Human immunodeficiency virus (HIV)

HIV: Updates on testing support global elimination efforts

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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.

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

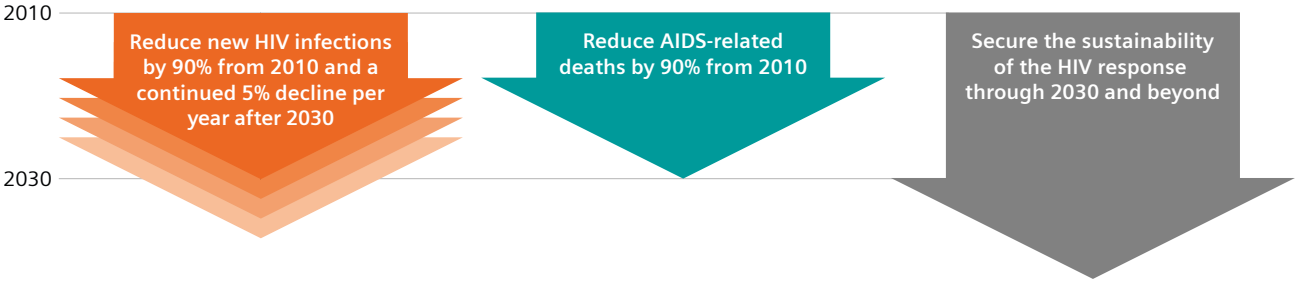
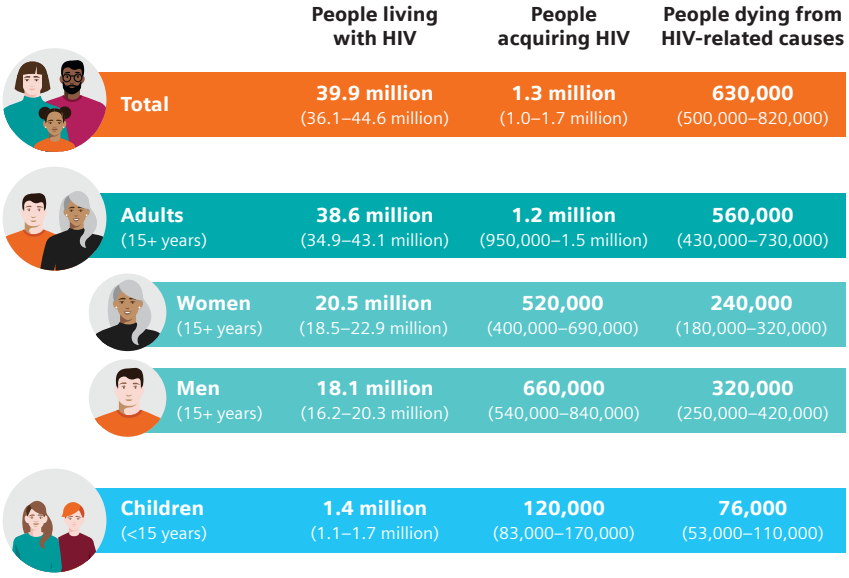


Figure 2. HIV reduction goals for countries by 2030.[1]

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] These alternate methods are intended to supplement and not replace provider-administrated and lab-based testing.



Source: UNAIDS/WHO estimates, 2024. www.who.int/teams/global-hiv-hepatitis-and-stis-programmes/hiv/strategic-information/hiv-data-and-statistics

Figure 3. Summary of the global HIV epidemic, 2023.[5]

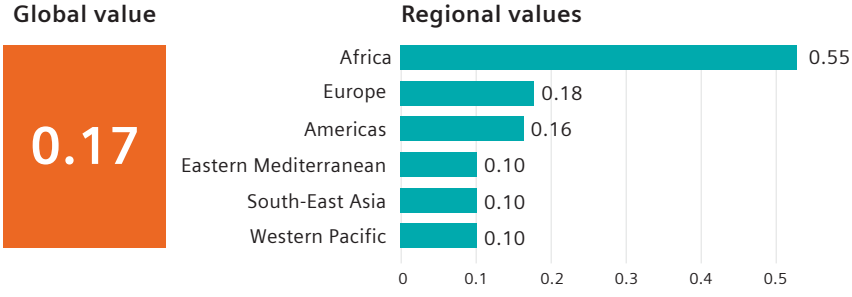


Figure 4. Rates of HIV transmission by region.[6] New HIV infections (per 1000 uninfected population).

Global overview of HIV infection

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]

As of 2023, an estimated 40 million people are living with HIV.[5] **(Figure 3)** Disease burden is higher in some regions, including Africa where overall prevalence is estimated at 3.4% of the population compared to a ~0.6% overall global prevalence (in ages 15–49).[5]

While adults comprise most infections **(Figure 3)**, more than a million children (<15 years) are living with HIV, with maternal transmission a leading factor. Rates of transmission vary by region, driven in part by prevalence and undiagnosed or untreated infection.[6] **(Figure 4)**.

"People's knowledge of their own and their partners' HIV status is essential to an effective HIV response."[4]

Reducing HIV transmission

While effective treatments to prevent or control infection and minimize risk of transmission exist, about 14% of existing infections are in individuals unaware of their status who may unknowingly spread infection.[7] Additionally, many diagnosed with HIV lack adequate access to treatment, leading to higher viral loads and increased infectivity.

Essential to elimination is identification of unknown infections, linkage to care for all diagnosed, and successful viral suppression therapies.[1,8]

NEW!

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

**Conditional recommendation, low-certainty evidence*

Figure 5. Updated testing modalities in addition to sensitive-lab-based assays.[4]

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. 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.[9]

To help close the gap and achieve a 95% rate of diagnosis in all people living with HIV, new guidance adds self-testing to existing testing recommendations.[4] **(Figure 5)** WHO and the ECDC have also recommended an integrated testing approach for hepatitis B and C viruses and HIV given shared mechanisms of transmission.[4,9]

Self-testing and rapid diagnostic tests should not replace sensitive lab-based assays

The updated WHO consolidated guidelines on differentiated HIV testing service discuss use of self-testing and rapid diagnostic tests (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 locally recommended testing algorithm to confirm infection.

