QUANTITATIVE HIV RNA (VIRAL LOAD)

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INSTRUCTIONS FOR USE

Physician Decision Support (PDS) is a lab ordering tool operated by BeaconLBS. This Clinical Guideline supports the Questions and Answers that appear in PDS for tests referenced in this document. UnitedHealthcare reserves the right, in its sole discretion, to modify its Clinical Guidelines as necessary. This Clinical Guideline is provided for informational purposes. It does not constitute a Medical Policy or medical advice.

GUIDELINES

Quantitative Human Immunodeficiency Virus (HIV) testing (viral load) for HIV infected patients in the following situations:

- To obtain a baseline value when the HIV patient enters care.
- To assess regimen efficacy (measurement within 2-4 weeks of initiation or modification of antiretroviral therapy).
- To monitor viral suppression (measurement every 3-4 months in patients with stable clinical and laboratory parameters).
- In pregnant women, should be measured at the initial visit, 2-4 weeks after antiretroviral therapy is initiated or modified, monthly until virus is undetectable and at least every 3 months thereafter. Testing should be repeated at 34-36 weeks’ gestation to inform decisions about mode of delivery.
- In children, should be measured at the time of diagnosis and every 3-4 months thereafter or more frequently on the basis of clinical or laboratory parameters.
- May be used in infants as a confirmatory test after a positive DNA PCR test.
- May be used to diagnose acute antibody negative HIV infection or resolve indeterminate serologic results.
These recommendations are based on current guidelines from the United States Department of Health and Human Services, Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children, International AIDS Society-USA Panel, Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission, and the HIV Medicine Association of the Infectious Diseases Society of America.1,12,20,29

**BACKGROUND**

The development of polymerase chain reaction (PCR) paved the way for progress in HIV testing. The detection of HIV-1 proviral DNA in peripheral blood mononuclear cells was reported in 1988.1 Previous viral detection studies relied on culture of virus from infected peripheral blood monocytes or plasma. The original nucleic acid tests were qualitative, and soon thereafter, quantitative assays were developed. In 1991 successful measurement of HIV RNA in plasma using polymerase chain reaction was reported.2 That same year, researchers demonstrated that plasma HIV RNA levels correlated with disease stage and response to antiretroviral therapy.3 In the 1990s automation improved the utility of nucleic acid testing as a clinical laboratory modality.4 Breakthroughs in HIV nucleic acid testing revolutionized safety standards for blood banks, decreasing the number of cases of HIV transmitted by transfusion.5-7

HIV nucleic acid testing has become a mainstay in the detection of HIV and the clinical management of HIV patients. Quantitative HIV plasma RNA viral load is used to monitor antiretroviral treatment efficacy, allowing comparisons of baseline, pretreatment and post-treatment levels to guide therapeutic decisions of when to initiate and when to modify antiretroviral therapy.8

Because quantitative HIV RNA polymerase chain reaction is used to measure baseline viral load, assays must be able to measure high titers like those representative of peak levels of viremia. Assays must also be able to measure low titers because the goal of antiretroviral therapy is to suppress viremia below detection limits. After initiation of antiretroviral therapy, the drug regimen is considered effective if viral load falls below 50 copies/mL within 24 weeks of treatment.9 Therefore, ideal assays should be sensitive at the lower limit of detection, but specificity is also important to avoid modifying regimens that could achieve viral suppression. Industry has attempted to improve sensitivity at the lower limit of detection while maintaining specificity, and platform comparisons have focused on assessing performance at low titers.

The clinical significance of low levels of viremia remains uncertain. A challenging area of laboratory interpretation has been discriminating between low-levels of viremia in an otherwise optimally treated patient and early treatment failure. There is no consensus on how to manage patients whose plasma HIV RNA measures between 48 and 200 copies/mL.8 Uncertainty still exists as to the source of this viremia, and possible theories include continued viral replication10 and populations of latently infected cells.10,11 Even though viral blips may transiently increase HIV RNA levels to 1,000 copies/mL, they are not considered evidence of virologic failure.12 Regardless of its etiology, the issue of persistent viremia has resulted in modification of guidelines for clinicians and has motivated industry to develop newer versions of quantitative HIV RNA assays.8 Until further studies can elucidate the significance of viremia at the lower level of detection, expert panels have revised their guidelines, shifting cut-offs for virologic failure up from the level of detection, which for most assays is less than 20 to 75 copies/mL, depending on the assay used, to 200 copies/mL to prevent elevations caused by blips and assay variability from influencing therapeutic decisions.1 Given that sensitivities vary with each methodology, it has also been recommended that the same testing platform is used consistently for a patient.13-15
Acute HIV infection is the period following viral transmission and before antibody seroconversion, during which the risk of HIV transmission is high relative to chronic HIV infection. Diagnosis of acute HIV infection remains a challenge as symptoms may not be present, and standard detection methods such as antibody tests will fail to detect the new infection. The use of HIV RNA tests may be recommended in high incidence areas to detect these individuals. Additionally, viral load or qualitative NAT could also be recommended for patients being seen with indeterminate serologic results.

