Human immunodeficiency virus (HIV)

Global elimination of HIV: Updates aid expanded testing and linkage to care

Introduction

Human immunodeficiency virus (HIV) elimination programs have achieved substantial progress in recent years, despite headwinds challenging eradication efforts. Recommendations released by UNAIDS (Joint United Nations Programme on HIV/AIDS) in 2025 identify a clear path to end the acquired immune deficiency syndrome (AIDS).[1] Goals include attaining the "95-95-95" testing and treatment targets **(Figure 1)** with defined reductions in new infections and AIDS-related deaths by 2030 **(Figure 2)**.[1] Global targets are set in five-year increments.

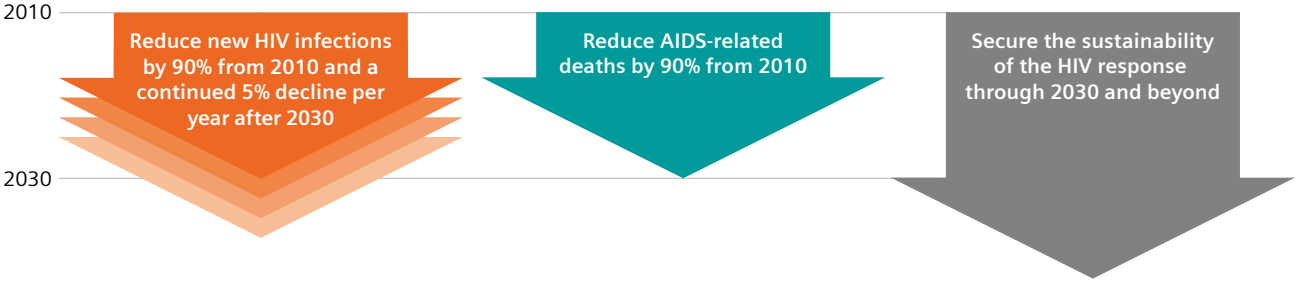
Figure 1. "95-95-95" HIV targets.[1]

Enable available, accessible, acceptable, and quality HIV treatment and care for people living with HIV.

95% of people living with HIV

- Know their status.
- Who know their status receive treatment.
- Who are on treatment have suppressed viral loads.

Figure 2. HIV reduction goals for countries by 2030.[1]



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Global HIV prevalence

An estimated 1.3 million individuals worldwide acquired HIV in 2023, representing a 39% decline in new HIV infections since 2010 and a 60% reduction since the peak in 1995.[2] In the United States, estimated new HIV infections decreased 12% overall from 2018 to 2022.[3]

Declines were associated with increased testing, improved rates of viral suppression with therapy, and broader use of pre-exposure prophylaxis (PrEP).[3] While a trend toward fewer infections is encouraging, greater decreases are necessary to achieve reduction and elimination targets.

A major barrier to eradication is identifying and treating those unaware of their infection who may unknowingly transmit disease. These include often marginalized populations in regions with limited access to provider and lab-supported testing. Expanded testing options to identify HIV infection in these populations and linkage to care are essential for continued progress towards elimination.[4] **Figure 3.**

Reducing HIV transmission

While effective therapies to prevent or control infection and minimize risk of transmission exist, about 14% of current infections are in individuals unaware of their status who may unknowingly spread infection.[5] Additionally, many diagnosed with HIV lack adequate access to treatment, leading to higher viral loads and increased infectivity.[4] Essential to elimination is identification of unknown infections, treatment for all diagnosed, and successful viral suppression therapies.[1,6]

NEW!

Updated guidelines include broadened population HIV testing modalities to support increased diagnostic rates

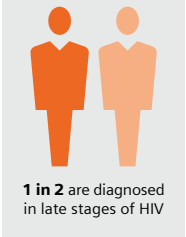
While sensitive and specific lab-based testing for HIV remains the primary method to identify infection, this updated guidance adds self-testing and includes rapid diagnostic testing (RDT) like point-of-care (POC) options to extend testing access, a key to achieving elimination goals.[4] **Figure 3**. These alternate methods are intended to supplement and not replace provider-administrated and lab-based testing.

