MODULE 10

TESTING PROVIDERS

# WHO IMPLEMENTATION TOOL FOR PRE-EXPOSURE PROPHYLAXIS (PrEP) OF HIV INFECTION

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World Health Organization

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# Introduction

Following the WHO recommendation in September 2015 that "oral pre-exposure prophylaxis (PrEP) should be offered as an additional prevention choice for people at substantial risk of HIV infection as part of combination HIV prevention approaches", partners in countries expressed the need for practical advice on how to consider the introduction of PrEP and start implementation. In response, WHO has developed this series of modules to support the implementation of PrEP among a range of populations in different settings.

Although there is growing acknowledgement of PrEP's potential as an additional HIV prevention option and countries are beginning to consider how PrEP might be most effectively implemented, there has been limited experience with providing PrEP outside research and demonstration projects in low- and middle-income countries. Consequently, there is often uncertainty around many implementation issues. The modules in this tool provide initial suggestions for the introduction and implementation of PrEP based on currently available evidence and experience. However, it is recognized that this evidence may evolve following wider PrEP use; therefore, it is likely that this tool will require regular updating.

PrEP should not replace or compete with effective and well-established HIV prevention interventions, such as comprehensive condom programming for sex workers and men who have sex with men and harm reduction for people who inject drugs. Many people who could benefit most from PrEP belong to key population groups that may face legal and social barriers to accessing health services. This needs to be considered when developing PrEP services. Although the public health approach underpins the WHO guidance on PrEP, the decision to use PrEP should always be made by the individual concerned.

## Target audience and scope of tool

This PrEP tool contains modules for a range of stakeholders to support them in the consideration, planning, introduction and implementation of oral PrEP. The modules can be used on their own or in combination. In addition, there is a module for individuals interested in or already taking PrEP. (See Summary of modules below.)

This tool is the product of collaboration between many experts, community organizations and networks, implementers, researchers and partners from all regions. The information presented is aligned with WHO's 2016 consolidated guidelines on the use of antiretroviral drugs for HIV treatment and prevention.

All modules make reference to the evidence-based 2015 WHO recommendation on PrEP. They do not make any new recommendations on PrEP, focusing instead on suggested implementation approaches.

## Guiding principles

It is important to adopt a public health, human rights and people-centred approach when offering PrEP to those at substantial risk of HIV. Similar to other HIV prevention and treatment interventions, a human rights-based approach gives priority to issues concerning universal health coverage, gender equality and health-related rights including accessibility, availability, acceptability and quality of PrEP services.

## SUMMARY OF MODULES

**Module 1: Clinical.** This module is for clinicians, including physicians, nurses and clinical officers. It gives an overview of how to provide PrEP safely and effectively, including: screening for substantial risk of HIV; performing appropriate testing before initiating someone on PrEP and while the person is taking PrEP; and how to follow up PrEP users and offer counselling on issues such as adherence.

**Module 2: Community educators and advocates.** For PrEP services to reach populations in an effective and acceptable way, community educators and advocates are needed to increase awareness about PrEP in their communities. This module provides up-to-date information on PrEP that should be considered in community-led activities that aim to increase knowledge about PrEP and generate demand and access.

**Module 3: Counsellors.** This module is for staff who counsel people as they consider PrEP or start taking PrEP and support them in addressing issues around coping with side-effects and adherence strategies. Those who counsel PrEP users may be lay, peer or professional counsellors and healthcare workers, including nurses, clinical officers and doctors.

**Module 4: Leaders.** This module aims to inform and update leaders and decision-makers about PrEP. It provides information on the benefits and limitations of PrEP so that they can consider how PrEP could be most effectively implemented in their own settings. It also contains a series of frequently asked questions about PrEP, with related answers.

**Module 5: Monitoring and evaluation.** This module is for people responsible for monitoring PrEP programmes at the national and site levels. It provides information on how to monitor PrEP for safety and effectiveness, suggesting core and additional indicators for site-level, national and global reporting.

**Module 6: Pharmacists.** This module is for pharmacists and people working in pharmacies under a pharmacist's supervision. It provides information on the medicines used in PrEP, including the optimal storage conditions. It also gives suggestions for how pharmacists and pharmacy staff can monitor PrEP adherence and support PrEP users to take their medication regularly.

**Module 7: Regulatory officials.** This module is for national authorities in charge of authorizing the manufacturing, importation, marketing and/or control of antiretroviral medicines used for HIV prevention. It provides information on the safety and efficacy of PrEP medicines.

