide delivery in HIV-positive women and compared it to routine cesarian delivery. A theoretical cohort of 1275 women was used, and the authors produced a decision-analytic model to compare the two techniques. The average cost of a point-of-care HIV RNA viral load test was placed at $15.22. The authors also assumed that each woman in the cohort would deliver two children. The authors defined the primary outcomes as "mother-to-child transmission, delivery mode, cesarean delivery-related complications, cost, and quality-adjusted life years", and the cost-effectiveness threshold was $100,000/quality-adjusted life year. The authors found that measuring viral load resulted in more HIV-infected neonates than routine cesarian delivery for all due to "viral exposure during more frequent vaginal births in this strategy". The authors found an increased cost of $3,883,371 and decreased quality-adjusted life years of 63 in the measurement strategy compared to the routine cesarian delivery strategy. At $100,000/quality-adjusted life year, measuring viral load was found to be cost-effective only "when the vertical transmission rate in women with high viral load below 0.68%" (compared to a baseline of 16.8%) and "when the odds ratio of vertical transmission with routine cesarean delivery for all compared with vaginal delivery was above 0.885" (compared to a baseline of 0.3). The authors concluded that "for HIV-infected pregnant women without prenatal care, quantifying viral load to guide mode of delivery using a point-of-care test resulted in increased costs and decreased effectiveness when compared with routine cesarean delivery for all, even after including downstream complications of cesarean delivery" (Avram, Greiner, Tilden, & Caughey, 2019).

V. Guidelines and Recommendations

Department of Health and Human Services (DHHS, 2019)

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 (AIII), 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, 2019).

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

- "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."

- "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, 2019).

The **CDC** refers to the above guidelines on their website (CDC, 2020).

International Antiviral Society (Michael S. Saag et al., 2020)

The International Antiviral Society published a 2020 update titled "Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults". Regarding the "HIV RT-PCR genotype test", the Society recommends performing this test at HIV diagnosis and at virological failure (Michael S. Saag et al., 2020). The guideline also recommends laboratory testing to "characterize" the HIV stage prior to starting antiretroviral testing (ART); this is done by assessing HIV RNA level.

The guideline also remarks on the frequency of testing during ART. Their recommendations are as follows:

- "If the patient continues to have viral suppression, is considered clinically stable, and is adherent to all prescribed medications, HIV RNA levels should be monitored every

3 months until the patient has achieved viral suppression for at least 1 year and monitored every 6 months thereafter (evidence rating: AIII). If an HIV RNA level above 50 copies/mL is detected after a patient previously had viral suppression, then measurement of the HIV RNA level should be quickly repeated and medication adherence and tolerability should be reassessed (evidence rating: AIa)."

- "If HIV RNA levels are above 200 copies/mL on 2 consecutive measurements, then an HIV reverse transcriptase–polymerase chain reaction genotype should be obtained and an integrase resistance test should be performed if the patient was receiving an InSTI [in integrase strand transfer inhibitor] (evidence rating: AIII)."

- "If plasma HIV genotypic resistance tests are unsuccessful, a proviral DNA analysis may be used (evidence rating: BIIa). Patients with intermittent or persistent low-level viremia between 50 copies/mL and 200 copies/mL should be assessed for treatment adherence, tolerability, and toxicity; however, changing ART regimens is not recommended unless ART toxicity or intolerability are identified (evidence rating: BIII)." (Michael S. Saag et al., 2020)

HIV Medicine Association (HIVMA, 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).

Infection Diseases Society of America (IDSA) (Thompson et al., 2020)

The IDSA recommends that "A quantitative HIV RNA (viral load) level should be obtained upon initiation of care (strong recommendation, high quality evidence)" (Thompson et al., 2020).

IDSA recommends rechecking HIV RNA after 2-4 weeks of initiating antiretroviral therapy (ART) (and no later than 8 weeks). From there, IDSA recommends "checking HIV RNA every 4-8 weeks until suppression is achieved". The IDSA also notes that viral load "should" be monitored every 3-4 months to "confirm maintenance of suppression below the limit of assay detection", 6 months for "adherent patients whose viral load has been suppressed for more than 2 years and whose clinical and immunologic status is stable", 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) (Thompson et al., 2020).