Figure 3. Updated testing modalities and recommendations in addition to use of sensitive-lab-based assays.[4]

- HIV self-testing may be offered as an additional option at facilities supporting HIV testing.*
- HIV self-testing may be used to deliver pre-exposure prophylaxis, including for initiation, re-initiation, and continuation.*

**Conditional recommendation, low-certainty evidence.*

Closing the gap on undiagnosed infection



1 in 2 are diagnosed in late stages of HIV

Many of those at higher risk of HIV remain unreached, untested, and less able to access conventional testing.[4] This is not limited to resource-constrained regions. According to the European Centre for Disease Prevention and Control (ECDC), one in two people living with HIV are diagnosed late in the course of their disease.[7] Increased testing is needed to close the gap towards achieving a 95% rate of diagnosis in all people living with HIV.[4] ECDC guidance promotes an integrated approach to include testing for syphilis, hepatitis B and C along with HIV.

"Despite a rapid increase in access to HIV testing services, many of those at highest risk of HIV remain unreached and untested."

Source: WHO Consolidated guidelines on differentiated HIV testing services. July 19, 2024. https://www.who.int/publications/i/item/9789240096394

Self-testing and RDT should not replace sensitive lab-based assays

The updated WHO consolidated guidelines on differentiated HIV testing service discuss use of self-testing and RDT.[4] According to WHO guidance, these may be offered by lay providers who are trained and supervised.[4]

Importantly, the guidance cautions that HIV self-testing and RDT's do not replace provider-administered testing. Individuals with a reactive self-test or RDT result should receive further testing from a trained provider using the recommended testing algorithm to confirm infection.

Reducing vertical transmission

Globally, an estimated 1.3 million women with HIV become pregnant every year.[8] Risk of mother-to-child transmission during pregnancy, labor and delivery, or breastfeeding ranges from 15 to 45%.[8] The updated WHO guidelines reinforce the need to test all pregnant women for HIV and other infections that can transmit vertically (including syphilis and hepatitis B) at least once, ideally at the first antenatal care visit.[4] Elimination of mother-to-child transmission of HIV, syphilis, and HBV is a global health priority.[4]

Testing analytes for HIV and recommended assays

Antibodies to HIV

Multiple viral proteins (antigens) elicit antibodies to HIV with infection. These include antibodies to HIV envelope proteins (including gp41 in HIV-1 and gp36 in HIV-2) and the p24 viral capsid protein.[9] **Figure 4A and B.** A given protein typically contains multiple antigenic sites. Most HIV assays are designed to detect antibodies to both HIV-1 and HIV-2, utilizing unique antigenic sequences within the respective envelope sequences. **(Figure 4B)**. Some assays also include recognition of antibody to p24.

Figure 4A. Simplified structure of HIV-1.[10]

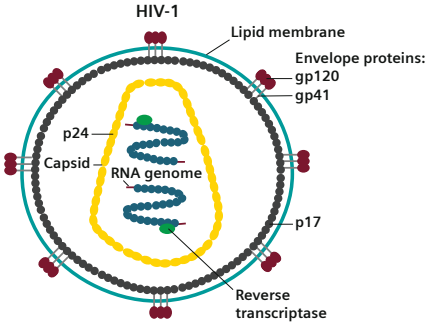


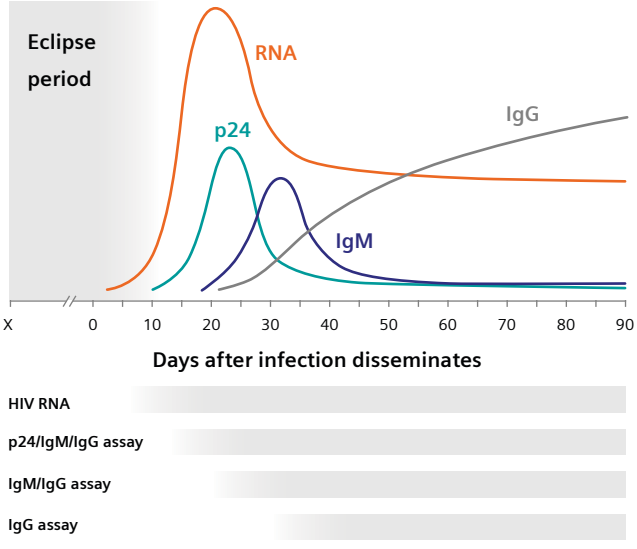
Figure 4B. Envelope proteins targeted by antibody assays in HIV-1 and HIV-2.[9]