**Clinical Implications**

*Implications for Ordering Resistance Tests:*

Viral load is used to determine if drug resistance testing can be performed; when plasma HIV RNA is less than 500 copies/mL, there may not be enough sequence for amplification for genotypic or phenotypic resistance testing.

*Implications for When to Modify Therapy:*

Plasma viral load is the most important clinical test used to identify treatment failure. If the viral load is confirmed to be greater than 200 copies/mL in a treated patient, virologic failure exists according to the 2013 recommendations of the Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents.

*Implications for the Decision to Perform Cesarean Section in Pregnant Women:*

If HIV viral load is greater than 1,000 copies/mL, cesarean section is recommended according to the 2012 guidelines of the Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission.

*Implications for When to Initiate Antiretroviral Therapy:*

While the CD4 count is used to guide when to initiate antiretroviral therapy, the Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children suggested in their 2012 guidelines for care of children that if plasma HIV RNA viral load is greater than 100,000 copies/mL, treatment is recommended regardless of CD4 count and symptomatology. The International AIDS Society-USA Panel no longer recommends initiating antiretroviral therapy based on HIV RNA levels.

**CLINICAL EVIDENCE**

By the late 1990s evidence was mounting that HIV RNA viral load predicted clinical outcomes to therapy. An AIDS Clinical Trials Group study of 391 adults at an intermediate stage of disease found a 90% risk reduction for disease progression with a reduction of 1.0 log in the plasma HIV RNA posttreatment. Another AIDS Clinical Trials Group study of 566 treated children showed a risk reduction for disease progression of roughly 50% for each log reduction in baseline plasma HIV RNA. In 1999, researchers at the FDA published a meta-analysis that correlated a reduced number of adverse clinical events in 5,000 patients with a decrease in HIV viral load at 24 weeks post-treatment.
HIV viral load predicts mother to child transmission. An AIDS Clinical Trials Group study of 497 women that controlled for covariates such as CD4+ lymphocyte count and p24 antibody levels found that only HIV-1 RNA levels correlated with risk of mother to child transmission.

In addition to measuring viral load in adults and children, quantitative HIV RNA serves another purpose for pediatric HIV patients. Quantitative HIV RNA assays are as sensitive as HIV DNA PCR for the diagnosis of HIV in infants. One study reported sensitivities of 29% during the first week of life and greater than 90% by 29 days of age. Subsequently, quantitative HIV RNA is a useful confirmatory test for diagnosis of HIV in infants.

Testing

There are several methodologies approved by the FDA for measuring plasma HIV viral load, and reviews of platform comparisons have been published. One FDA approved test, the COBAS® AmpliPrep/COBAS® TaqMan® system, uses a reverse transcriptase-polymerase chain reaction that targets the gag p24 region of HIV-1. The system combines an automated extraction unit with an automated amplification, detection and quantification system. The COBAS® Ampliprep Instrument is an automated sample preparation device. COBAS® Taqman® is a real-time PCR system that uses a fluorogenic probe to detect specific amplification products. The assay was approved by the US Food & Drug Administration on May 11, 2007. The initial version of the COBAS Ampliprep assay (version 1) had a lower limit of detection (LLOD) of 48c/mL. This assay version has largely been replaced by the TaqMan version 2. The current Taqman version 2 has a LLOD of 20 copies/mL and better performance with non-B subtypes. The Abbott RealTime assay has a LLOD of 40 with good performance with subtypes and low viral loads. bDNA assays are also available with LLOD of 75c/mL.

New versions of HIV RNA assays are being developed to improve detection at the lower level of range. It remains to be seen if a lower level of detection will provide clinicians with clinically actionable information.

Guidelines and Recommendations

The following guidelines are current group consensus recommendations for measuring plasma HIV RNA and for diagnosing HIV.

