Human Immunodeficiency Virus (HIV)

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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.[1] 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.[2] Terms such as male and female are used when necessary to refer to sex assigned at birth.

II. 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) For individuals 11 to 65 years of age, initial screening for HIV infection with an antigen/antibody combination assay **MEETS COVERAGE CRITERIA**.

2) For individuals 11 to 65 years of age, repeat antigen/antibody screening for HIV infection (see Note 1) **MEETS COVERAGE CRITERIA**.

3) For individuals who will begin pre-exposure prophylaxis (PrEP), for individuals receiving PrEP, or for individuals with elevated risk factors for an HIV infection (see Note 2), screening for an HIV infection with an antigen/antibody combination assay or with a rapid antibody test (see Note 1) **MEETS COVERAGE CRITERIA.**

4) For individuals for whom initial screening was positive for an HIV infection, the HIV-1/HIV-2 antibody differentiation assay (see Note 1) **MEETS COVERAGE CRITERIA.**

5) Nucleic acid testing (qualitative or quantitative) for HIV-1 and HIV-2 (see Note 1) **MEETS COVERAGE CRITERIA** in **any** of the following situations:
   a) For individuals for whom initial screening was positive for an HIV infection.
   b) For individuals for whom initial screening was indeterminate for an HIV infection.
   c) For individuals for whom recent exposure is suspected or reported.

6) HIV genotyping or phenotyping **MEETS COVERAGE CRITERIA** for **any** of the following situations:
   a) Prior to initiating doravirine therapy (genotyping and phenotyping is required).

b) For individuals who have failed a course of antiviral therapy.

c) For individuals who have suboptimal viral load reduction.

d) For individuals who have been noncompliant with therapy.

e) To guide treatment decisions in individuals with acute or recent infection (within the last 6 months).

f) For antiretroviral naïve individuals entering treatment.

g) For all HIV-infected pregnant individuals in the following situations:

i) Before initiation of antiretroviral therapy.

ii) For those with detectable HIV RNA levels.

7) For treatment-experienced individuals on failing regimens who are thought to have multidrug resistance, HIV phenotyping **MEETS COVERAGE CRITERIA**.

8) Plasma quantification of HIV-1 RNA or HIV-2 RNA (see Note 1, Note 3) **MEETS COVERAGE CRITERIA** for **any** of the following situations:

a) For monitoring disease progression in HIV-infected individuals.

b) For monitoring response to antiretroviral therapy.

c) For infants younger than 18 months born to HIV-positive mothers (antibody tests may be confounded by maternal antibodies in this time frame).

d) For predicting maternal-fetal transmission of HIV-1 or HIV-2.

9) Screening for HIV-1 and HIV-2 using an antibody test that does not provide rapid results and does not incorporate antigen testing **DOES NOT MEET COVERAGE CRITERIA**.

The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of an individual's illness.

10) HIV antigen testing independent of antigen/antibody testing **DOES NOT MEET COVERAGE CRITERIA.**

11) Routine use of combined genotyping and phenotyping **DOES NOT MEET COVERAGE CRITERIA**.

12) Drug susceptibility phenotype prediction using genotypic comparison to known genotypic/phenotypic database **DOES NOT MEET COVERAGE CRITERIA**.

NOTES:

Note 1: Antibody and antibody/antigen testing should not be repeated more often than once every 90 days. Nucleic acid testing (qualitative or quantitative) should not be repeated more often than once every month.

Note 2: Risk factors for HIV infection:[3,4]

- Men who have sex with men (MSM), men who have sex with men and women (MSM/W), and transgender individuals
- Having a sexual encounter with an individual who has an HIV infection
- Having had multiple sexual partners since the individual's last HIV test
- Sharing needles, syringes, or other drug injection equipment (e.g., cookers)
- Exchanging sex for money or drugs
- Having a previous or concurrent STI, hepatitis, or tuberculosis
- Having sex with an individual with the above high-risk factors or with an individual with unknown sexual history

Note 3: 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.

III. Table of Terminology

Term	Definition
AAP	American Academy of Pediatrics
AI/A1	Strong panel support – Evidence from ≥1 RCTs published in the peer-reviewed literature or presented in abstract form at peer-reviewed scientific meetings
ACOG	American College of Obstetricians and Gynecologists
AIDS	Acquired Immune Deficiency Syndrome
AII/A2	Strong panel support - Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes
AIIa	Strong panel support – Evidence from cohort or case-control studies published in the peer-reviewed literature
AIII	Strong panel support – Based on the panel's analysis of the available evidence
ART	Antiretroviral treatment (also refers in some instances to antiretroviral testing and antiretroviral therapy)
ARV	Antiretroviral
ASHM	The Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine
ATCC	American Type Culture Collection
BHIVA	British HIV Association
BII/B2	Moderate panel support - Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes
BIIa	Moderate panel support – Evidence from cohort or case-control studies published in the peer-reviewed literature
BIII	Moderate panel support – Based on the panel's analysis of the available evidence
CCR5	C-C chemokine receptor type 5
CD4	Cluster of differentiation 4
CDC	Centers for Disease Control and Prevention
CIII	Limited or weak panel support – Based on the panel's analysis of the available evidence
CMS	Centers for Medicare and Medicaid
CPD	Citrate-phosphate-dextrose
CSF	Cerebrospinal fluid

CTM	COBAS TaqMan
DHHS	Department Of Health and Human Services
DNA	Deoxyribose nucleic acid
EACS	European Acquired Immune Deficiency Syndrome Clinical Society
EDTA	Ethylenediaminetetraacetic acid
FDA	Food and Drug Administration
GIS	Genotypic interpretation systems
GPP	General practice point
GT	Genotype
HIV	Human Immunodeficiency Virus
HIV-1	Human Immunodeficiency Virus, Type 1
HIV-2	Human Immunodeficiency Virus, Type 2
HIVDR	HIV drug resistance
HIVMA	HIV Medicine Association
HIV-VL	HIV viral load
IDSA	Infection Diseases Society of America
INSTI	Integrase strand transfer inhibitor
K103N	Lysine to aspartate polymorphism
LADRV	Low abundant drug-resistant variant
LDT	Laboratory-developed test
MSM	Men who have sex with men
MSM/W	Men who have sex with men and women
NAT	Nucleic acid tests
NAAT	Nucleic acid amplification test
NGS	Next-generation sequencing
NNRTIs	Non-nucleoside reverse transcriptase inhibitors
NRTIs	Nucleoside reverse transcriptase inhibitors
NYSDOH	New York State Department of Health
PCR	Polymerase chain reaction
PEP	Postexposure prophylaxis
PIs	Protease inhibitors
PR	Protease
PrEP	Pre-exposure prophylaxis
RAL	Raltegravir
RCT	Randomized controlled trial
RNA	Ribonucleic acid
RT	Reverse transcriptase
RT-PCR	Reverse transcriptase polymerase chain reaction
RVA	Recombinant virus assay
SMFM	Society for Maternal-Fetal Medicine
SS	Sanger sequencing
TDR	Total drug resistance
USPSTF	United States Preventive Services Task Force

IV. Scientific Background

Human immunodeficiency virus (HIV) targets the immune system, eventually hindering the body's ability to fight infections and diseases. If not treated, a HIV infection may lead to AIDS which is a condition caused by the virus. There are two main types of HIV: HIV-1 and HIV-2; both are genetically different. HIV-1 is more common and widespread than HIV-2.