Limiting vertical transmission

Globally, an estimated 1.3 million women with HIV become pregnant every year.[10] Risk of mother-to-child transmission during pregnancy, labor and delivery, or breastfeeding ranges from 15 to 45%.[10] 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]

HIV in resource-limited settings

HIV testing may be especially vital in regions experiencing loss of international programs such as the President's Emergency Plan for AIDS Relief (PEPFAR) and other resources dedicated to prevention and treatment. Low and middle-income countries are particularly susceptable.[11,12] Implications include an estimated 4–10 million new HIV infections between 2025-30.[11,12] Increased identification of infection will be paramount in helping curb onward transmission, especially if a significant rise in new infections occurs.

Table 1. Testing populations for HIV identified in guidelines include:

WHO recommendations (2024)[4] https://iris.who.int/bitstream/handle/10665/378162/9789240096394-eng.pdf?sequence=1	• **High HIV burden settings:** Offer testing to all, including adults and adolescents. • **Low HIV settings:** Test those who present with symptoms or medical conditions that could indicate HIV infection (examples, TB, STI's)	HIV testing is recommended during each pregnancy
2021 European guideline on HIV testing in genito-urinary medicine settings[13]	Includes recommendations to test for HIV infection in individuals aged 16 years and older who present to sexually transmitted infection, genito-urinary or dermato-venereology clinics across Europe.	Any pregnant woman regardless of risk factors
US (CDC)[14] **USPSTF[15] (United States Preventive Services Taskforce)**	• Higher risk should be tested more often • **CDC:** Test everyone between the ages of 13 and 64 for HIV at least once. • **USPSTF:** Screen for HIV infection in adolescents and adults aged 15 to 65 years. Younger adolescents and older adults who are at increased risk of infection should also be screened.	HIV testing is recommended during each pregnancy
European Centre for Disease Control (ECDC)[16] https://www.ecdc.europa.eu/sites/default/files/documents/DD_HIV_TestingBrief_May%202022-revised-final.pdf	• Recommends HIV testing for key populations every 3–12 months depending on local epidemiology and individual risk assessment. • Risk-based testing (factors are identified) • Test ages 16 and older in patients presenting in Genito-Urinary settings	HIV testing is recommended during each pregnancy
ASEAN[47] Community-based testing includes workers aged 15–49 as they comprise 90% of people living with HIV	Testing must be voluntary and follow-up counseling offered.	For negative results, it is recommended that there be a retest at least annually for those at high risk of infection.

Increased access to HIV testing is essential, emphasizing the necessity of adopting the updated screening guidance from WHO, particularly in regions with high endemic rates.[4] **Table 1** lists several guidelines, including WHO, on recommended testing populations for HIV.

HIV overview

HIV is an RNA lentivirus that attacks and destroys specific cells (including "T-helper cells" critical to adaptive immunity). Left untreated, compromised immune functionality results in AIDS and susceptibility to opportunistic disease.[17,18]

While HIV is not curable, available antiretroviral therapies inhibit viral replication and disease pathogenesis (including progression to AIDS). Transmission risk is also low with successful viral suppression. Current guidance suggests starting therapy as soon as possible following diagnosis.[2]

HIV diversity

HIV is highly mutable, resulting in ongoing viral evolution and diversity, a key challenge in the development of an efficacious vaccine.[19,20] HIV infection is caused by two genetically diverse lentiviruses, HIV-1 and HIV-2 **(Figure 6)** thought to have been separately introduced into humans from simian viruses found in nonhuman primates.[21] Globally, HIV-1 dominates, causing an estimated >95% of infections.[22]

Subtypes have been identified for both HIV-1 and HIV-2, with HIV-1 displaying the highest diversity.[22] While HIV-2 appears less pathogenic than HIV-1, infection can still result in AIDS if untreated.[23] HIV-2 is limited primarily to some regions in western Africa, though a small number of infections have been documented elsewhere, including in the U.S. and Europe.

HIV-1 Groups and subtypes

HIV-1 is further divided into groups: M, N, O, and P, with Group M causing most (~95%) HIV-1 infections globally.[22] **Figure 6**. Group O is associated with a tiny fraction of overall infections and is found primarily in Cameroon, while groups N and P are exceedingly rare.[22,24]

Group M is further subdivided into nine subtypes or clades (A-D, F-H, J, K). Clades A, B, and C dominate globally, causing ~70% of HIV-1 infections. Subtype prevalence varies significantly between regions. Subtype B is common in the Americas and Europe while in other regions alternate subtypes dominate.[22,25] **Figure 7.**

HIV-2

HIV-2 is limited principally to parts of Africa, but has also been found globally. While subtypes for HIV-2 have also been identified, it lacks the diversity observed with HIV-1.[26] Given the high diversity of HIV-1, robust testing methods capable of broad type and subtype detection are essential.

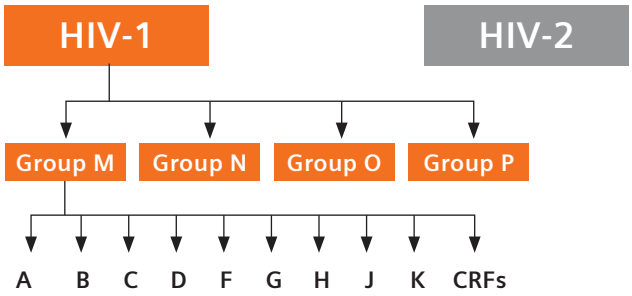


Figure 6. HIV types and strains.