Gene and Product	HIV-1	HIV-2
Envelope		
Envelope Precursor	**gp160**	**gp140**
External Glycoprotein	gp120	gp105
Transmembrane Protein	gp41	gp36

HIV Antigen

The most sensitive (for early infection) HIV immunoassays include designed detection for HIV antigen as well as antibody ("antigen-antibody" assays).[11-15] This supports identification of some early infections prior to antibody seroconversion, when viral loads are often elevated. Data indicate about three to five days average earlier detection of some HIV infections with antigen-antibody assays versus sensitive antibody-only assays capable of detecting both IgM and IgG.[11,13] **Figure 5.**

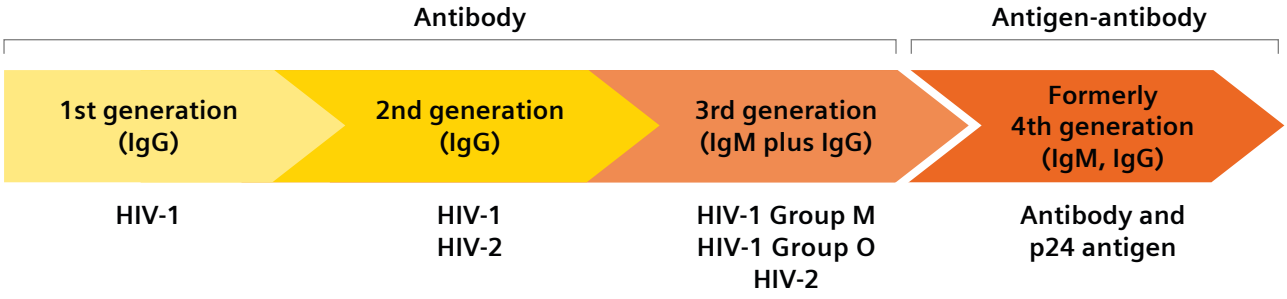
Figure 5. Antigen-antibody assays improve early detection for HIV.[13]



HIV assay generations

Testing for HIV has evolved over the years, from "first-generation" assays to the current sensitive laboratory-based "fourth generation" (antigen-antibody) assays widely recommended.[4,14,15] Assay sensitivity improved with each new generation. Fourth generation (antigen-antibody), also called "combo" assays, are designed to detect both IgM and IgG antibodies to HIV, along with p24 (capsid protein) antigen detection. **Figure 6** provides an overview of HIV test generations, and the analytes detected.

Figure 6. HIV immunoassay generations.[13,16,17]

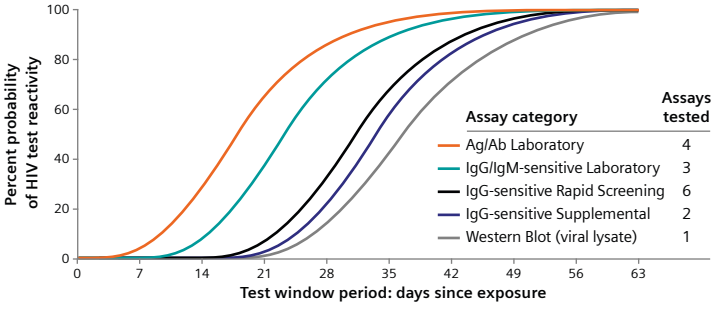


Evolving HIV assay nomenclature: "fourth generation" vs. "antigen-antibody immunoassay"

The use of "generations" as terminology to define HIV assays has been challenged, due in part to differing sensitivities observed between lab-based fourth generation tests versus RDTs when both are designed for antibody and antigen detection.[13,16,17] The term "antigen-antibody" immunoassay is suggested instead of "fourth generation" to reflect the analytes detected without implying comparable sensitivities in assay performace.[16]

Sensitivity should be considered specific to the assay used. However, data indicate that commonly used lab-based antigen-antibody assays offer similar sensitivities for detection of early infection.[11,13,17] **Figure 7.**

Figure 7. Improved sensitivity using lab-based antigen-antibody (Ag/Ab) assays.[11]



Antigen-Antibody HIV assay (lab-based) 4 assays compared:
Siemens Healthineers HIV Ag/Ab Combo (CHIV)
BioPlex 2200 HIV Ag-Ab
Abbott ARCHITECT HIV Ag/Ab Combo
BioRad GS HIV Combo Ag/Ab EIA