Overall, IDSA lists two primary uses for viral load testing; to establish baseline and to monitor viral suppression (Thompson et al., 2020).

American College of Obstetricians and Gynecologists (ACOG, 2018)

ACOG notes that current and ongoing research has shown that "treatment of HIV-infected pregnant women with combined antiretroviral therapy can achieve a 1–2% or lower risk of mother-to-child transmission if maternal viral loads of 1,000 copies/mL or less can be sustained, independent of the route of delivery or duration of ruptured membranes before delivery". ACOG further observes that "the risk of mother-to-child transmission in HIV-infected women with high viral loads can be reduced by performing cesarean deliveries before the onset of labor and before rupture of membranes [cesarean delivery in this document [the ACOG guideline]), in conjunction with the use of peripartum maternal antiretroviral therapy".

ACOG recommends offering a "scheduled prelabor cesarean delivery at 38 0/7 weeks of gestation to reduce the risk of mother-to-child transmission" if an HIV-positive pregnant woman is found to have a viral load of over 1000 copies/mL at or near delivery, independent of antepartum antiretroviral therapy. This recommendation also applies to patients whose viral load is unknown (ACOG, 2018).

Society for Maternal-Fetal Medicine (SMFM) (Gibson & Toner, 2020)

The SMFM published a "checklist for pregnancy management in persons with HIV". Although these checklists are not definitive, they are intended to "help ensure that all relevant elements are considered for every person with HIV during prepregnancy, antepartum, intrapartum, and postpartum periods." During the third trimester, the checklist calls for viral load to be assessed at 34-36 weeks for delivery planning (and to assess adherence and viral resistance if viral load is not suppressed). Further, if the viral load is found to be ≥1000 copies/mL at 37-38 weeks, a caesarean delivery should be scheduled for 38 weeks (Gibson & Toner, 2020).

British HIV Association (BHIVA, 2019)

BHIVA makes several recommendations regarding assessment of viral load during the routine investigation and/or maintenance of HIV-1 positive adults. Relevant recommendations are as follows:

- "We recommend that an HIV viral load should be performed at the first visit following serological diagnosis (1A).
- We recommend that undetectable viral load result whilst not on treatment needs repeating, review of serology to exclude HIV-2 and measurement on a different viral load assay (1D).
- We recommend a repeat HIV viral load in all new transfers prior to repeat prescriptions if it is not possible to confirm a recent viral load from the previous clinic (1A).
- We recommend that viral load measurements be taken at 1, 3 and 6 months after starting ART (1B).

- We recommend that additional viral load measurements are taken between 2 and 5 months after starting ART if viral load has not decreased at least 10-fold after 1 month of ART or there are concerns about the patient's adherence to therapy (1D).

- We recommend that viral load testing should be performed routinely every 6 months (1A) and might be at intervals of up to 12 months for patients established on ART that includes a PI (GPP) [general practice point].

- We recommend that viral load rebound to above 50 copies/mL should be confirmed by testing a subsequent sample (2A). Repeat testing of the same sample is not recommended.

- For patients stable on ART we recommend that:
- Frequent (3–4 monthly) viral load follow-ups of individuals with stable unsuppressed (<200 copies/mL) viral loads if they are managed as low-level viraemic patients according to the BHIVA treatment guidelines (1D).

- CSF HIV viral load measurement should be considered to exclude compartmentalisation (1C)." (BHIVA, 2019)

VI. 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). On November 20, 2020, this assay was given an FDA approval for dual use for diagnosis and viral load monitoring for HIV-1 (BusinessWire, 2020; FDA, 2020).

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.

VII. Applicable CPT/HCPCS Procedure Codes

Code Number	Code Description
87536	Infectious agent detection by nucleic acid (DNA or RNA); HIV-1, quantification, includes reverse transcription when performed
87539	Infectious agent detection by nucleic acid (DNA or RNA); HIV-2, quantification, includes reverse transcription when performed

Procedure codes appearing in Medical Policy documents are included only as a general reference tool for each policy. They may not be all-inclusive.