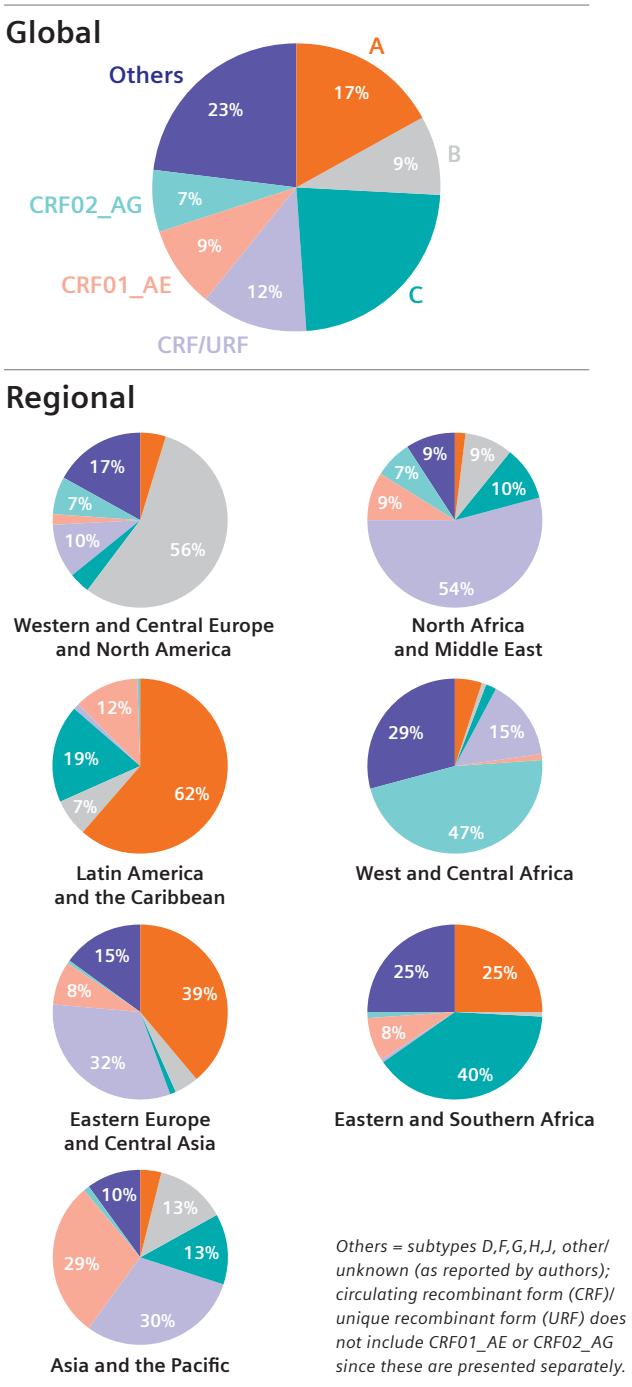


Figure 7. Global distribution of HIV-1 subtypes and CRF's (2010–2021).[22]

Circulating recombinant forms (CRF) of HIV-1

Globally, circulating recombinant forms (CRFs) or unique recombinant forms (URFs) cause a substantial percentage (29%) of HIV-1 infections.[22] CRF's are mosaic viruses that form when differing subtypes infect the same individual and combine their genetic material, producing a hybrid virus capable of transmission.

Multiple CRF's have been identified with varying frequency.[27] Two commonly identified CRF's are CRF-02_AG (formed by recombination with subtypes A and G) and CRF-01_AE (formed by recombination with subtypes A and E).[22] **Figure 7** shows the known distribution of the leading CRF's.

HIV viral structure

A simplified structure for HIV-1 is shown in **Figure 8.** It is a membrane-bound virus with envelope proteins that enable attachment to the host cell.[28] The RNA viral genome is present in duplicate and is contained within the capsid composed of p24 protein. The capsid is surrounded by a matrix comprised of the p17 protein.

While HIV-2 has a similar structure, it displays significant sequence divergence from HIV-1, including in the envelope proteins that bind the CD4 host cell receptor.[29,30] **Figure 8.**

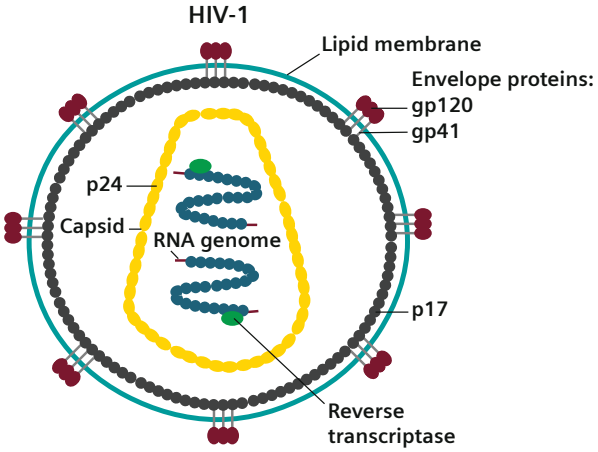


Figure 8. Simplified structure of HIV-1.[10]

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

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

HIV infection

HIV infection is complex, but initiates with binding, membrane fusion, and entry of the virus into the host cell, resulting in viral replication (and host cell destruction) or latency.[31-37] Both HIV-1 and HIV-2 can bind and enter CD4-expressing cells. **(Table 2)**

Following CD4-binding, viral fusion and entry is facilitated using one of two main coreceptors expressed on the host cell. **Table 2**. While T-helper cells (CD4 T-lymphocytes) are the primary target, monocytes and macrophages expressing CD4 can also be infected and may provide an important reservoir of virus.[35,36]

Table 2. adapted from references 32–34.