Assays capable of separate detection of antibody and antigen

A few manufacturers offer assays capable of separate antigen and antibody detection in the same sample or the ability to also differentiate HIV-1 antibody from HIV-2. These are sometimes referred to as "5th generation". However, data indicate comparable performance between "fourth gen" and assays capable of separate analyte detection, signifying an increase in sensitivity is not necessarily associated with the fifth generation labeling or the capacity to differentiate analytes.[17-20]

Sensitivity of RDT and self-testing

While typically not as sensitive for early infection, RDT assays like POC along with self-testing may reach populations less likely to access antigen-antibody lab-based testing and can identify established infections.[4,11,17] Importantly, the updated testing guidance suggests positive RDT, or self-tests, be followed up with lab-based testing to confirm infection.[4]

HIV Testing Guidelines

Recommended testing populations for HIV

In the U.S., the CDC recommends all patients between the ages of 13 and 64 be tested for HIV at least once as part of routine health care.[21] Repeat testing at least once a year is advocated for those with on-going risk factors.

The WHO guidelines identify recommended testing populations based in part on regional prevalence.[4] Testing of the general population in high HIV-burden settings or in those presenting with other sexually transmitted diseases (STD) are included.[4] Testing for other infections frequently acquired as STD's are discussed, including new recommendations on syphilis and HCV self-testing.[4]

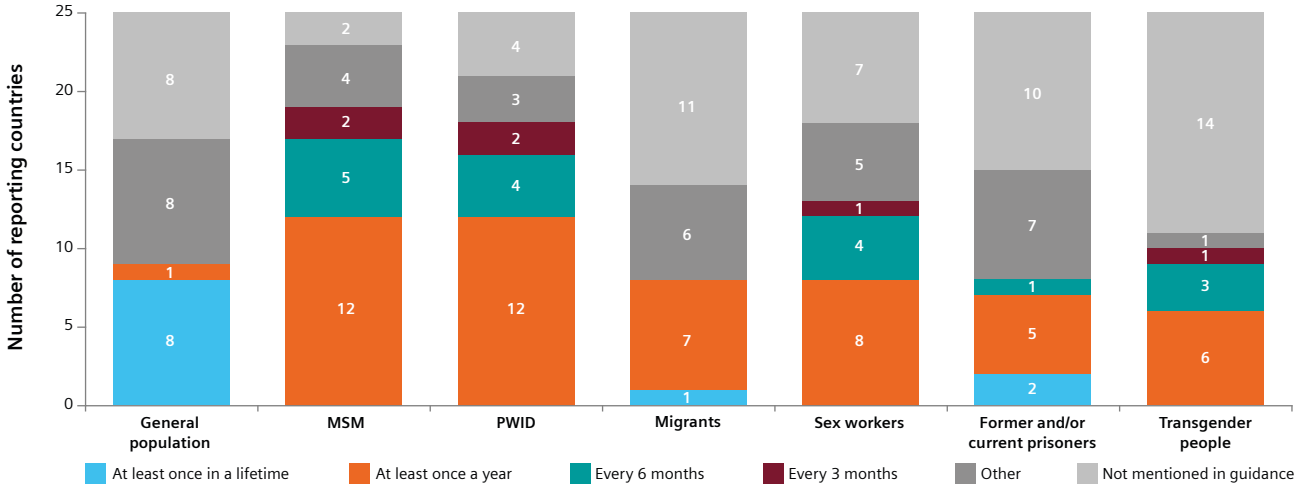
Get tested for HIV...

CDC recommends that **everyone** between the ages of 13 and 64 get tested **at least once** as part of routine care.

People with certain risk factors should get tested at least once a year.

Globally, guidance varies by region, including testing algorithms and retesting frequency.[22] Most recommend repeat testing for those with risk factors. **Figure 8** shows a compilation of testing frequency guidance by risk factor for 25 countries in in Europe and Central Asia.[22] ASEAN guidelines include testing in the workplace, including repeat based on risk assessment and an emphasis on avoiding stigmatism.[23]

Figure 8. Testing frequency in 25 European countries by key population.[22]
Numbers indicate reporting countries by category.