**Module 8: Site planning.** This module is for people involved in organizing PrEP services at specific sites. It outlines the steps to be taken in planning a PrEP service and gives suggestions for personnel, infrastructure and commodities that could be considered when implementing PrEP.

**Module 9: Strategic planning.** As WHO recommends offering PrEP to people at substantial HIV risk, this module offers public health guidance for policy-makers on how to prioritize services, in order to reach those who could benefit most from PrEP, and in which settings PrEP services could be most cost-effective.

**Module 10: Testing providers.** This module is for people who are responsible for providing testing services at PrEP sites and associated laboratories. It offers guidance in selecting relevant testing services, including appropriate screening of individuals before PrEP is initiated and monitoring while they are taking PrEP. Information is provided on testing for HIV, creatinine, hepatitis B and C virus, pregnancy and sexually transmitted infections.



**Module 11: PrEP users.** This module provides information for people who are interested in taking PrEP to reduce their risk of acquiring HIV and people who are already taking PrEP – to support them in their choice and use of PrEP. This module gives ideas for countries and organizations implementing PrEP to help them develop their own tools.

## ANNEXES

**Review of evidence.** A wide range of evidence including the following two systematic reviews informed the 2015 WHO recommendation on PrEP for people at substantial risk of HIV infection: (i) Fonner VA et al. *Oral tenofovir-based HIV pre-exposure prophylaxis (PrEP) for all populations: a systematic review and meta-analysis of effectiveness, safety, behavioural and reproductive health outcomes*; (ii) Koechlin FM et al. *Values and preferences on the use of oral pre-exposure prophylaxis (PrEP) for HIV prevention among multiple populations: a systematic review of the literature*.

**Annotated Internet resources.** This list highlights some of the web-based resources on PrEP currently available together with the stakeholder groups they are catering to. WHO will continue to provide updates on new resources.

# The testing providers module

This module is designed to support national HIV programme managers and other decision-makers who have an interest in implementing pre-exposure prophylaxis (PrEP) and require guidance in selecting the relevant testing services, including appropriate screening of clients before PrEP is initiated and monitoring while taking PrEP. Information is provided on testing for HIV, creatinine, hepatitis B virus (HBV), hepatitis C virus (HCV), pregnancy and sexually transmitted infections (STIs) such as Treponema pallidum (syphilis), Neisseria gonorrhoeae (NG) and Chlamydia trachomatis (CT).

This module also describes the frequency with which PrEP users may require different types of testing services. In addition, testing strategies and testing algorithms are discussed, including how to use testing results to inform clinical decisions about PrEP initiation and management.

**WHO Recommendation for PrEP**

The World Health Organization recommends that oral PrEP containing TDF should be offered as an additional prevention choice for people at substantial risk of HIV infection as part of combination prevention approaches *(strong recommendation; high-quality evidence)*.

## Key messages: testing services in the context of PrEP

Several testing services must be delivered before a person can start taking PrEP safely and effectively. Periodic retesting while a person is taking PrEP is also needed. (See Table 1 below for a summary of suggested testing services for individuals starting and taking PrEP.)

**Testing for HIV** is required to rule out infection prior to initiating PrEP. Once an individual has been initiated on PrEP, HIV testing is suggested every three months and whenever restarting PrEP after a gap in use to rule in or rule out HIV infection. Some services and programmes are currently conducting an additional HIV test one month after starting PrEP.

Individuals on PrEP with an **HIV-inconclusive status** should be retested in 14 days; stopping PrEP to determine their true HIV status may also need to be considered. Individuals on PrEP with an HIV-positive diagnosis will need to be placed on a fully suppressive antiretroviral treatment (ART) regimen.

**Monitoring kidney function** is particularly important to ensure safety among PrEP users. Since tenofovir disoproxil fumarate (TDF) is known to have an impact on the glomerular filtration rate, testing for serum creatinine is suggested.