HIV-1 envelope membrane proteins	HIV-2 envelope membrane proteins	Host cell receptor	Host cell coreceptors include
gp120 and gp41	gp105 and gp36	CD4 (CD4 cells include T-helper lymphocytes, monocytes, and macrophages)	CCR5 or CXCR4

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 capsid protein. 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 regions, or antibody to the p24 capsid protein.

Testing for HIV and recommended assays

Testing for HIV has evolved over the years, from "first-generation" assays to the current sensitive laboratory-based "fourth generation" assays widely recommended. Assay sensitivity improved with each new generation. Fourth generation, or "combo" assays, are designed to detect both IgM and IgG antibodies to HIV-1 and HIV-2, along with p24 (capsid protein) antigen detection (antigen-antibody assays). **Figure 9** provides an overview of HIV test generations, and the analytes detected.

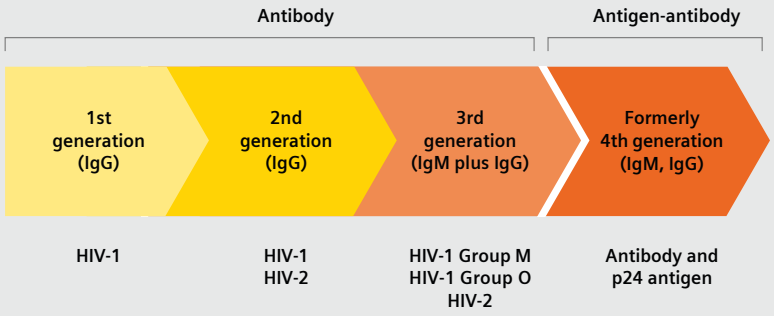


Figure 9. HIV immunoassay generations.

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.[38,39] The term "antigen-antibody" immunoassay is suggested instead to describe the assay without implying comparable sensitivities. Sensitivity should be considered specific to the assay used.

"Fifth generation" assays

Some manufacturers have adopted the term "fifth generation" (or fifth gen) to describe an HIV assay capable of separate antigen and antibody detection in the same sample. While these assays can differentiate antigen from antibody, most do not also differentiate HIV-1 antibody from HIV-2. Data indicate comparable performance between fourth gen and so-called fifth gen assays, signifying an increase in sensitivity is not necessarily associated with the "fifth gen" nomenclature.[39-41]

Early detection with antigen-antibody HIV assays

Sensitive lab-based antigen-antibody assays can reduce the time to early detection of infection, principally by detection of HIV p24 antigen prior to measurable antibody.[42] **Figure 10** depicts an "average" seroconversion profile and a representation of second-fourth generation tests to identify early infection vs. RNA.[42] RNA is the earliest detectable analyte, with antigen-antibody assays detecting a subset of early RNA-positive infections (associated with limitations for p24 sensitivity versus RNA nucleic acid amplification).[42-46]

Seroconversion and loss of p24 antigen

With antibody seroconversion, levels of p24 decline rapidly in most early infections and are associated with a drop in viral load and binding of antigen by p24 antibody. **Figure 10** data indicate approximately three-five days earlier detection if using a sensitive lab-based fourth gen test (for those w/sufficient levels of p24) vs. a sensitive-lab-based third gen test.[43,44,46] For established infections (converted to IgG antibody), most antibody testing modalities perform similarly.[42]

While generally not as sensitive for early infection, point of care (POC) along with self-testing may reach populations less likely to access lab-based testing. Importantly, the updated testing guidance suggests positive POC, or self-tests, be followed up with lab-based testing to confirm infection.

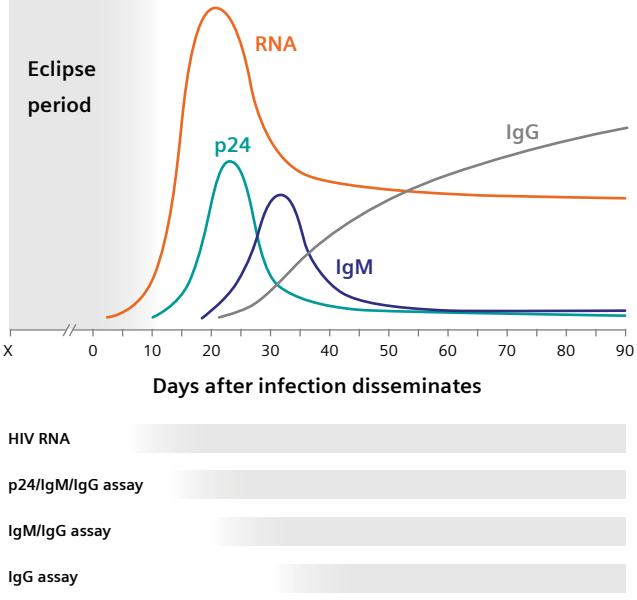


Figure 10. Antigen-antibody assays improve early detection for HIV.[42]

Guidelines

Recommended testing populations for HIV (see Table 1)

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. Repeat testing at least once a year is advocated for those with on-going risk factors.

Globally, guidance varies by region, including testing algorithms and retesting frequency. Most recommend a higher incidence of testing for those with risk factors. **Figure 11** shows a compilation of testing frequency guidance by risk factor for 26 countries compiled by the ECDC.[9] ASEAN guidelines include testing in the workplace, including repeat based on risk assessment and an emphasis on avoiding stigmatism.[47]

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.