HIV transmission in lower-risk populations

While risk factors account for a significant percent of HIV transmission, infection can occur through heterosexual contact absent known risk behaviors. According to the U.S. CDC for 2022, people reporting HIV transmission from **heterosexual contact accounted for 22% of new HIV diagnoses**.[3] While both men and women can be infected by their partner, women were at higher risk (**15% for females vs. 7% for males** as a percent of all new infections).[3]

Testing algorithms for HIV

Recommendations for testing vary by region, but most start with a sensitive antigen-antibody assay when available. Importantly, confirmatory testing as recommended by agencies such as the CDC or WHO (or local regulatory bodies) should be performed on all initially reactive samples. Confirmatory testing is useful to reduce reporting of false-positive (FP) results and improve the positive predictive value (PPV).[4,14,15]

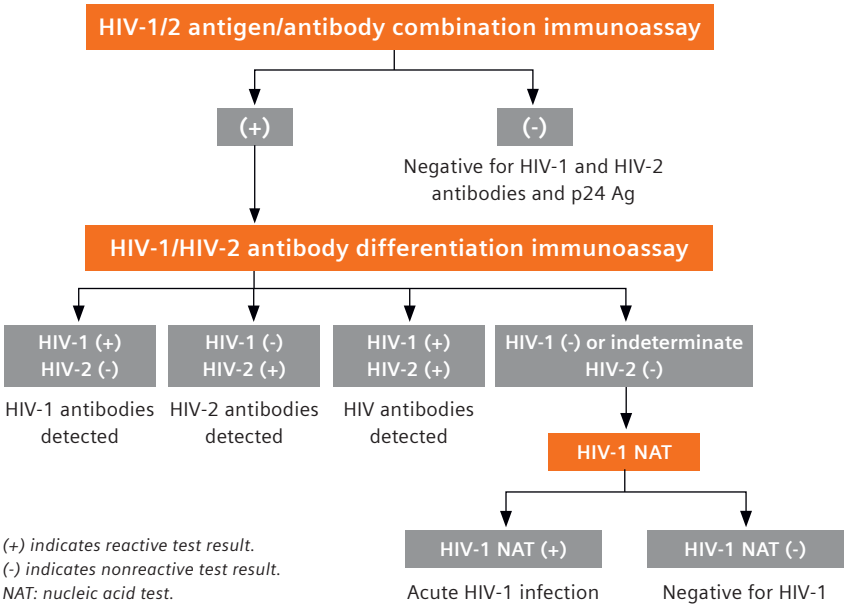
CDC (United States) recommended algorithm

The U.S. CDC-defined testing algorithm is depicted in **Figure 9**.[14,15] An antigen-antibody HIV test is preferred for initial testing, with reactive samples followed up with an immunoassay able to differentiate HIV-1 antibody from HIV-2.[14,24] If this second test is reactive, the sample can be considered confirmed. While HIV-2 infection is rare in the U.S. (<0.01% of infections), identifying HIV-2 is important for follow-up molecular testing and patient management, including in pregnant women.[25]

HIV-1 vs. HIV-2 differentiating test non-reactivity

If the follow-up test is non-reactive following a reactive initial test, the CDC recommends an HIV-1 RNA test should be conducted to rule-in or exclude infection (as the commonly-used supplemental assay detects antibody but not antigen).[14,15] **Figure 9**. RNA can confirm antigen reactivity from the initial test in samples not yet positive for antibody. If early infection/exposure is suspected, but the antigen-antibody immunoassay results are negative, an HIV-1 RNA test can be ordered as it provides higher sensitivity.[14]

Figure 9. U.S. CDC testing algorithm for HIV.[14,15]



Use of rapid HIV tests for initial testing in the U.S.

Per the CDC, preliminary positive results using rapid HIV test in a CLIA-waived setting (like POC) should be followed up with the recommended algorithm starting with an antigen/antibody immunoassay.[15]