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).[5]

Three primary realtime 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 AmpliPrep/ TaqMan HIV-1 Test version 2" by Roche Diagnostics, "RealTime HIV-1" and the Alinity m HIV-1 test (both by Abbott Molecular), and "Aptima HIV-1 Quant Dx Assay" by Hologic.[5] In 2020, the Aptima assay received FDA approval to aid in diagnosis, in addition to its original use of quantitation.[6,7]

Sources of variability between HIV-1 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.[8] 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.[5]

Overall, studies of realtime RT-PCR tests have shown high concordance, high correlation values, and good agreement among all assays.[9] However, their manufacturers have reported that variation and error tend to increase at the lower limits of quantitation of the assays.[10] 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 consistent with the current HIV treatment guidelines' definition of virological failure.[11]

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.[12,13] Viral RNA levels can also transiently rise due to acute illness, herpes outbreak, or vaccination; however, values usually return to baseline within one month.[5] 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.[5]

HIV-2

Human immunodeficiency virus type 1 (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.[14] 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.[15] This is particularly crucial as HIV-1 assays typically do not properly detect HIV-2 viral load.[16] 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.[15]

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.[16]

Although HIV-2 is endemic to West Africa 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. There were 24 cases of HIV-2 identified in New York City between 2010 and 2020, with 25 additional probable cases. Additionally, as much as 5% of HIV cases are thought to be HIV-2.[14,17]

Drug Resistance

Human immunodeficiency virus replicates rapidly; a replication cycle rate of approximately one to two days ensures that after a single year, the virus in an infected individual may be 200 to 300 generations removed from the initial infection-causing virus.[18] This leads to great genetic diversity of each HIV infection in an individual. As an RNA retrovirus, HIV requires the use of a reverse transcriptase for replication purposes. A reverse transcriptase is an enzyme which generates complimentary DNA from an RNA template. This enzyme is error-prone with the overall single-step point mutation rate reaching about 3.4×10^{-5} mutations per base per replication cycle,[19] leading to approximately one genome in three containing a mutation after each round of replication (some of which confer drug resistance). This rate is comparable to other RNA viruses. This pace of replication, duration of infection, and size of the replicating population allows the retrovirus to evolve rapidly in response to selective influences.[18]

Due to the high rate of mutation in HIV viruses, drug resistance mutations are common. Some drugs may be resisted by a single mutation—these drugs have a "low genetic barrier" to resistance. Such mutations are common enough to be termed "signature mutations," which are frequently associated with a specific drug resistance. For example, the K103N mutation commonly leads to resistance for efavirenz. Efavirenz is a standard retroviral medication used to treat and prevent HIV and AIDs. Accessory mutations occur during ART. These mutations can increase drug resistance. It is important to switch ART to avoid the accumulation of additional resistance mutations. To combat this, medical professionals can now assess drug-resistant HIV variants using phenotypic testing and genotypic testing.[20]

Genotypic assays detect the presence of specific drug resistance mutations in several different genes (protease, reverse transcriptase, and integrase genes). For example, assays may test for resistance in nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), or protease inhibitors (PIs). The definition of a resistance conferring mutation is blurred, but generally includes one or more of the following conditions:

- The mutation confers phenotypic resistance when introduced into a drug-sensitive laboratory strain of HIV.
- The mutation is selected for during serial in vitro passage of the virus in the presence of a drug.
- The mutation is selected for during clinical therapy with that drug.
- The presence of the mutation in clinical isolates is associated with phenotypic resistance and virologic failure.[21]

Interpretation of genotypic data may be done either by clinical expertise or through a database (in which the genotype is correlated with the phenotype). Phenotypic resistance assays measure the extent to which an antiretroviral drug inhibits viral replication. Phenotypic testing typically assesses the fold-change in susceptibility of a patient's virus and the treatment response, while also correlating the mutations present with the fold-change in susceptibility. Recombinant virus assays (RVAs) are used; protease, reverse transcriptase, or integrase gene sequences from circulating viruses are inserted into a reference strain of HIV, and this new HIV strain is measured by the phenotypic assay.[21]

Several HIV genotypic assays are available. The ViroSeq HIV-1 Genotyping System by Abbott helps to detect HIV-1 genomic mutations that may lead to resistance to certain types of antiretroviral drugs.[22] The ATCC® HIV-1 Drug Resistance Genotyping Kit has been developed by the American Type Culture Collection, the Centers for Disease Control and Prevention (CDC) and Thermo Fischer Scientific; this is a realtime- polymerase chain reaction (rt-PCR) assay which may help to identify and monitor HIV-1 drug resistance.[23]

The primary phenotypic assay is "PhenoSense" from LabCorp. The human immunodeficiency virus 1 (HIV-1) PhenoSense GT® Plus Integrase (Monogram® Phenotype + Genotype) test by LabCorp measures HIV genotypic and phenotypic resistance from plasma samples.[24]

Advantages of the genotype assays include lower cost, more readily available, and shorter turnaround time. However, interpretation of these assays is complicated by combinations of individual mutations that may have a differential effect on resistance that differs from the individual mutation alone.[21] Mutation combinations are known to cause resistance to certain drugs, but increase susceptibility to others, impact viral fitness, and contribute to major pathways of resistance; additionally, the interactions of mutations affecting various mechanisms can be difficult to predict. Over 20 rules-based genotypic interpretation systems (GIS) have been proposed.[21,25]

Advantages of phenotypic assays include an ability to measure resistance more directly and examine the relative effect of multiple mutations on drug resistance. Limitations of the phenotypic assays include a longer turnaround time, greater expense, and biologic cut-offs above achievable drug levels. Phenotypic resistance assays may be helpful when evaluating HIV strains with known or suspected complex drug resistance mutation patterns as their actual resistance may not be accurately predicted by simply detecting the presence of multiple mutations.[21] Both assays are limited by decreased sensitivity for low-level minority variants that comprise less than one to 20 percent of the virus population.[21]

Analytical Validity

Rosemary, et al. (2018) performed a comparison of two genotyping assays, ViroSeq and ATCC (manufactured by Thermo-Fisher Scientific) kit. A total of 183 samples with a viral load ≥1000 copies/mL were sequenced by ViroSeq and randomly selected (85 successfully genotyped, 98 unsuccessfully genotyped). The ATCC kit also genotyped 115 of the 183 samples, and out of the 98 unsuccessfully genotyped samples, the ATCC kit was able to genotype 42. Overall, 127 of the 183 samples were

genotyped. The authors noted that the sequences of the genotyped samples were 98% identical and had "similar HIVDR profiles at individual patient level."[26]

Braun, et al. (2020) evaluated the diagnostic performance and analytical validity of the Alinity m HIV-1 assay, a test which uses a dual target and dual probe "against the highly conserved target regions of the HIV-1 genome." As part of the international and multisite study, Alinity m was compared with four other commercially available tests. The Alinity assay performed comparatively to currently available HIV-1 tests with "comparable detection of 16 different HIV-1 subtypes (R2 = 0.956). A high level of agreement (>88 %) between all HIV-1 assays was seen near clinical decision points of 1.7 Log10 copies/mL (50 copies/mL) and 2.0 Log10 copies/mL (200 copies/mL)." Additionally, a high level of detectability (≥97 % hit rate) was shown with reproducibility across sites.[27]

Clinical Utility and Validity

Zhang, et al. (2005) compared two phenotyping assays, Antivirogram and PhenoSense. Reverse transcriptase inhibitor susceptibility results were evaluated for 202 isolates from Antivirogram and 126 from PhenoSense. The authors found the median deviance for wild-type and mutant isolates to be lower for PhenoSense compared to Antivirogram, and PhenoSense was more likely to detect resistance to abacavir, didanosine, and stavudine when common drug resistance mutations were present.[28]

Hopkins, et al. (2015) 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.[29]

Sempa, et al. (2016) 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.[30]

Shen, et al. (2016) assessed the ability to predict phenotypic drug resistance from genotypic data. The authors used two machine learning algorithms to predict drug resistance to HIV PIs and reverse transcriptase inhibitors as well as the severity of that resistance from a query sequence. The accuracy of these classifications was found to be >0.973 for eight PR inhibitors and 0.986 for ten RT inhibitors and the r^2 was 0.772–0.953 for the PR cohort and 0.773–0.995 for the RT cohort. The algorithms' results were verified by "five-fold cross validation" on the genotype-phenotype datasets.[31]