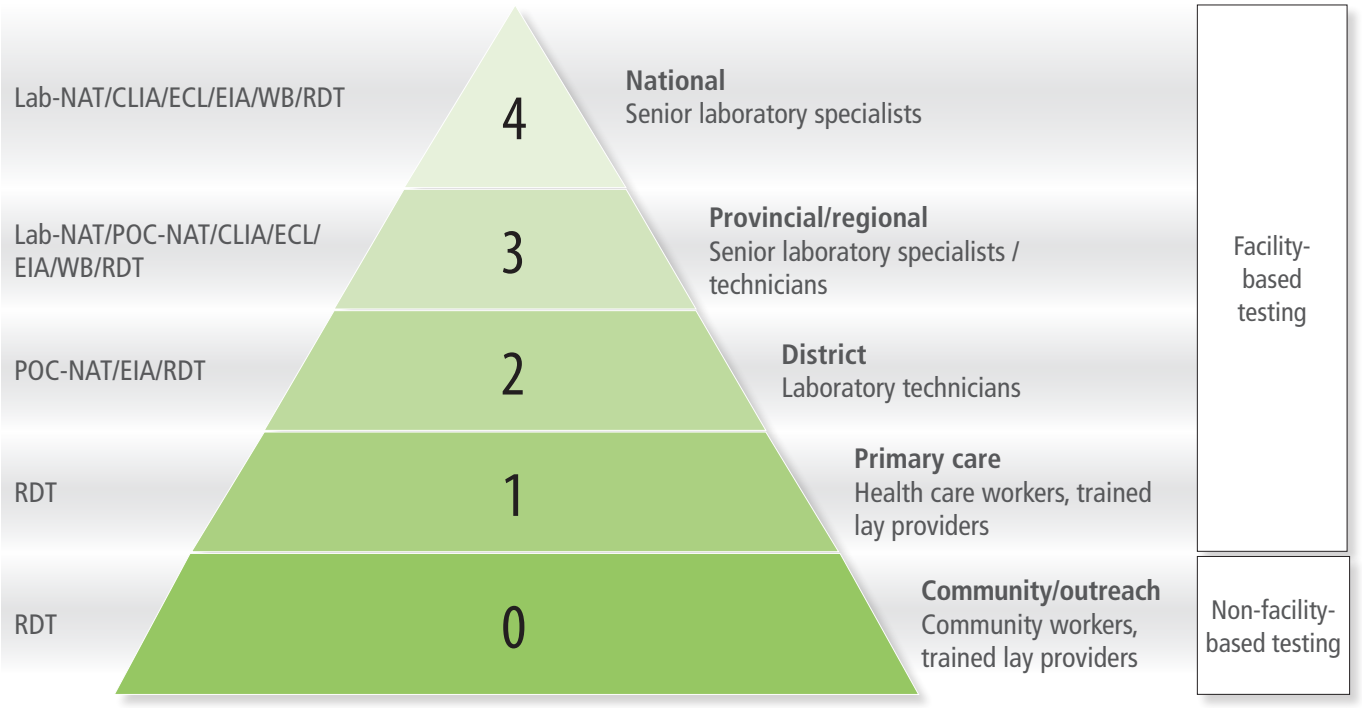
**Testing for chronic HBV** is important for people before they start PrEP, as it will help in making decisions about PrEP initiation, HBV vaccination and future management of HBV. It is safe for people with HBV to use PrEP, and PrEP can be initiated before HBV testing results are available. For those who are **hepatitis B surface antigen** (HBsAg) negative, HBV vaccination could be considered. For individuals who are **HBsAg** positive, and therefore likely to be chronically infected with HBV, further laboratory tests and clinical assessment will be needed.

**Screening for** STIs prior to PrEP initiation, and periodically while taking PrEP, is important. People who are eligible for or who are using PrEP are often at risk for other STIs and may have an STI that requires treatment. Initial and periodic screening of PrEP users for syphilis, gonorrhea and chlamydial infections should be considered. If signs and symptoms of STIs are visible, individuals should be treated syndromically.