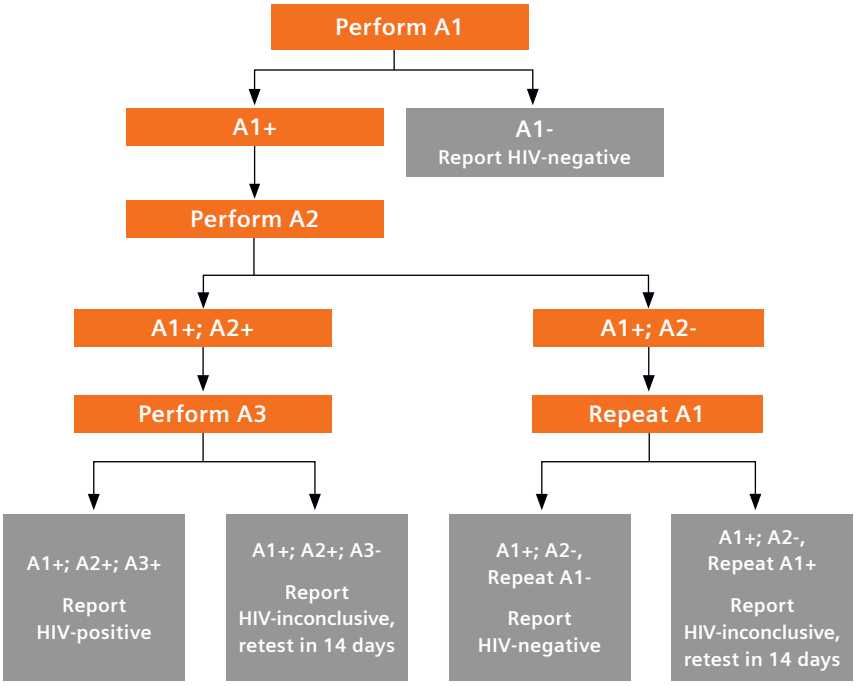
HIV infection with undetectable viral RNA

In rare cases, HIV infection detected by antibodies may have non-detectable viral RNA.[11,26] An estimated 3 to 5% of people with HIV infection may have a negative RNA test.[11] Reasons can include so-called "elite suppressors" associated with mutations in the cell HIV coreceptors and other genetic factors.[26-28] Testing for the integrated proviral DNA is one alternative to identify true infection vs. a false-positive in these rare cases.[24]

WHO recommended HIV testing algorithm

WHO recommendations suggest use of three alternate HIV assays (typically obtained from differing manufacturers) to aid confirmation and improve PPV.[4,29] **Figure 10** Test sensitivity and specificity is important. The guidance states Assay 1 must be highly sensitive (such as an antigen—antibody test) to optimize detection of infection, so may include some individuals who are falsely reactive.[4] Assay 2 and Assay 3 must have high specificity to minimize reporting of false positive (FP) results. This three-test strategy offers an improved PPV and is considered cost-effective versus the long-term consequences of an HIV misdiagnosis.[4,29]

Figure 10. WHO HIV testing algorithm (≥18 months of age).[4]



A1: Assay 1 (first test); A2: Assay 2 (second test); A3: Assay 3 (third test).

- All individuals are tested on Assay 1 (A1). Anyone with a non-reactive test result (A1-) is reported HIV-negative.
- Individuals who are reactive on Assay 1 (A1+) should then be tested on a separate and distinct Assay 2 (A2).
- Individuals who are reactive on both Assay 1 and Assay 2 (A1+; A2+) should then be tested on a separate and distinct Assay 3 (A3)
  - Report HIV-positive if Assay 3 is reactive (A1+; A2+; A3+).
  - Report HIV-inconclusive if Assay 3 is non-reactive (A1+; A2+; A3-). The individual should be asked to return in 14 days for additional testing.
- Individuals who are reactive on Assay 1 but non-reactive on Assay 2 (A1+; A2-) should be repeated on Assay 1.
  - If repeat Assay 1 is non-reactive (A1+; A2-; repeat A1-), the status should be reported as HIV-negative;
  - If repeat Assay 1 is reactive (A1+; A2-; repeat A1+), the status should be reported as HIV-inconclusive, and the individual asked to return in 14 days for additional testing.

Conclusion

To achieve global targets for HIV reduction, expanded HIV testing, diagnosis, and treatment are essential. While sensitive lab-based antigen-antibody tests offer the highest performance for early detection and typically the convenience of automation, use of RDT or self-testing can augment detection, especially in populations with limited access to central lab testing. Confirmation of HIV infection in those with initially reactive assays and linkage to care are important elements to achieve a meaningful reduction in HIV transmission and morbidity/mortality.

For more information on the Siemens Healthineers CHIV or other ID assays available on the Atellica IM and CI Systems please visit siemens-healthineers.com or contact your local representative.

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