Department of Health and Human Services

The 2013, Department of Health and Human Services guidelines recommend the following:

- Viral load testing is recommended when the HIV patient enters into care.
- Viral load testing is recommended every 3-6 months until therapy is initiated.
- Viral load testing is recommended when therapy is initiated and 2-8 weeks after. If plasma load is detectable after initiation of therapy, levels should be repeated every 4-8 weeks until the level is less than 200 counts/mL, then every 3-6 months.
- Viral load testing is recommended when therapy is modified and 2-8 weeks thereafter, then every 3-6 months.
- Viral load testing is recommended in the setting of virologic failure and if otherwise clinically indicated.

For patients with viral suppression and stable clinical status for 2-3 years or more, the panel notes that some experts may extend the testing interval to monitoring HIV RNA levels every 6 months.
In 2012, the Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children\textsuperscript{12} made the following recommendations:

- HIV RNA can be used as a confirmatory test for infants with a positive DNA PCR test; the benefits include confirmation at a lower cost, measurement of baseline viral load, and increased sensitivity for detection of HIV non-subtype B. Tests with low levels of HIV RNA (less than 5,000 copies/mL) should be repeated for confirmation of diagnosis of HIV in an infant.
- Viral load testing is recommended at the time of diagnosis and at least every 3-4 months thereafter. More frequent viral load testing should be considered on the basis of clinical and laboratory parameters.
- When viral load is greater than 100,000 copies/mL, antiretroviral treatment is recommended for children, even for those with minimal or no clinical symptoms and normal immune status.

International AIDS Society-USA Panel\textsuperscript{9}

In 2012, the International AIDS Society-USA Panel\textsuperscript{9} made the following recommendations:

- HIV-1 RNA should be measured at least every 3 months after therapy is initiated or changed following virologic failure, until virologic suppression is confirmed.
- After one year of suppression, monitoring can be done every 6 months if adherence is not a question.
- HIV-1 RNA should be suppressed to less than 50 copies/mL by 24 weeks of antiretroviral therapy.
- If viral rebound occurs, as confirmed by two HIV-1 RNA levels at least 2-4 weeks apart, clinical investigation of regimen tolerability, drug-drug interactions and adherence is recommended. Resistance testing is recommended for confirmed virologic failure.

Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission\textsuperscript{20}

In 2012, the Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission\textsuperscript{20} included the following recommendations:

- Viral load testing is recommended for HIV patients during pregnancy at the initial visit, 2-4 weeks after antiretroviral therapy is initiated or modified and then monthly until virus is undetectable and at least every 3 months thereafter. Testing is recommended more frequently if adherence is uncertain.
- Viral load testing is recommended at approximately 34 to 36 weeks gestation, and women with levels greater than 1,000 copies/mL should be counseled on cesarean section.
- Viral load testing is recommended in women with HIV to ensure viral levels are stable and suppressed before conception.

HIV Medicine Association of the Infectious Diseases Society of America\textsuperscript{29}

In 2013, the HIV Medicine Association of the Infectious Diseases Society of America published new primary care guidelines for the management of HIV infected patients.\textsuperscript{29} Those guidelines included the following recommendations for plasma HIV RNA levels (viral load testing):

- A quantitative HIV RNA (viral load) level should be obtained upon initiation of care.
- Viral load is generally monitored every 3–4 months in untreated patients and patients on stable ART. This interval may be prolonged to 6 months for adherent patients whose viral load has been suppressed for more than 2–3 years and whose clinical and immunologic status is stable. Viral load should be monitored more frequently after initiation or change in ART: preferably within 2–4 weeks, and not more than 8 weeks, after initiation or modification, with repeat testing every 4–8 weeks until viral load
becomes undetectable.

**US FOOD AND DRUG ADMINISTRATION (US FDA)**

There are several HIV viral load assays available that are US Food and Drug Administration (FDA) approved for clinical use. Clinicians should be aware of changes in the type of assay used and the associated variability and the interpretation of results between assays.

**CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)**

For Medicare populations, CMS does not pay for screening procedures (tests) performed in the absence of signs or symptoms. (Section 1862(a)(7) of the Social Security Act)

There are several CMS policies that apply to HIV Testing (Prognosis, including Monitoring). In some cases, CMS reimbursement is limited to FDA approved and “home-brew” tests only.

Additionally, there may be a limit to the number of viral load assays per patient per 12 month time period. Physicians should consult their state’s regulations.

**APPLICABLE CODING**

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<td>Infectious agent detection by nucleic acid (DNA or RNA); HIV-1, quantification</td>
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REFERENCES


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POLICY HISTORY/REVISION HISTORY

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