## TABLE 1. SUMMARY OF TESTING SERVICES FOR STARTING AND MONITORING PREP

| PATHOGEN / ANALYTE | TESTING LOCATION | TIMING AND FREQUENCY |
|---|---|---|
| **HIV**<br>(HIV antibodies (anti-HIV)) | Community/outreach;<br>Primary care;<br>Laboratory (district/ provincial/ national) | Prior to starting or restarting PrEP and every three months during PrEP use. Programmes can also consider testing at 1 month after starting PrEP. |
| **Creatinine** | Primary care;<br>Laboratory (district/ provincial/ national) | Consider testing prior to starting or restarting PrEP and consider every six months during PrEP use. Increasing testing frequency may be considered if there are comorbid conditions affecting renal function. |
| **HBV**<br>(Hepatitis B surface antigen (HBsAg)) | Community/outreach;<br>Primary care;<br>Laboratory (district/ provincial/ national) | **If HBsAg test is reactive**, evaluate for HBV treatment indications based on WHO hepatitis B treatment guidelines. PrEP can be started before the result is available.<br><br>For those being treated for chronic HBV, it is important to undertake further laboratory testing before PrEP is stopped to help with deciding how to monitor for HBV flares or how to continue treatment.<br><br>**If HBsAg is not detected**, with no history of immunization, vaccinating against HBV can be considered. |
| **HCV**<br>(HCV antibodies (anti-HCV)) | Community/outreach;<br>Primary care;<br>Laboratory (district, provincial, national) | Consider testing for HCV in certain populations, such as men who have sex with men and people who inject drugs, prior to PrEP initiation and annually thereafter. |
| **Pregnancy** | Community/outreach;<br>Primary care;<br>Laboratory (district, provincial) | When clinically indicated, for example women who report missed menses or symptoms of pregnancy. |
| **Syphilis** (treponemal antibodies)<br><br>**Syphilis**<br>(rapid plasma reagin titer) | Community/outreach;<br>Primary care;<br>Laboratory (district, provincial) | When starting PrEP, consider testing and every three to six months during PrEP use to check for active syphilis infection and to evaluate response to treatment.<br><br>Pregnant women seeking or taking PrEP with a single reactive treponemal or nontreponemal test result should be started on treatment. |
| **Neisseria gonorrhoeae (GC)**<br><br>**Chlamydia trachomatis (CT)** | Laboratory<br>(district, provincial, national) | Consider testing when starting PrEP and every three to six months during PrEP use. Use of nucleic acid testing (NAT) technologies is preferred for testing for gonorrhoeae and chlamydia.<br><br>If NAT technologies are not available, probe for symptoms and look for signs of STIs and treat syndromically. |

## FIGURE 1. SUGGESTED HIV, STI AND HEPATITIS TESTING SERVICES WITH ASSAY FORMAT MENU AND STAFF QUALIFICATIONS *(6)*




Source: Short, medium, long term product development priorities in HIV-related diagnostics. WHO expert meeting report Geneva: World Health Organization; 2012.
Note: with evolving technology development, POC-NAT may soon be possible at Level 1 health facilities.

## HIV testing services

All people at substantial risk of HIV infection who could be eligible for PrEP should be offered HIV testing services. Prior to starting or restarting PrEP, it is critical to rule in or rule out HIV infection in order to:

i) Identify and diagnose people with HIV;

ii) Refer and link people with HIV to treatment and care as early as possible;

iii) Ensure people who have HIV do not start PrEP *(3–5).*

HIV testing services prior to and throughout PrEP use can be delivered in a variety of settings, depending on the type of test being performed (see Fig. 1).

### Providing an HIV diagnosis in the context of PrEP

To diagnose HIV infection, WHO recommends using serial testing strategies shown in Fig. 2 (for high (≥5%) HIV prevalence settings) and Fig. 3 (for low (<5%) HIV prevalence settings), within a validated testing algorithm, and preferably using WHO prequalified assays. Individuals may be tested at the point of care and provided with the results on the same day. In most low- and middle-income settings where PrEP is delivered, HIV testing prior to and throughout PrEP use will follow the national testing algorithm, usually a combination of rapid diagnostic tests (RDTs), at the point of care.

If the initial HIV serology test result is non-reactive (negative) and there is no history or signs or symptoms of an acute viral syndrome, the person could be offered and initiated on PrEP, if desired.

A single reactive (positive) test result is not sufficient to make an HIV-positive diagnosis. If the initial serology test result is reactive, additional testing is needed to confirm an HIV-positive diagnosis (see Figs. 2 and 4). For high prevalence settings, two consecutive reactive serology test results on the first-line and second-line assays (A1+ A2+) are sufficient to rule in HIV infection. For low prevalence settings, three consecutive reactive serology test results on the first-line, second-line and third-line assays (A1+ A2+ A3+) are required to rule in HIV infection.

Individuals with discrepant testing results, i.e. the test result of the first-line assay is reactive (A1+) and the test result of the second-line assay is nonreactive (A2-), a third-line assay should be employed, irrespective of the prevalence.