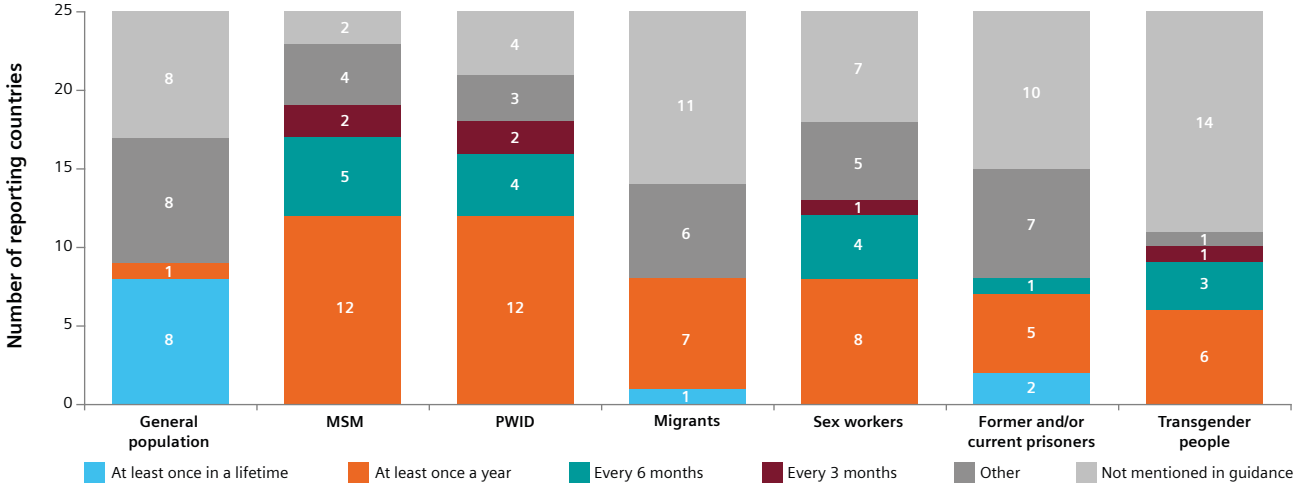


Figure 11. Testing frequency in 25 European countries by key population.[9] Numbers indicate reporting countries by category.

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 US CDC in 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 are 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 to minimize reporting false-positive (FP) and improve the positive predictive value (PPV).

CDC (United States) recommended algorithm

The U.S. CDC-defined testing algorithm is shown in **Figure 12**.[48,49] An antigen-antibody HIV test is preferred, with reactive samples followed up with an immunoassay able to differentiate HIV-1 antibody from HIV-2.[48,50] 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.[51]

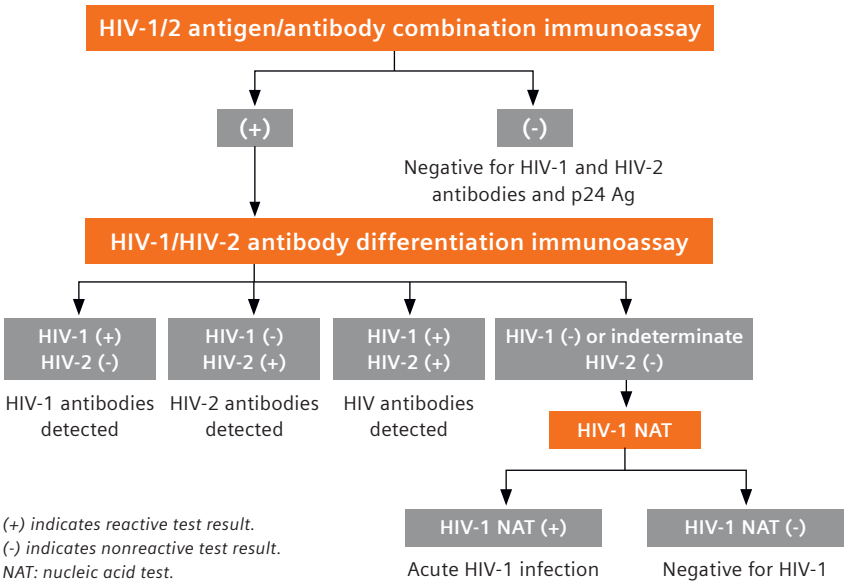


Figure 12. U.S. CDC testing algorithm for HIV.[48,49]

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

If the follow-up test is non-reactive after a reactive initial test, an HIV-1 RNA test should be conducted to rule-in or exclude infection (as the supplemental assay does not detect antigen).[48,49] RNA can confirm antigen detection reactivity 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.[48]

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

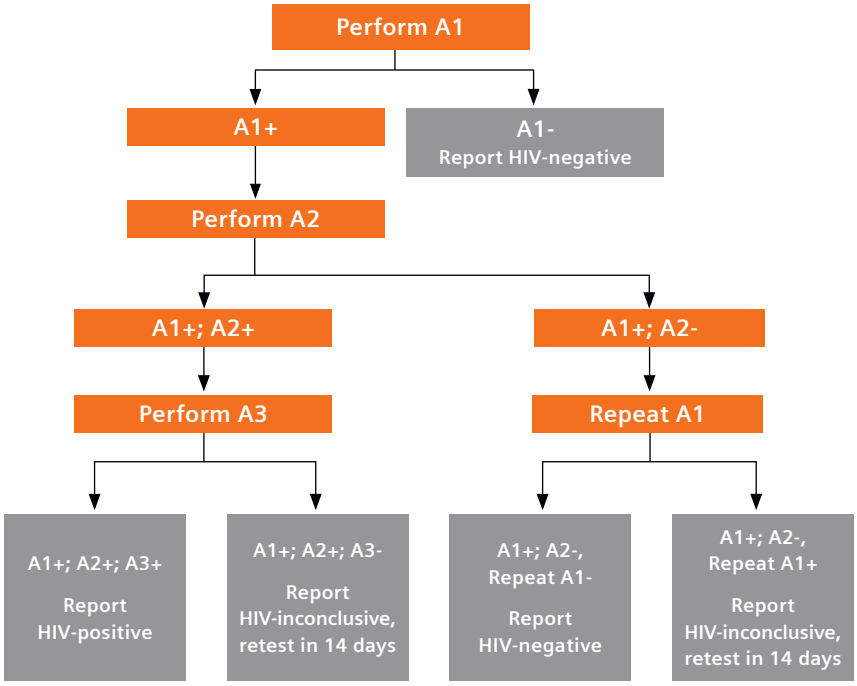
Per the CDC, preliminary positive results using a rapid HIV test in a CLIA-waived setting (like POC) should be followed up with the recommended algorithm starting with an antigen/antibody immunoassay.[49]

HIV infection with undetectable viral RNA

In rare cases, HIV infection detected by antibodies may have non-detectable viral RNA.[52] An estimated 3 to 5% of people with HIV infection may have a negative RNA test.[43] Reasons can include so-called "elite suppressors" associated with mutations in the cell HIV coreceptors and other genetic factors.[52-54] Testing for the integrated proviral DNA is one alternative to identify true infection vs. a false-positive in these rare cases.