Lindman, et al. (2019) 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. There were 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.[32]

Avram, et al. (2019) 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."[33]

Raymond, et al. (2020) evaluated the performance of the Vela Dx Sentosa next-generation sequencing (NGS) system for HIV-1 DNA genotypic resistance. There were 40 DNA samples analyzed with Vela Dx Sentosa assay and the results were compared with Sanger sequencing. The Vela Dx Sentosa assay was 100% successful in amplifying and sequencing the protease and reverse transcriptase, and 86% successful in amplifying integrase sequences when the HIV DNA load was greater than 2.5 log copies/million cells. The Sentosa and Sanger sequencing were concordant for predicting protease-reverse transcriptase resistance in 20% of the 14/18 samples which were successfully sequenced. Sentosa was able to predict a higher level of resistance in three of the samples. The Vela Dx Sentosa predicted the prevalence of drug resistance to PIs (7%), nucleoside reverse transcriptase inhibitor (59%), non-nucleoside reverse transcriptase inhibitor (31%), and integrase inhibitors (20%). Overall, the authors conclude that the Vela Dx Sentosa assay can accurately predict HIV DNA drug resistance.[34]

Fogel, et al. (2020) also analyzed the ability of next-generation sequencing methods to analyze HIV drug resistance. In this case, 145 plasma samples were analyzed using the ViroSeq HIV-1 Genotyping System and the veSEQ-HIV assay. Results were compared with the Abbott RealTime Viral Load assay. A total of 142 HIV protease and reverse transcriptase sequences and 138 integrase sequences were obtained with ViroSeq. On the other hand, veSEQ-HIV detected 70.4% of the samples with protease, reverse transcriptase, and integrase sequences. Drug resistance mutations were detected in 33 ViroSeq samples and 42 veSEQ-HIV samples. Overall, veSEQ-HIV predicted more drug resistance mutations and worked better for larger viral loads. Results from veSEQ-HIV strongly correlated with the results from Abbott RealTime Viral Load assay. The authors conclude that the veSEQ-HIV assay provided results for most samples with higher viral loads, was accurate for predicting drug resistance mutations, but detected mutations at lower levels compared with the ViroSeq assay.[35]

Pröll, et al. (2022) investigated whether NGS from proviral DNA and RNA could be an alternative to using plasma viral RNA as the material of choice for genotypic resistance testing at the start of ART and virologic failure for patients with low viremia. When taking samples from 36 patients, with varying viral loads of 96 to 390,000 copies/mL, the researchers found 2476 variants/drug resistance mutations by SS, while 2892 variants were found by NGS. Researchers stated, "An average of 822/1008 variants were

identified in plasma viral RNA by Sanger or NGS sequencing, 834/956 in cellular viral RNA, and 820/928 in cellular viral DNA." This demonstrates that cellular RNA and cellular viral DNA could serve as viable substitutes when testing for variant detection and genotypic resistance among patients with HIV and low viremia.[36]

Ehret, et al. (2022) tested the performance of the "Xpert® HIV-1 Viral Load (VL) XC" HIV RNA quantitative assay made by Cepheid. This assay has been redesigned to use a dual target approach. The authors tested 533 fresh and frozen samples from HIV-1 positive patients on the Abbott HIV assay and the Xpert XC assay. "The Xpert XC assay yielded valid results in 98.5% (N = 528/536) of cases." The authors conclude that "the Xpert XC assay showed excellent correlation with the Abbott assays for all tested HIV-1 subtypes."[37]

V. Guidelines and Recommendations

Department of Health and Human Services (DHHS)

The DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents updated the guidelines on use of antiretroviral drugs in 2022. The panel states "Viral load is the most important indicator of initial and sustained response to ART and should be measured in all people with HIV at entry into care **(AI),** at initiation of therapy (if treatment is delayed) **(AI),** and on a regular basis thereafter. For those people in whom therapy is delayed, repeat viral load testing is recommended approximately every 3 to 6 months **(BIII),** aligning with CD4 count testing. Repeating viral load testing at these intervals provides an opportunity for discussions about the benefits of ART, both for the treatment of HIV and prevention of HIV transmission. Pre-treatment viral load level is also an important factor in the selection of an initial ARV regimen because some ARV drugs or regimens have been associated with poorer responses in people with high baseline viral load "

The panel's recommendations on the frequency of viral load monitoring are summarized below:[16]

- **"After initiation of ART:** Plasma viral load should be measured when ART is initiated **(AI)** and within 4 to 8 weeks after treatment initiation **(AIII).** The purpose of these measurements is to confirm an adequate virologic response to ART, indicating appropriate regimen selection and individual adherence to therapy. Repeat viral load measurement should be performed every 4 to 8 weeks until the level falls below the assay's limit of detection **(BIII).**
- **In people with viral suppression, with ART modification because of regimen simplification or drug toxicity:** 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 people on a stable, suppressive ARV regimen:** Viral load measurement should be repeated every three to four months **(AIII)** or as clinically indicated to confirm continuous viral suppression. Clinicians may extend the interval to six months for adherent people whose viral load has been suppressed for more than a year, whose clinical and immunologic status is stable, and who are not at risk for inadequate adherence **(AIII).**
- **In people with virologic failure who require a change in ARV regimen:** Plasma viral load should be measured before ART change and within four to eight weeks after treatment modification **(AIII).** The purpose of the measurements is to confirm an adequate virologic response to the new regimen. Repeat viral load measurement should be performed every four to eight weeks until the level falls below the assay's limit of detection **(BIII).** If viral suppression is not possible, repeat viral load measurement every three months or more frequently if

indicated **(AIII).**

- **In people 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, several other factors—such as individual adherence to prescribed medications, suboptimal drug exposure, or drug interactions—should be assessed. People who fail to achieve viral suppression should undergo drug-resistance testing to aid in the selection of an alternative ARV regimen."

The DHHS note that CD4 count is in one of the most important indicator of immune function in people with HIV, with lower pre-treatment counts being strongly associated with disease progression and increased mortality. The following are recommendations related to CD4 count monitoring and assessment:

- "Monitoring of lymphocyte subsets other than CD4 (e.g., CD8, CD19) **is not recommended (BIII)** because it has not been proven to be clinically useful and is more expensive than monitoring CD4 count alone."
- "CD4 count should be measured in all people with HIV at entry into care **(AI).** It is the key factor in determining the need to initiate OI prophylaxis and the urgency to initiate ART **(AI),** even though ART is recommended for all people with HIV, regardless of CD4 count **(AI).**"
- "ART is recommended for all people with HIV. For people with HIV and pre-treatment CD4 count <300 cells/mm^3, repeating CD4 count 3 months after ART initiation will provide information regarding the magnitude of immune reconstitution **(AIII).** This repeat measurement is most important in people who initiate ART with more advanced disease and require OI prophylaxis or treatment."

The guideline also comments on HIV-2. Although the optimal treatment strategy has not been defined, the guideline does recommend that quantitative plasma HIV-2 RNA viral load testing should be performed before initiating ART (AIII). 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.[16]

In an updated review in 2022, the DHHS also strongly recommended (AIII) hat "A blood sample for genotypic resistance testing should be sent to the laboratory before initiation of ART." Moreover, "Pregnancy testing should be performed in persons of childbearing potential before initiation of ART."