VIII. Evidence-based Scientific References

Abana, C. Z., Sagoe, K. W. C., Bonney, E. Y., Maina, E. K., Aziati, I. D., Agbosu, E., . . . Ampofo, W. K. (2019). Drug resistance mutations and viral load in human immunodeficiency virus type 2 and dual HIV-1/HIV-2 infected patients in Ghana. *Medicine (Baltimore), 98*(6), e14313. doi:10.1097/md.0000000000014313

ACOG. (2018). ACOG Committee Opinion No. 751: Labor and Delivery Management of Women With Human Immunodeficiency Virus Infection. *Obstet Gynecol, 132*(3), e131-e137. doi:10.1097/aog.0000000000002820

Avram, C. M., Greiner, K. S., Tilden, E., & Caughey, A. B. (2019). Point-of-care HIV viral load in pregnant women without prenatal care: a cost-effectiveness analysis. *Am J Obstet Gynecol, 221*(3), 265.e261-265.e269. doi:10.1016/j.ajog.2019.06.021

BHIVA. (2019). BHIVA guidelines for the routine investigation and monitoring of adult HIV-1-positive individuals (2019 interim update). Retrieved from https://www.bhiva.org/file/DqZbRxfzlYtLg/Monitoring-Guidelines.pdf

BusinessWire. (2020). Aptima HIV-1 Quant Dx Assay Receives Additional FDA Approval for Use as an Aid in the Diagnosis of HIV Infection. Retrieved from https://www.businesswire.com/news/home/20201120005242/en/

Caliendo, A. (2019). Techniques and interpretation of HIV-1 RNA quantitation. In Bartlett (Ed.), *UpToDate*. Waltham. MA.

CDC. (2014). Revised surveillance case definition for HIV infection--United States, 2014. *MMWR Recomm Rep, 63*(Rr-03), 1-10. Retrieved from https://www.cdc.gov/mmwr/preview/mmwrhtml/rr6303a1.htm

CDC. (2020). HIV Treatment and Care. Retrieved from https://www.cdc.gov/hiv/clinicians/treatment/treatment-clinicians.html

DHHS. (2019). Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Retrieved from https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/AdultandAdolescentGL.pdf

FDA. (2007a). Abbott RealTime HIV-1 PMA BP060002. Retrieved from https://www.fda.gov/downloads/biologicsbloodvaccines/.../ucm091196.pdf

FDA. (2007b). COBAS® AmpliPrep/COBAS® TaqMan® HIV-1 Test, Summary of Safety and Effectiveness Retrieved from https://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/PremarketApprovalsPMAs/ucm092879.pdf

FDA. (2015). BioPlex 2200 HIV Ag-Ab Assay. Retrieved from https://www.fda.gov/media/92862/download

FDA. (2016). Aptima® HIV-1 Quant Assay. Retrieved from https://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/PremarketApprovalsPMAs/UCM534609.pdf

FDA. (2019). Geenius™ HIV 1/2 Supplemental Assay. Retrieved from https://www.fda.gov/media/130312/download

FDA. (2020). HIV-1 Quant Dx Assay. Retrieved from https://www.fda.gov/media/102425/download

Gibson, K. S., & Toner, L. E. (2020). Society for Maternal-Fetal Medicine Special Statement: Updated checklists for pregnancy management in persons with HIV. *American Journal of Obstetrics & Gynecology, 223*(5), B6-B11. doi:10.1016/j.ajog.2020.08.064

Gottlieb, G. (2019). Clinical manifestations and diagnosis of HIV-2 infection. Retrieved from https://www.uptodate.com/contents/clinical-manifestations-and-diagnosis-of-hiv-2-infection?search=HIV-2&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1#H643008091

Gottlieb, G. (2020). Epidemiology, transmission, natural history, and pathogenesis of HIV-2 infection. Retrieved from https://www.uptodate.com/contents/epidemiology-transmission-natural-history-and-pathogenesis-of-hiv-2-infection?search=HIV-2&topicRef=16727&source=see_link

HIVMA. (2016). Avoid quarterly viral load testing of patients who have durable viral suppression, unless clinically indicated. *Choosing Wisely.* Retrieved from http://www.choosingwisely.org/clinician-lists/hivma-avoid-quarterly-viral-load-testing-with-durable-viral-supression/