WHO recommended HIV testing algorithm

WHO recommendations suggest use of three alternate HIV immunoassays (typically obtained from differing manufacturers) to aid confirmation and improve PPV.[4,55] **Figure 13** Test sensitivity and specificity is important. The guidance states Assay 1 must be highly sensitive to optimize detection of infection, so may be more likely to 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]



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

Figure 13. WHO HIV testing algorithm (≥18 months of age).[4]

- 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.

Comparing performance of lab-based fourth gen HIV assays

Design characteristics of antigen-antibody immunoassays

Multiple fourth gen "antigen-antibody" assays are commercially available. Manufacturers assay constructs vary; commonly shared characteristics in assay design are shown in **Table 3**. While p24 is an important element for acute (antigen-positive/antibody negative) detection, both antibody and antigen detection play essential roles in early detection. Following seroconversion, antibody reactivity identifies infection as p24 levels drop or become immune-undetectable through binding of p24 antibody.

Table 3. Common design characteristics in antigen-antibody HIV assays (adapted from references 4 and 43).

Design options for HIV antibody detection include:	HIV antigen
Detection of HIV-1 and HIV-2 antibodies (IgM and IgG) using select peptide sequences specific to HIV-1 (gp41) or HIV-2 (gp36)	HIV p24 antibody is used to detect p24 antigen

Performance of automated HIV antigen-antibody assays for early detection

Multiple studies indicate comparable performance between widely used automated antigen-antibody assays, although some minor variations have been reported.[43,44,56-62] These include investigations using the ADVIA Centaur or Atellica IM CHIV assay, which utilize the same CHIV reagents.

In a study performed by the CDC, performance for multiple immunoassays (including automated fourth generation assays, third generation, and POC) was investigated relative to IA detection in the days following initial HIV viral RNA positivity. Some comparative findings are shown in **Figure 14 A–C**.

Lab-based antigen-antibody assays displayed the highest sensitivity, **(Figure 14 A and B)** and no statistically significant differences were observed between the tested antigen-antibody assays for early detection following RNA seroconversion **(Figure 14 C)**[42,43]

Category (No. of inclusive tests)	Median	99th Percentile (Days)
Antigen-antibody laboratory (4)	17.8	44.3
IgG/IgM-sensitive laboratory (3)	23.1	49.5
IgG-sensitive rapid screening (6)	31.1	56.7
IgG-sensitive supplemental (2)	33.4	58.2
Western blot (viral lysate) (1)	36.5	64.8

Figure 14A. Automated antigen-antibody assays and detection of early HIV infection.[43]

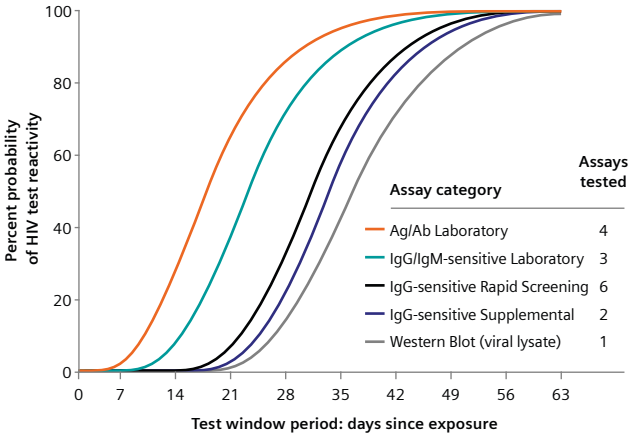


Figure 14B. Improved sensitivity using lab-based antigen-antibody (Ag/Ab) assays.

Lab-based antigen-antibody tests	Median days for detection (IQR)*	Detection (days) 99th percentile
ADVIA Centaur HIV Ag/Ab Combo (CHIV)	18.4 (14.1, 23.6)*	42.0
Abbott HIV Ag/Ab Combo on ARCHITECT	17.9 (13.6, 23.1)*	41.6
BioPlex 2200 HIV Ag-Ab	17.4 (12.8, 23.2)*	43.1

**IQR defined as the 25th and 75th percentiles, and 99th percentiles.*

Figure 14C. Similar performance for detection of early HIV infection with lab-based antigen-antibody assays.

Comparative performance in a higher prevalence population[44]

Another published study included comparison of the 4th gen Siemens Healthineers CHIV (on ADVIA Centaur) to the Abbott HIV Ag/Ab Combo assay (on Abbott ARCHITECT) using a variety of defined samples from a higher-risk population (HIV prevalence of 1.3%).[44] Overall, comparable performance was observed, although some minor differences were reported, including a comparatively higher rate of false positives (FP) with the Abbott assay. **Table 4A.**

Interestingly, all FP results on the Abbott ARCHITECT were appropriately negative on ADVIA Centaur and vice-versa for the ADVIA Centaur FP results, suggesting false reactivity could be associated with the assay designs. Observed values associated with a FP result were lower on ADVIA Centaur versus Abbott ARCHITECT. **Table 4B.**

Early detection of acute infection

Samples characterized as "early seroconversion" were equally recognized by both assays.[44] In a small (6) number of samples defined as RNA positive but antibody negative, the Abbott assay detected 4 vs. 2 of the 6 samples. One of those two samples was characterized by the authors as a high non-reactive (Index 0.927) on ADVIA Centaur (near the Index of 1.0 or greater for reactivity) and was subsequently reactive when a new sample was collected 6 days later.