The DHHS propounds further, stating the following:

- "Combination immunoassays that detect HIV-1 and HIV-2 antibodies and HIV p24 antigen (Ag/Ab assays) are part of the recommended initial laboratory HIV testing algorithm, primarily due to their enhanced ability to detect acute HIV infection. Specimens that are reactive on an initial Ag/Ab assay should be tested with an immunoassay that differentiates HIV-1 from HIV-2 antibodies. Specimens that are reactive on the initial assay and have either negative or indeterminate antibody differentiation test result should be tested for quantitative or qualitative HIV RNA; an undetectable HIV RNA test result indicates that the original Ag/Ab test result was a false positive. Detection of HIV RNA in this setting indicates that acute HIV infection is highly likely."
- "HIV infection should be confirmed by repeat quantitative HIV RNA testing or subsequent testing to document HIV antibody seroconversion."
- "The proposed threshold of <3,000 copies/mL is based on historical data that used laboratory

methods that are now considered obsolete. These older viral load assays demonstrated false-positive cases of acute HIV infection at HIV RNA levels of <3,000 copies/mL. However, improvements in plasma viral load methodology suggest that any positive result on a quantitative plasma HIV RNA test in the setting of a negative or indeterminate antibody test result is highly consistent with acute HIV infection, including at HIV RNA levels of <3,000 copies/mL. HIV RNA levels in acute infection are generally very high (e.g., >100,000 copies/mL); however, levels may be <3,000 copies/mL in the earliest weeks following infection as viral load continues to rise. Therefore, when a low-positive quantitative HIV RNA test result is present at this level, the HIV RNA test should be repeated on a new blood specimen to confirm the diagnosis. Repeated false-positive HIV RNA test results are unlikely. When acute HIV infection is suspected in a person with a negative or indeterminate HIV antibody test result, a quantitative or qualitative HIV RNA test should be performed. A negative or indeterminate HIV antibody test result and a positive HIV RNA test result indicate that acute HIV infection is highly likely."[16]

As persons who acquire HIV while taking pre-exposure prophylaxis (PrEP) may present ambiguous HIV test results, the DHHS proposes that:

- "A positive HIV Ag/Ab test result or a positive HIV RNA test result in the setting of a negative HIV antibody test result should prompt immediate confirmation of HIV diagnosis. It is important to collect a new blood specimen to verify the HIV diagnosis before initiating HIV treatment."
- "In people with HIV RNA level ≥200 copies/mL who are taking PrEP, immediate initiation of an effective HIV treatment regimen is recommended while awaiting confirmation of HIV diagnosis (AIII)."
- "In people taking PrEP who have a negative HIV antibody test result and a very low-positive quantitative HIV RNA test result (<200 copies/mL) a confirmatory HIV antibody test and repeat quantitative plasma HIV RNA test should be performed, and results should be available before initiating ART."
- "In rare cases, particularly when PrEP is transitioned to an ARV regimen and HIV RNA and antibody diagnostic testing are inconclusive, HIV DNA testing may be of value."[16]

The DHHS updated their guidelines regarding HIV screening and treatment during pregnancy as well as the use of ARV drugs to prevent perinatal and postnatal HIV transmission. The recommendations below cover pregnancy and postpartum HIV testing and the identification of perinatal and postnatal HIV exposure.[38]

- "HIV testing is recommended for all sexually active people and should be a routine component of pre-pregnancy care (AII).
- For all pregnancies, opt-out HIV testing should be done as early as possible during each pregnancy (AII).
- For all pregnancies, partners should be referred for HIV testing when their status is unknown (AIII).
- Repeat HIV testing in the third trimester is recommended during pregnancies in which there are negative initial HIV tests and increased risk of acquiring HIV, including pregnancies in which the care is received in facilities that have an HIV incidence of ≥1 case per 1,000 patients experiencing pregnancy per year, those who reside in jurisdictions (states or counties) with elevated HIV incidence among females aged 15 to 45 years (>17 per 100,000 females aged 15–45 years), or those who reside in states or territories that require third-trimester testing (AII).
- Repeat HIV testing is recommended when there is a sexually transmitted infection during pregnancy, when there are signs and symptoms of acute HIV infection, or when there is ongoing

exposure to HIV (AIII). Initiation of pre-exposure prophylaxis (PrEP) is recommended if HIV testing is negative (AIII).

- Expedited HIV testing should be performed during labor or after delivery when HIV status is undocumented as well as when HIV tests were negative early in pregnancy but there is increased risk of HIV infection and there was no retest in the third trimester (AII). HIV antigen/antibody testing should be available 24 hours a day, and results should be available within 1 hour. If results of expedited HIV testing are positive, intrapartum intravenous zidovudine prophylaxis should be initiated immediately (AI).
- When acute HIV infection is suspected during pregnancy or the intrapartum period or while breastfeeding, a plasma HIV RNA assay should be performed in conjunction with an antigen/antibody immunoassay (AIII).
- When there is a positive HIV test result during labor and delivery or postpartum, a maternal HIV-1/HIV-2 antibody differentiation assay and an HIV RNA assay should be performed (AI). In these situations, an HIV nucleic acid test (NAT) should be performed on the infant, with immediate initiation of presumptive HIV therapy appropriate for an infant at high risk of perinatal HIV transmission (AI).
- If maternal HIV test results are unavailable at birth, the newborn should be tested using an expedited antibody test to identify perinatal HIV exposure (AI). If positive, an HIV NAT should be performed on the infant, and standard maternal HIV diagnostic testing should be offered as soon as possible (AI).
    - In this situation, presumptive HIV therapy appropriate for infants who are at high risk of perinatal HIV transmission should be initiated immediately (AI).
    - When there is an initial positive HIV test during labor or delivery or immediately postpartum and there are plans to breastfeed, the Panel on Treatment of HIV During Pregnancy and Prevention of Perinatal Transmission recommends against breastfeeding. Breast milk should be expressed and stored appropriately until all supplemental HIV tests are reviewed and are negative (AI).
- When there is increased risk of HIV acquisition postpartum, HIV testing and PrEP should be offered. If breastfeeding is occurring, consult an HIV specialist regarding frequency of HIV testing for the breastfeeding dyad (AIII).
- Maternal HIV test results should be documented in the newborn's medical record and communicated to the newborn's primary care provider (AIII).
- To identify perinatal HIV exposure and possible HIV infection, HIV testing is recommended for infants and children in foster care and adoptees for whom maternal HIV status is unknown (AIII)."[38]

The guideline also notes that "When determining the timing of repeat HIV testing in the third trimester, some clinicians conduct testing at or around 28 weeks of gestation in conjunction with the recommended timing of syphilis testing. This approach limits the number of blood draws and allows adequate time for syphilis treatment and congenital syphilis prophylaxis. Some clinicians also conduct a third test for HIV at the time of delivery hospitalization admission."[38]

Among adults and adolescents living with HIV, the DHHS recommends the following for drug resistance testing:

- "For initial treatment:

- HIV drug-resistance testing is recommended at entry into care for persons with HIV to guide selection of the initial antiretroviral therapy (ART) regimen (AII). If therapy is deferred, repeat testing may be considered at the time of ART initiation (CIII)
- Genotypic, rather than phenotypic, testing is the preferred resistance testing to guide therapy in antiretroviral (ARV)-naïve patients (AIII)
- In persons with acute or recent (early) HIV infection, in pregnant people with HIV, or in people who will initiate ART on the day of or soon after HIV diagnosis, ART initiation should not be delayed while awaiting resistance testing results; the regimen can be modified once results are reported (AIII)
- Standard genotypic drug-resistance testing in ARV-naïve persons involves testing for mutations in the reverse transcriptase and protease genes. If transmitted integrase strand transfer inhibitor (INSTI) resistance is suspected or if the person has used long-acting cabotegravir (CAB-LA) as pre-exposure prophylaxis (PrEP) in the past, providers should ensure that genotypic resistance testing also includes the integrase gene (AIII).