Hopkins, M., Hau, S., Tiernan, C., Papadimitropoulos, A., Chawla, A., Beloukas, A., & Geretti, A. M. (2015). Comparative performance of the new Aptima HIV-1 Quant Dx assay with three commercial PCR-based HIV-1 RNA quantitation assays. *Journal of Clinical Virology, 69*, 56-62. doi:https://doi.org/10.1016/j.jcv.2015.05.020

Hughes, M. D., Johnson, V. A., Hirsch, M. S., Bremer, J. W., Elbeik, T., Erice, A., . . . D'Aquila, R. T. (1997). Monitoring plasma HIV-1 RNA levels in addition to CD4+ lymphocyte count improves assessment of antiretroviral therapeutic response. ACTG 241 Protocol Virology Substudy Team. *Ann Intern Med, 126*(12), 929-938. Retrieved from http://dx.doi.org/

Mor, O., Gozlan, Y., Wax, M., Mileguir, F., Rakovsky, A., Noy, B., . . . Levy, I. (2015). Evaluation of the RealTime HIV-1, Xpert HIV-1, and Aptima HIV-1 Quant Dx Assays in Comparison to the NucliSens EasyQ HIV-1 v2.0 Assay for Quantification of HIV-1 Viral Load. *J Clin Microbiol, 53*(11), 3458-3465. doi:10.1128/jcm.01806-15

Quinn, T. (2019). Global epidemiology of HIV infection. Retrieved from https://www.uptodate.com/contents/global-epidemiology-of-hiv-infection?sectionName=ORIGIN%20OF%20THE%20HIV%20EPIDEMIC&search=HIV-2&topicRef=13966&anchor=H2&source=see_link#H2

Saag, M. S., Gandhi, R. T., Hoy, J. F., Landovitz, R. J., Thompson, M. A., Sax, P. E., . . . Volberding, P. A. (2020). Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults: 2020 Recommendations of the International Antiviral Society–USA Panel. *Jama, 324*(16), 1651-1669. doi:10.1001/jama.2020.17025

Saag, M. S., Holodniy, M., Kuritzkes, D. R., O'Brien, W. A., Coombs, R., Poscher, M. E., . . . Volberding, P. A. (1996). HIV viral load markers in clinical practice. *Nat Med, 2*(6), 625-629. Retrieved from http://dx.doi.org/

Sax, P. E., Wood, Brian. (2019). The natural history and clinical features of HIV infection in adults and adolescents. Retrieved from https://www.uptodate.com/contents/the-natural-history-and-clinical-features-of-hiv-infection-in-adults-and-

adolescents?search=HIV1%20vs%20HIV2&source=search_result&selectedTitle=3~150&usage_type=default&display_rank=3

Sempa, J. B., Dushoff, J., Daniels, M. J., Castelnuovo, B., Kiragga, A. N., Nieuwoudt, M., & Bellan, S. E. (2016). Reevaluating Cumulative HIV-1 Viral Load as a Prognostic Predictor: Predicting Opportunistic Infection Incidence and Mortality in a Ugandan Cohort. *Am J Epidemiol, 184*(1), 67-77. doi:10.1093/aje/kwv303

Sollis, K. A., Smit, P. W., Fiscus, S., Ford, N., Vitoria, M., Essajee, S., . . . Peeling, R. W. (2014). Systematic review of the performance of HIV viral load technologies on plasma samples. *PLoS One, 9*(2), e85869. doi:10.1371/journal.pone.0085869

Swenson, L. C., Cobb, B., Geretti, A. M., Harrigan, P. R., Poljak, M., Seguin-Devaux, C., . . . Wensing, A. M. (2014). Comparative performances of HIV-1 RNA load assays at low viral load levels: results of an international collaboration. *J Clin Microbiol, 52*(2), 517-523. doi:10.1128/jcm.02461-13

Thompson, M. A., Horberg, M. A., Agwu, A. L., Colasanti, J. A., Jain, M. K., Short, W. R., . . . Aberg, J. A. (2020). Primary Care Guidance for Persons With Human Immunodeficiency Virus: 2020 Update by the HIV Medicine Association of the Infectious Diseases Society of America. *Clinical Infectious Diseases*. doi:10.1093/cid/ciaa1391

IX. Review/Revision History

Effective Date	Summary
05/15/2022	Initial Policy Implementation