The other sample reported as non-reactive on ADVIA Centaur had a very low single to cutoff value on the Abbott ARCHITECT of 1.14 (just above the reactive value defined by the manufacturer for the assay). No evidence was presented on if any samples were repeated if initially reactive. Detection of p24 correlated to samples with higher viral loads.

For earliest detection, the authors observed pooled RNA (as a more cost-effective alternative to individual RNA samples) offered greater sensitivity for detection of acute infection compared to either of the antigen-antibody assays.[44] Similar findings have been reported elsewhere.[63] If an early acute infection is suspected, RNA testing (even when pooled) may offer superior performance.

Tables 4A and 4B. Comparison of assay performance in a high-risk population.[44]*

Table 4A		Siemens Healthineers 3rd gen	Siemens Healthineers 4th gen	Abbott 4th gen
No evidence of HIV infection	Reactive Non-reactive Not tested	13 9422 0	33 9402 0	74 9361 0
Established HIV infection[a]	Reactive Non-reactive Not tested	79 0 0	79 0 0	79 0 0
Pre-seroconversion HIV infection[a]	Reactive Non-reactive Indeterminate Not tested	0 6 0 0	2 4 0 0	4 2 0 0
Early seroconversion HIV infection[a]	Reactive Non-reactive Indeterminate Not tested	9 0 0 0	9 0 0 0	9 0 0 0

Table 4B	Median false reactive s/c (range)
Siemens Healthineers 3rd gen	1.5 (1.08–2.93)
Siemens Healthineers 4th gen	1.23 (1.02–4.03)
Abbott 4th gen	2.32 (1.01–23.83)

gen: generation
s/c: signal/cutoff

**ADVIA Centaur CHIV and Atellica CHIV assay.*

Role of antigen versus antibody detection in early seroconversion

Detection of both antibody and antigen play important roles in identifying early infection.[64] Antigen may be detected in some samples with higher viral loads and low/absent antibodies. A very brief "2nd diagnostic" window may occur in rare samples if the drop in antigen and rise in antibodies is insufficient for the threshold of detection with the assay used.

Detection data in samples defined as early infection are shown in **Table 5.** Not all early infections were detected, and similar sensitivities between antigen-antibody assays were reported, with just one sample showing differential detection.

This may help explain why sensitivity for p24 alone is insufficient, and assay-specific thresholds for both antigen and antibody are important. Importantly, these differential findings in early infection are rare, and data show good performance for sensitivity across lab-based fourth generation assays.[43]

Table 5. Detection of early infection using HIV antigen-antibody assays (CDC data).[57]*

Antigen-antibody assay	True positive detected	False negative	Percent of early infections detected
ADVIA Centaur CHIV	9	6	60%
BioPlex 2200 Ag/Ab	9	6	60%
Abbott ARCHITECT HIV Ag/Ab Combo	8	7	53.3%

False positives and HIV prevalence

Most approved HIV tests offer good specificity, but as with any test, false positive results can occur. While FP's can be associated with technical and biological issues, a lower prevalence of disease in the testing population is associated with generally higher rates of falsely reactive immunoassays.[65] To highlight the impact on test reactivity relative to disease prevalence in the testing population, the CDC has provided an infographic and discussion specific to HIV.[65]

Figure 15 shows the example used by the CDC of the potential impact on false test results in a "high" HIV (2%) vs. "low" HIV (0.1%) setting.[65] False positive results can be a common finding with all sensitive HIV assays,[66-72] highlighting the importance of confirming infection in reactive results in algorithms such as those suggested by the WHO and U.S. CDC.[66-72]

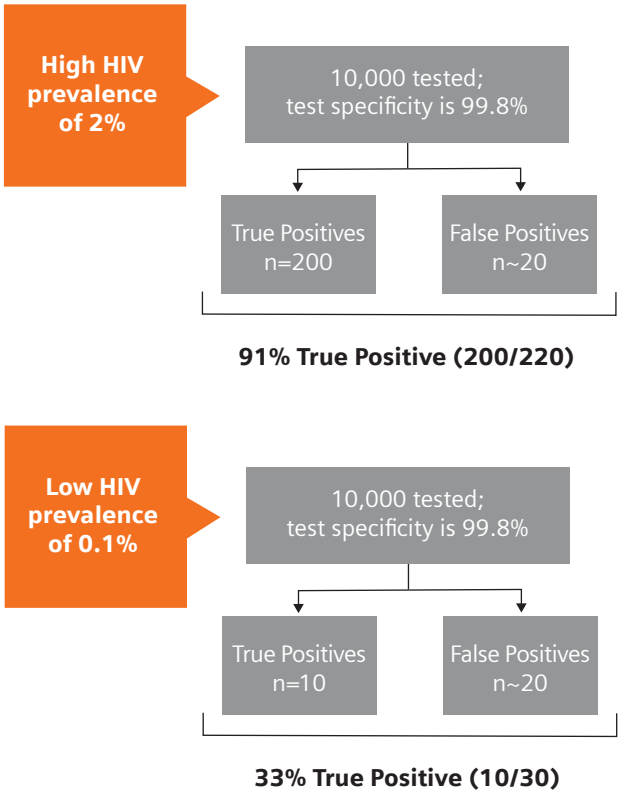


Figure 15. Lower HIV prevalence is associated with a higher rate of false-positive results.[65]

**ADVIA Centaur CHIV and Atellica CHIV assay.*

Alternate HIV testing populations

While most HIV testing occurs in adults, some HIV assays have been validated for other testing populations. **Table 6** shows the populations validated for the CHIV assay from Siemens Healthineers.[73,74]

Table 6. U.S. and global claims for the Siemens Healthineers CHIV assay (on ADVIA Centaur and Atellica IM).