- For Antiretroviral Therapy-Experienced Persons:
  - HIV drug-resistance testing should be performed to assist the selection of active drugs when changing ART regimens in the following patients:
    - People with virologic failure and HIV-RNA levels >200 copies/mL (AI for >1,000 copies/mL, AIII for 501–1,000 copies/mL, CIII for confirmed HIV RNA 201–500 copies/mL). For people with confirmed HIV-RNA levels >200 copies/mL but >500 copies/mL, drug-resistance testing may be unsuccessful but should still be considered.
    - Persons with suboptimal viral load reduction (AII).
  - Reverse transcriptase and protease genotypic resistance testing should be performed on everyone with virologic failure; integrase resistance testing (which may need to be ordered separately) should be performed on individuals experiencing virologic failure while receiving an INSTI-based regimen (AII).
  - For persons taking a non–long-acting ARV regimen, drug-resistance testing in the setting of virologic failure should be performed while the person is still taking their ARV regimen or, if that is not possible, within 4 weeks after discontinuing their ARV regimen (AII). If more than 4 weeks have elapsed since the non–long-acting agents were discontinued, resistance testing may still provide useful information to guide therapy; however, it is important to recognize that previously-selected resistance mutations can be missed due to lack of drug-selective pressure (CIII).
  - Given the long half-lives of the long-acting injectable ARV drugs, resistance testing (including testing for resistance to INSTIs) should be performed in all persons who have experienced virologic failure on a regimen of long-acting CAB and rilpivirine or acquired HIV after receiving CAB-LA as PrEP, regardless of the amount of time since drug discontinuation (AIII).
  - Genotypic testing is preferred over phenotypic resistance testing to guide therapy in people with suboptimal virologic response or virologic failure while on first- or second-line regimens and in people in whom resistance mutation patterns are known or not expected to be complex (AII).
  - The addition of phenotypic to genotypic resistance testing is recommended for people with known or suspected complex drug-resistance mutation patterns (BIII).
  - All prior and current drug-resistance test results, when available, should be reviewed and considered when constructing a new regimen for a patient (AIII)."[16]

In terms of the usage of drug-resistance assays among adolescents and adults with HIV, the DHHS recommends the following:

- "In acute or recent (early) HIV infection: Drug-resistance testing is recommended (AII). A genotypic assay is generally preferred (AIII). Treatment should not be delayed while awaiting results of resistance testing (AIII).
    - If ART is deferred, repeat resistance testing may be considered when therapy is initiated (CIII). A genotypic assay is generally preferred (AIII)."
- "In ART-naïve patients with chronic HIV: Drug-resistance testing is recommended at entry into HIV care to guide selection of initial ART (AII). A genotypic assay is generally preferred."
    - For pregnant persons, or if ART will be initiated on the day of or soon after HIV diagnosis, treatment can be initiated prior to receiving resistance testing results.
    - If an INSTI is considered for an ART-naïve patient and/or transmitted INSTI resistance is a concern, providers should supplement standard resistance testing with a specific INSTI genotypic resistance assay, which may need to be ordered separately (AIII).
    - If therapy is deferred, repeat resistance testing may be considered when therapy is initiated (CIII). A genotypic assay is generally preferred (AIII)."
- "In patients with virologic failure: Drug-resistance testing is recommended in patients on combination ART with HIV-RNA levels >200 copies/mL (AI for >1,000 copies/mL, AIII for 501–1,000 copies/mL) and a confirmed HIV RNA 201–500 copies/mL (CIII). In patients with confirmed HIV-RNA levels between 200–500 copies/mL, testing may not be successful but should still be considered.
    - Resistance testing should be done while the patient is taking ART or, if that is not possible, within 4 weeks after discontinuation of non–long-acting ARV drugs (AII). If >4 weeks have elapsed, resistance testing may still be useful to guide therapy; however, previously selected mutations can be missed due to lack of drug-selective pressure (CIII).
    - A standard genotypic resistance assay is generally preferred for patients experiencing virologic failure on their first or second ARV regimens and for those with expected noncomplex resistance patterns (AII).
    - All prior and current drug-resistance testing results should be reviewed and considered when designing a new ARV.
    - When virologic failure occurs in a patient on an INSTI-based regimen or in a patient with a history of INSTI use, genotypic testing for INSTI resistance should be performed to determine whether to include drugs from this class in subsequent regimens (AII).
    - Adding phenotypic testing to genotypic testing is generally preferred in patients with known or suspected complex drug-resistance patterns (BIII)."
- "In patients with suboptimal suppression of viral load: Drug-resistance testing is recommended in patients with suboptimal viral load suppression after initiation of ART (AII)."
- "In Pregnant People with HIV: Genotypic resistance testing is recommended for all pregnant people before initiation of ART (AIII) and for those entering pregnancy with detectable HIV-RNA levels while on therapy (AI)."
- "In Patients with Undetectable Viral Load or Low-Level Viremia Who Are Planning to Change Their ARV Regimen HIV-1: proviral DNA resistance assays may be useful in patients with HIV RNA below the limit of detection or with low-level viremia, where a HIV-RNA genotypic assay is unlikely to be successful (CIII)."[16]

The DHHS also added guidelines on testing for pediatric HIV infection:

- "[39]Infants and children with potential HIV exposure after birth (e.g., HIV diagnosed during breastfeeding, premasticated feeding, sexual abuse, contaminated blood products, percutaneous exposure) require age-appropriate testing. Infants with perinatal HIV exposure who have these

additional exposures after birth require HIV NAT testing for diagnosis. Infants aged <18 months who were not exposed to HIV at delivery and infants aged ≥18 months who have these potential exposures require HIV antigen/antibody testing, unless the time between potential exposure and testing indicates that the patient is in the window for seroconversion, when an HIV NAT is more sensitive.

- Phenotypic resistance testing should be considered in addition to genotypic resistance testing for patients with known or suspected complex drug resistance mutation patterns, which generally arise after a patient has experienced virologic failure on multiple ARV regimens. Viral co-receptor tropism assays are recommended whenever a CCR5 antagonist is being considered for treatment. The use of tropism assays also should be considered for patients who demonstrate virologic failure while receiving therapy that contains a CCR5 antagonist."[39]

Centers for Disease Control and Prevention

The "CDC recommends all patients between the ages of 13 and 64 get tested for HIV at least once as part of routine health care." Individuals with ongoing HIV risk factors (e.g., MSM, people who inject drugs, multiple sex partners, or partners with HIV or other STIs) "should be screened at least annually" and "sexually active gay, bisexual, and other men who have sex with men (more frequent testing may be beneficial [e.g., every 3–6 months])."[40]

Initial diagnostic testing should use a fourth-generation HIV antigen/antibody (Ag/Ab) assay, which detects both p24 antigen and HIV antibodies (IgM/IgG), allowing earlier identification than antibody-only tests. If reactive, follow-up with an HIV-1/HIV-2 antibody differentiation assay is required. If results are negative or indeterminate but clinical suspicion remains high, an HIV-1 nucleic acid test (NAT) should be obtained to detect viral RNA.[40,41] Rapid testing (antibody testing) may be used in settings where expedited results "allow for the earliest possible detection of newly acquired HIV and is preferred for PrEP initiation and continuation." The CDC advises against oral fluid rapid tests in these contexts due to their reduced sensitivity during early infection.[41]

Pre-exposure prophylaxis is the use of antiretroviral medication to prevent HIV. It is intended for people without HIV who may be exposed to the virus through sex or injection drug use. The CDC recommends "PrEP as part of a comprehensive HIV prevention plan that includes discussing how to take PrEP as prescribed, proper condom use, screening for other sexually transmitted infections (STIs), and other risk-reduction methods."[42] To ensure patients do not acquire HIV while on PrEP, the CDC recommends to "repeat HIV antigen/antibody and HIV-1 RNA tests and assess for signs or symptoms of acute HIV infection to confirm that patients do not have HIV" "at least every 3 months."

The CDC also provides guidance on the type of testing that can be used to detect HIV infections:

"There are three types of HIV tests: antibody tests, antigen/antibody tests, and nucleic acid tests (NAT). . . . HIV tests are typically performed on blood or oral fluid. They may also be performed on urine. . . . An antibody test looks for antibodies to HIV in your blood or oral fluid. . . . Antibody tests that use blood from a vein can detect HIV sooner than tests done with blood from a finger stick or with oral fluid. . . . An antigen/antibody tests look for both HIV antibodies and antigens. Antigen/antibody tests are recommended for testing done in labs and are common in the United States. . . . A NAT looks for the actual virus in the blood. . . . This test can tell if a person has HIV or how much virus is present in the blood (HIV viral load test). A NAT can detect HIV sooner than other types of tests. This test should be considered for people who have had a recent exposure or a possible exposure and have early symptoms of HIV and who have tested negative with an antibody or antigen/antibody test."[3]

It is important to note that no HIV test can detect HIV immediately after infection. This is because of what's known as the window period, the time between HIV exposure and when the test can detect HIV in the body. The window period is different for the different types of HIV tests.

- "Antibody tests can usually detect HIV 23 to 90 days after exposure. Most rapid tests and self-tests are antibody tests.
- A rapid antigen/antibody test done with blood from a finger stick can usually detect HIV 18 to 90 days after exposure.
- An antigen/antibody lab test using blood from a vein can usually detect HIV 18 to 45 days after exposure.
- A NAT can usually detect HIV 10 to 33 days after exposure."[3]

"If you get an HIV test after a potential HIV exposure and the result is negative, get tested again after the window period for the test you took."

If an antibody test is positive, follow-up NAT testing will be required to confirm the results.[3]

Specific to NAT testing, the CDC provides the following information: "Nucleic Acid Tests- A qualitative RNA test has been FDA-approved for diagnosis of acute HIV infection in antibody-negative persons. This test may also be used to confirm a reactive antibody screening test. Quantitative tests for HIV RNA are available, but are not FDA-approved for diagnosis. These RNA tests are routinely used to quantify viral load for monitoring progression of HIV disease. HIV-1 RNA tests do not detect HIV-2, and the FDA has not approved an HIV-2 RNA or DNA test. Plasma viral load is characteristically low in HIV-2 infection and RNA testing is unreliable for the detection of HIV-2. DNA testing for HIV-2 can be performed to confirm HIV-2 infection."[43]

United States Preventive Services Task Force

The USPSTF recommends "screening adolescents under 15 who are at increased risk, adolescents and adults aged 15 to 65 years, and younger adolescents and older adults who are at increased risk, clinicians should consider the risk factors of the individual, especially those with new sex partners, and offer testing to patients at increased risk."[44]

"Current CDC guidelines recommend testing for HIV infection with an antigen/antibody immunoassay approved by the US Food and Drug Administration that detects HIV-1 and HIV-2 antibodies and the HIV-1 p24 antigen, with supplemental testing following a reactive assay to differentiate between HIV-1 and HIV-2 antibodies. If supplemental testing for HIV-1/HIV-2 antibodies is nonreactive or indeterminate (or if acute HIV infection or recent exposure is suspected or reported), an HIV-1 nucleic acid test is recommended to differentiate acute HIV-1 infection from a false-positive test result."[44]

The USPSTF also recommends screening all pregnant women for HIV, including those in labor who are untested and whose HIV status is unknown.[44] The CDC recognizes and supports these guidelines.[45]

International Antiviral Society

The International Antiviral Society published a 2022 update titled "Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults." 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.[46]

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

- "Within six weeks of starting ART, assessment of treatment adherence and tolerability is recommended, along with the measurement of HIV RNA level."
- "If the HIV RNA level has not declined by 2 log10 copies/mL within 12 weeks of therapy and adherence appears to be sufficient, then a genotype based on the patient's regimen is recommended."
- "If the patient remains virally suppressed, clinically stable, and adherent to medications, then HIV RNA levels should be monitored every three months until virally suppressed for at least one year. Afterward, the frequency of viral monitoring can be changed to every six months."
- "If HIV RNA level is greater than 200 copies/mL on 2 consecutive measurements, then HIV RT-pro genotype and INSTI [in integrase strand transfer inhibitor] genotype (if the patient was receiving an INSTI) testing are recommended."
- "For patients with intermittent or persistent low-level viremia between 50 and 200 copies/mL, assessments for ART adherence, tolerability, and toxic effects are recommended, but changing ART regimens is not recommended unless ART toxicity or intolerability are identified."[46]

On resistance test, the 2022 update notes that, "in persons diagnosed with HIV while receiving TXF-based PrEP, resistance testing should be performed but initiation of ART need not be delayed while awaiting genotype results." The panel further recommends:

- "Unless there is documented or suspected history of treatment failure, proviral resistance testing is not required prior to switching to 2-drug therapy, even if there is no available pre-treatment resistance test result."
- "For patients who have maintained viral suppression, switching from long-acting injectable cabotegravir plus rilpivirine back to daily oral therapy can be done without the need for proviral DNA resistance testing."
- "If virologic failure is confirmed, genotype resistance testing should be performed, preferably while patients are taking the failing therapy. Resistance testing is still recommended even if a regimen has been discontinued or a person acknowledges poor medication adherence."[46]

The International Antiviral Society updated its recommendations in 2024, reaffirming that HIV RNA measurement remains the primary laboratory method for characterizing HIV infection at baseline and for monitoring response to antiretroviral therapy. The updated guidance continues to recommend viral load testing within four–eight weeks of ART initiation, monitoring every three– four months until suppression, and extending monitoring to every six months in stable, virologically suppressed patients. Resistance testing thresholds and management of low-level viremia remain unchanged from prior guidance, with expanded discussion of long-acting antiretroviral regimens and treatment simplification strategies.[47]

Infectious Diseases Society of America (IDSA)

The IDSA recommends that "A quantitative HIV RNA (viral load) level should be obtained upon initiation of care (strong recommendation, high quality evidence)."[48]

The IDSA recommends rechecking HIV RNA after two-four weeks of initiating ART (and no later than eight weeks). From there, IDSA recommends "checking HIV RNA every four to eight weeks until suppression is achieved." The IDSA also notes that "viral load should be monitored every three to four

months to confirm maintenance of suppression below the limit of assay detection. This interval may be prolonged to every six months for patients whose viral load has been suppressed for more than one year and whose clinical and immunologic status is stable", and more frequently after initiation or change in ART "preferably within two to four weeks, with repeat testing every four to eight weeks until viral load becomes undetectable."[48,49]

In a 2024 guideline update the IDSA recommends that "CD4 cell counts should generally be monitored every three to six months for the first two years or if the virus is not suppressed. After two years, for patients on suppressive ART regimens with CD4 counts of 300–500 cells/µL, CD4 cell count can be monitored every 12 months unless there are changes in the patient's clinical or virologic status."[49]

They also note that "Repeat HIV genotypic resistance testing for mutations in the reverse transcriptase and protease genes, including in the integrase genes, when there is history of INSTI use, should be performed if virologic failure occurs and when clinically indicated. If ART initiation has been delayed, repeat genotype testing prior to ART initiation should be considered."[49]

American College of Obstetricians and Gynecologists (ACOG)

In 2014, ACOG released "Committee on Gynecologic Practice: Routine human immunodeficiency virus screening," which they reaffirmed in 2020. Regarding routine human immunodeficiency screening, "The American College of Obstetricians and Gynecologists (the College) recommends routine HIV screening for females aged 13–64 years and older women with risk factors. Screening after age 64 years is indicated if there is ongoing risk of HIV infection, as indicated by risk assessment (e.g., new sexual partners)."[50]

The College also expatiates upon repeat testing, entrusting obstetrician–gynecologists to annually review patients' risk factors for HIV and assess their needs, and recommends that "HIV testing should be offered at least annually to women who

- are injection drug users
- are sex partners of injection drug users
- exchange sex for money or drugs
- are sex partners of HIV-infected persons
- have had sex with men who have sex with men since the most recent HIV test
- have had more than one sex partner since their most recent HIV test

The opportunity for repeat testing should be made available to all women even in the absence of identified risk factors. Repeat screening after age 64 years is indicated if there is ongoing risk of HIV infection, as indicated by an individualized risk assessment. Obstetrician–gynecologists also should encourage women and their prospective sex partners to be tested before initiating a new sexual relationship. The benefits of periodic retesting should be discussed with patients and provided if requested, regardless of risk factors. Patients may be concerned about their status and do not know about or want to disclose risk-taking behavior to their health care providers."[50]

In their 2018 committee opinion "Labor and Delivery Management of Women With Human Immunodeficiency Virus Infection," 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."