US populations[74]	Outside the US (OUS) populations[73]
Adults (including pregnant women)	Adults (including pregnant women)
Pediatric (>2 years)	Children and Adolescents (>2 years)
The ADVIA Centaur CHIV assay is not intended for the screening of blood or plasma donors. Although the effectiveness of the assay for screening blood or plasma donors has not been established, the assay can be used as a blood donor screening assay in urgent situations where traditional licensed blood donor screening tests are unavailable, or if their use is impractical.	Blood donors or cadaveric donors whose cells, tissues, and organs are intended for transplant.

CHIV on Atellica vs. ADVIA Centaur

The Atellica IM uses the same reagents as the ADVIA Centaur CHIV assay, and good correlations have been reported by Siemens Healthineers.[75] An internal study comparing CHIV performance using the same samples on Atellica IM and ADVIA Centaur CHIV observed 100% agreement in a range of HIV sample types.[61] **Table 7A.**

Table 7A. Clinical Sensitivity for Atellica IM vs. ADVIA Centaur CHIV.[61]

	Atellica IM CHIV Assay			ADVIA Centaur CHIV Assay		
Specimen category	Number tested	Nonreactive	Reactive	Number tested	Nonreactive	Reactive
Group O Contrived	24	0	24	24	0	24
Group O Native	33	0	33	33	0	33
HIV-positive Pediatric	75	0	75	73	0	73
HIV-positive Pregnant	57	0	57	57	0	57
HIV-1 positive	919	0	919	919	0	919
HIV-2 positive	201	0	201	201	0	201
Contrived/spiked p24	41	0	41	41	0	41
Authentic p24 Ag+/Ab- specimens	16	0	16	13	0	13
Total	**1366**	**0**	**1366**	**1361**	**0**	**1361**
Total (%)	—	**0.00%**	**100.00%**	—	**0.00%**	**100.00%**

Table 7B. Sensitivity and specificity for Atellica IM CHIV in low and high-risk populations.[61]

Overall clinical sensitivity	Clinical specificity (HIV-1 low risk population)	Clinical specificity (HIV-2 high risk population)	Clinical specificity (HIV-2 high risk endemic population)
100%	99.9%	99.6%	99.79%

Sensitivity/specificity performance in low and high-risk populations as well as for HIV-2 is shown in **Table 7B.** Overall sensitivity and specificity correlations are shown in **Table 7C.**

Table 7C. Positive and negative agreement for Atellica and ADVIA Centaur for CHIV.[61]

	Atellica IM Analyzer/ ADVIA Centaur XP System	Agreement (%)	95% Confidence Interval
Nonreactive (negative)	7389/7391	99.97%	99.90–100.00%
Reactive (positive)	1390/1393	99.78%	99.37–99.96%

Subtype detection with CHIV

Data show broad subtype detection using CHIV, including the most common subtypes (A, B, and C) as well as multiple CRF's. **Table 8.**

Table 8. Broad subtype detection with CHIV.[76]*

Panel member	Genotype	ADVIA Centaur CHIV Index	Vendor CoA Anti-HIV1/2
WWRB304-01	A	>12	Reactive
WWRB304-02	A	11.4	Reactive
9249313	A1	>12	Reactive
9249722	A1	11.3	Reactive
WWRB304-03	B	>12	Reactive
WWRB304-04	B	>12	Reactive
9249734	C	>12	Reactive
WWRB304-05	C	5.2	Reactive
WWRB304-06	C	>12	Reactive
9249721	CRF01 (AE)	>12	Reactive
9249728	CRF01 (AE)	>12	Reactive
WWRB304-07	CRF01 (AE)	11.2	Reactive
WWRB304-08	CRF01 (AE)	>12	Reactive
9249731	CRF02 (AG)	11.7	Reactive
9249736	CRF02 (AG)	>12	Reactive
WWRB304-09	CRF02 (AG)	>12	Reactive
WWRB304-10	CRF02 (AG)	>12	Reactive
9249316	CRF06	>12	Reactive
9249732	CRF06	>12	Reactive
9249318	CRF11	10.4	Reactive
9249310	CRF13	>12	Reactive
9249725	D	>12	Reactive
9249730	D	>12	Reactive
WWRB304-11	D	>12	Reactive
WWRB301-06	E	>12	Reactive
WWRB301-12	E	3.8	Reactive
WWRB301-34	E	1.2	Reactive
WWRB301-40	E	7.4	Reactive
9249726	F	>12	Reactive
9249729	F	>12	Reactive
WWRB304-12	F	>12	Reactive
WWRB304-13	F	>12	Reactive
9249312	F2	>12	Reactive
9249724	F2	6.0	Reactive
9249723	G	>12	Reactive
9249727	G	>12	Reactive
WWRB304-14	G	>12	Reactive
WWRB304-15	G	>12	Reactive
WWRB304-16	H	>12	Reactive
WWRB304-17	J	7.9	Reactive
9243004	O	>12	N/A
PRD301-01	O	1.6	Reactive
PRD301-02	O	4.9	Reactive
PRD301-03	O	1.2	Reactive
PRD301-04	O	1.1	Reactive

**ADVIA Centaur CHIV and Atellica CHIV assay.*

Conclusion

To achieve global targets for HIV reduction, expanded HIV testing is essential. While sensitive lab-based antigen-antibody tests offer the highest performance, use of POC 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 mortality. Data support the good performance and correlation for the CHIV assay on the ADVIA Centaur and Atellica IM immunoassay systems.

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

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