The 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 ART. This recommendation also applies to patients whose viral load is unknown.[51]

Society for Maternal-Fetal Medicine (SMFM)

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 cesarean delivery should be scheduled for 38 weeks.[52]

British HIV Association

The British HIV Association (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 one, three, and six months after starting ART (1B).
- We recommend that additional viral load measurements are taken between two and five months after starting ART if viral load has not decreased at least 10-fold after one 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 six 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 (three to four 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)."[53]

The BHIVA released guidelines for the management of HIV-2.[54] For the diagnosis of HIV-2, the BHIV

recommends:

For the diagnosis of chronic HIV-2:

- "An initial diagnosis of chronic HIV-2 infection should be made using a total of three CE-marked serology tests (i.e. tests conform to EU health and safety requirements) performed in an ISO 15189-accredited laboratory. There must be reactivity in two CE-marked fourth-generation tests for HIV-1 and HIV-2, followed by differentiation of HIV-2 by a third CE-marked antibody-only test."
- "Clinicians should consider revisiting a previous diagnosis of HIV-1 by repeating HIV-2 serology and molecular tests in individuals with an undetectable HIV-1 viral load in the absence of ART, but a falling CD4 count. This is in order to detect the possibility of missed HIV-1 and HIV-2 dual infection."
- "In those with diagnosed HIV-2 with an undetectable viral load in the absence of ART, clinicians should consider repeating HIV-1 diagnostic tests, if their CD4 count falls. This is to investigate the possibility of HIV-1 superinfection."

For the diagnosis of acute primary HIV-2

- "Investigation for acute or very recent HIV-2 infection should start as for diagnosis of chronic HIV-2 infection. A negative HIV-2 screening result on a blood sample taken within 3 months of the likely exposure should be further investigated at six weeks and three months, with parallel testing for HIV-2 viral RNA and, if necessary, HIV-2 proviral DNA."

For the investigation of indeterminate HIV-1 or HIV-2:

- "We recommend that any HIV-1 or HIV-2 serology that does not fit into a clear pattern of a confirmed laboratory diagnosis is fully investigated for the presence or absence of HIV-2 infection, and that this should be established by PCR for HIV-2 proviral DNA."

For measuring HIV-2 viral load:

- "If the pre-treatment viral load was detectable, the viral load should be measured at one, three, and six months after starting or changing ART and then three to six monthly.
- If the pre-treatment viral load was undetectable, the viral load should be measured at one month and then six monthly.
- The HIV-2 viral load should be repeated in those on ART when it has been maximally suppressed and then becomes detectable.
- Testing for drug resistance should be performed in those on ART when the HIV-2 viral load has been maximally suppressed and then becomes repeatedly detectable."

For resistance testing:

- "Resistance testing should be performed at diagnosis, prior to treatment initiation and at virological failure, if the HIV-2 viral load meets the threshold of ≥500 copies/mL."[54]

The BHIVA released guidelines on antiretroviral treatment for adults living with HIV, largely reaffirming the above recommendations and noting that "It is now recommended that all people with HIV start ART as soon as they can after their diagnosis."[55]

European AIDS Clinical Society

The EACS recommends a genotypic resistance test to be ideally done at the time of HIV diagnosis; testing "should not delay ART initiation (it may be re-adjusted after genotypic test results). Resistance testing is also recommended to be performed in the setting of virological failure, "preferably on failing therapy (usually routinely available for HIV-VL levels >200-500 copies/mL and in specialized laboratories for lower levels of viremia) and obtain historical resistance testing for archived mutations." For pregnant women, the EACS recommends performing resistance testing on women whose HIV-VL is not undetectable at third trimester, and "consider changing to or adding INSTI (RAL or DTG) if not on this class to obtain rapid HIV-VL decline." When considering PEP, the EACS recommends resistance testing if the HIV-VL is detectable in an HIV-positive source person on ART. They also recommend baseline resistance testing when considering a combination regiment for ART-naïve children and adolescents living with HIV. Resistance testing should also be used to help guide the choice of treatment.

Additional genotypic recommendations include if the patient was not previously tested or if the patient is at risk of a superinfection. Genotypic resistance testing is also required prior to beginning treatment with doravirine. When switching strategies for "virologically suppressed persons," Proviral DNA genotyping may be useful in persons with multiple virological failures, unavailable resistance history or low-level viremia at the time of switch. Results ought to be taken cautiously as proviral DNA genotype may not detect previous resistance mutations and can also detect clinically irrelevant mutations. Therefore, routine proviral DNA genotyping is currently not recommended." The EACS recommends a genotypic test over a phenotypic test as genotype tests are more available and more sensitive.[56]

The European AIDS clinical society also released guidelines on the treatment and monitoring of persons with HBV/HIV co-infections, recommending that "All persons with HBV/HIV co-infection (HBsAg positive) should receive ART that includes TDF or TAF unless history of tenofovir intolerance."[57]

The American Academy of Pediatrics (AAP)

The AAP recommends:

- "Routine HIV screening is recommended for all youth 15 years or older, at least once, in health care settings."
- "After initial screening, youth at increased risk, including sexually active youth, should be rescreened at least annually, potentially as frequently as every three to six months if at high risk (male youth reporting male sexual contact, active injection drug users, transgender youth; having sexual partners who are HIV-infected, of both genders, or injection drug users; exchanging sex for drugs or money; or those who have had a diagnosis of or request testing for other STIs)."
- "Youth who request HIV screening at any time should be tested, even in the absence of reported risk factors."[58]

The Bright Futures/AAP Periodicity Schedule describes the screenings, assessments, physical examinations, procedures, and timing of anticipatory guidance recommended for each age-related visit. These guidelines provide the following recommendation for HIV screening:

- STI/HIV screening annually starting at 11 years old, with at least one HIV screening between 15 and 18.[59]

VI. Applicable State and Federal Regulations

Food and Drug Administration (FDA)

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). LDTs are not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

The primary RT-PCR tests for HIV-1 have been approved by the FDA:

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."[60]

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 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." On November 20, 2020, this assay was given an FDA approval for dual use for diagnosis and viral load monitoring for HIV-1.[6,7]

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." There were 200 known HIV-2 positive samples 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.[61]

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").[62]

In 2020 and 2022, the FDA-approved the Alinity m HIV-1 assay as an in vitro reverse transcription-polymerase chain reaction (RT-PCR) assay for the detection and quantification of HIV-1. It is to be used both for confirmation of HIV-1 infection and for monitoring of HIV-1 infected individuals. From the FDA website: "The Alinity m HIV-1 assay is intended for use to monitor disease prognosis by measuring baseline plasma HIV-1 RNA level and to assess response to antiretroviral treatment by measuring changes in plasma HIV-1 RNA levels. Performance for quantitative monitoring is not established with serum specimens." The assay can also be used as a supplemental test to confirm HIV-1 in individuals who have "reactive results" with HIV immunoassays.[63]

VII. Applicable CPT/HCPCS Procedure Codes

Procedure codes appearing in medical policy documents are only included as a general reference. This list may not be all inclusive and is subject to updates. In addition, codes listed are not a guarantee of payment.

CPT	Code Description
86701	Antibody; HIV-1
86702	Antibody; HIV-2
86703	Antibody; HIV-1 and HIV-2, single result
87389	Infectious agent antigen detection by immunoassay technique, (eg, enzyme immunoassay [EIA], enzyme-linked immunosorbent assay [ELISA], fluorescence immunoassay [FIA], immunochemiluminometric assay [IMCA]) qualitative or semiquantitative; HIV-1 antigen(s), with HIV-1 and HIV-2 antibodies, single result
87390	Infectious agent antigen detection by immunoassay technique (eg, enzyme immunoassay [EIA], enzyme-linked immunosorbent assay [ELISA], fluorescence immunoassay [FIA], immunochemiluminometric assay [IMCA]), qualitative or semiquantitative; HIV-1
87391	Infectious agent antigen detection by immunoassay technique (eg, enzyme immunoassay [EIA], enzyme-linked immunosorbent assay [ELISA], fluorescence immunoassay [FIA], immunochemiluminometric assay [IMCA]), qualitative or semiquantitative; 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
87806	Infectious agent antigen detection by immunoassay with direct optical (ie, visual) observation; HIV-1 antigen(s), with HIV-1 and HIV-2 antibodies
87900	Infectious agent drug susceptibility phenotype prediction using regularly updated genotypic bioinformatics
87901	Infectious agent genotype analysis by nucleic acid (DNA or RNA); HIV-1, reverse transcriptase and protease regions
87903	Infectious agent phenotype analysis by nucleic acid (DNA or RNA) with drug resistance tissue culture analysis, HIV 1; first through 10 drugs tested

CPT	Code Description
87904	Infectious agent phenotype analysis by nucleic acid (DNA or RNA) with drug resistance tissue culture analysis, HIV 1; each additional drug tested (List separately in addition to code for primary procedure)
87906	Infectious agent genotype analysis by nucleic acid (DNA or RNA); HIV-1, other region (eg, integrase, fusion)
0219U	Infectious agent (human immunodeficiency virus), targeted viral next-generation sequence analysis (ie, protease [PR], reverse transcriptase [RT], integrase [INT]), algorithm reported as prediction of antiviral drug susceptibility Proprietary test: Sentosa® SQ HIV-1 Genotyping Assay Lab/Manufacturer: Vela Diagnostics USA, Inc
G0432	Infectious agent antibody detection by enzyme immunoassay (EIA) technique, HIV-1 and/or HIV-2, screening
G0433	Infectious agent antibody detection by enzyme-linked immunosorbent assay (ELISA) technique, HIV-1 and/or HIV-2, screening
G0435	Infectious agent antibody detection by rapid antibody test, HIV-1 and/or HIV-2, screening
G0475	HIV antigen/antibody, combination assay, screening
S3645	HIV-1 antibody testing of oral mucosal transudate

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VIII. Evidence-based Scientific References

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IX. Revision History

Revision Date	Summary of Changes
01/01/2022	Initial Effective Date
07/19/2022	Updated background, guidelines, and evidence-based scientific references. Literature review did not necessitate any modifications to the coverage criteria: Revised code disclaimer statement

06/28/2023	Literature review necessitated the following changes in coverage criteria: Information and coverage for HIV from G2009, G2042, M2093, and M2116 were combined into a single policy. This led to a title change from “Plasma HIV-1 and HIV-2 RNA Quantification for HIV Infection" to “Human Immunodeficiency Virus (HIV)” Information and coverage for HIV from G2009, G2042, M2093, and M2116 were combined into a single policy (M2116 - Human Immunodeficiency Virus) Added 86689, 86701, 86702, 86703, 87389, 87390, 87391, 87534, 87535, 87537, 87538, 87806, 87900, 0219U, G0432, G0433, G0435, G0475, S3645 Policy Name Change: Previously titled Plasma HIV-1 and HIV-2 RNA Quantification for HIV Infection Committee approved: 06/28/2023
05/14/2024	Reviewed and Updated: Updated the background, guidelines and recommendations, and evidence-based scientific references. Literature review did not necessitate any modifications to coverage criteria. Committee approved: 05/14/2024
05/21/2025	Reviewed and Updated: Updated background, guidelines, and evidence-based scientific references. Literature review necessitated the following changes in coverage criteria: Updated appropriated testing for screening vs follow up to screening, results in addition of “antigen/antibody” testing to CC1 and CC2, addition of new CC3. Now read: “1) For individuals 11 to 65 years of age, initial screening for HIV infection with an antigen/antibody combination assay MEETS COVERAGE CRITERIA. 2) For individuals 11 to 65 years of age, repeat antigen/antibody screening for HIV infection (no more than one test every 90 days) MEETS COVERAGE CRITERIA. 3) Nucleic acid testing (qualitative or quantitative) for HIV-1 and HIV-2 (no more than one test every month) MEETS COVERAGE CRITERIA in any of the following situations: a) For individuals for whom initial screening was positive for HIV infection. b) For individuals for whom initial screening was indeterminate for HIV infection. c) For individuals for whom recent exposure is suspected or reported.” Addition of CC3 results in removal of former CC5: “5) When the risk of HIV infection is significant and the initiation of therapy is anticipated, a baseline HIV quantification MEETS COVERAGE CRITERIA in any of the following situations: . . .” Addition of “(no more than one test every month)” to CC6, now reads: “6) Plasma quantification of HIV-1 RNA or HIV-2 RNA (see Note 1) (no more than one test every month) MEETS COVERAGE CRITERIA for any of the following situations:” Committee approved: 05/21/2025
02/11/2026	CAB Review Q4 2025: Reviewed and Updated: Updated background, guidelines, and evidence-based scientific references. Literature review necessitated the following changes in coverage criteria: New CC3, CC4, and CC9: “3) For individuals who will begin pre-exposure prophylaxis (PrEP), for individuals receiving PrEP, or for individuals with elevated risk factors for an HIV infection (see Note 2), screening for an HIV infection with an antigen/antibody combination assay or with a rapid antibody test (see Note 1) MEETS COVERAGE CRITERIA.

	4) For individuals for whom initial screening was positive for an HIV infection, the HIV-1/HIV-2 antibody differentiation assay (see Note 1) MEETS COVERAGE CRITERIA. 9) HIV antigen testing independent of antigen/antibody testing DOES NOT MEET COVERAGE CRITERIA." Frequency of antigen/antibody and NAAT testing moved from referenced within CC2, former CC3, now CC5, former CC6, now CC8, to new Note 1: "Note 1: Antibody and antibody/antigen testing should not be repeated more often than once every 90 days. Nucleic acid testing (qualitative or quantitative) should not be repeated more often than once every month." New Note 2: "Note 2: Risk factors for HIV infection: • Men who have sex with men (MSM), men who have sex with men and women (MSM/W), and transgender individuals • Having a sexual encounter with an individual who has an HIV infection • Having had multiple sexual partners since the individual's last HIV test • Sharing needles, syringes, or other drug injection equipment (e.g., cookers) • Exchanging sex for money or drugs • Having a previous or concurrent STI, hepatitis, or tuberculosis • Having sex with an individual with the above high-risk factors or with an individual with unknown sexual history" New Notes 1 and 2 makes former Note 1 now Note 3. Committee Approved: 02/11/2026
06/17/2026	CAB Review Q2 2026: Reviewed and Updated: Updated background, guidelines, and evidence-based scientific references. Literature review necessitated the following changes in coverage criteria: Antibody testing that does not provide rapid results and does not incorporate antigen testing is outdated methodology and should no longer be used as part of initial HIV screening. Addition of new CC9: "9) Screening for HIV-1 and HIV-2 using an antibody test that does not provide rapid results and does not incorporate antigen testing DOES NOT MEET COVERAGE CRITERIA." Removed CPT code 86689 Committee Approved: 06/17/2026