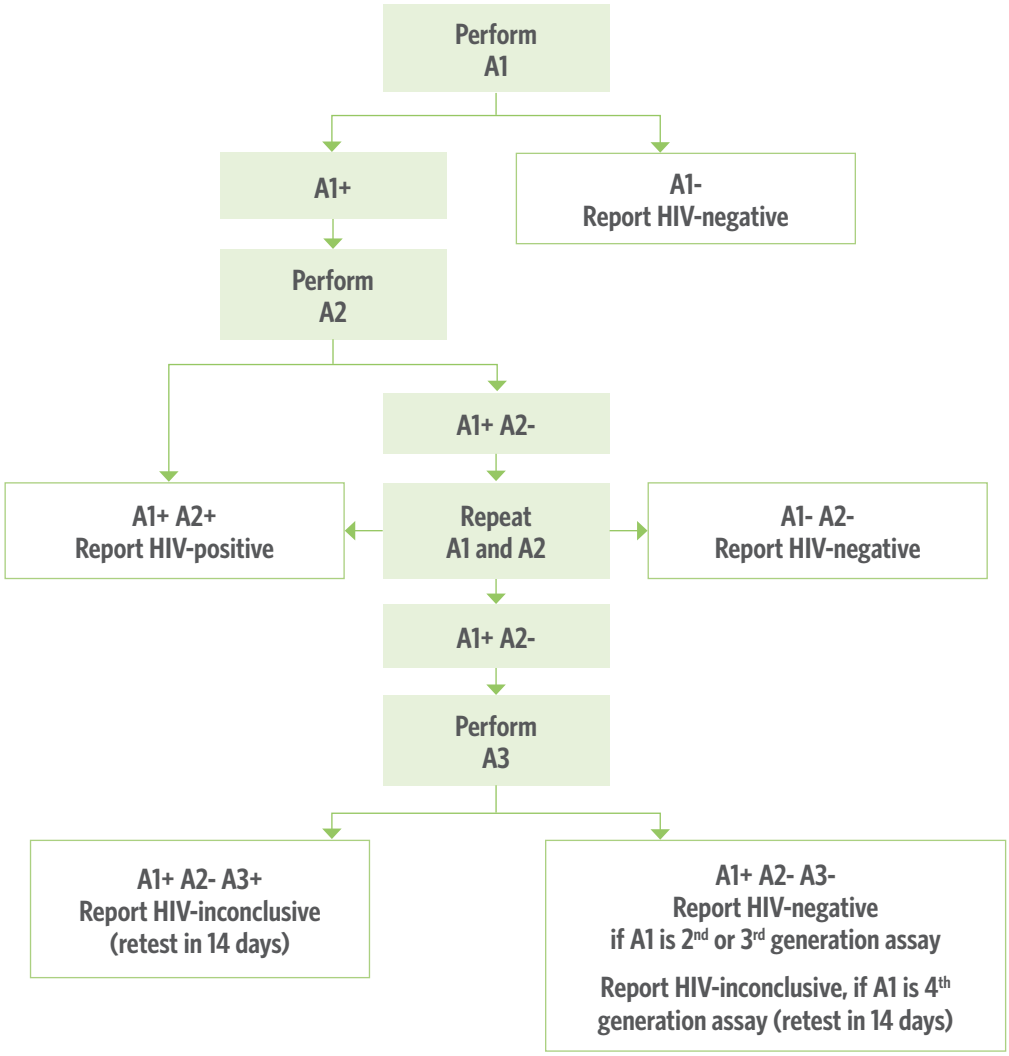
- In high prevalence settings, when the test result of the third-line assay is non-reactive (A3-), the individual is considered to be HIV-negative (A1+ A2- A3-). But if the test result for the third-line assay is reactive (A1+ A2- A3+), the individual should be considered HIV-inconclusive and referred for retesting in 14 days to rule in or rule out possible seroconversion.
- In low prevalence settings, when the test result of the third-line assay is non-reactive (A3-), the individual is considered to be HIV-negative (A1+ A2- A3-). But if the test result for the third-line assay is reactive (A1+ A2- A3+), the individual should be considered HIV-inconclusive and asked to retest in 14 days to rule in or rule out possible seroconversion.

For those with HIV-inconclusive status who return for testing after 14 days:

- If the testing results are still the same, the individual should be considered HIV-negative as seroconversion has been ruled out and the reactive test results are truly false reactive. If desired, PrEP can be initiated.
- If the first-line assay is non-reactive (A1-), the individual should be given a HIV-negative status.
- If the first-line and second-line assays are reactive (A1+ A2+), then a third-line assay is needed. If all assays are reactive (A1+ A2+ A3+), seroconversion is ruled in and the individual is diagnosed HIV-positive and linked to treatment and care.

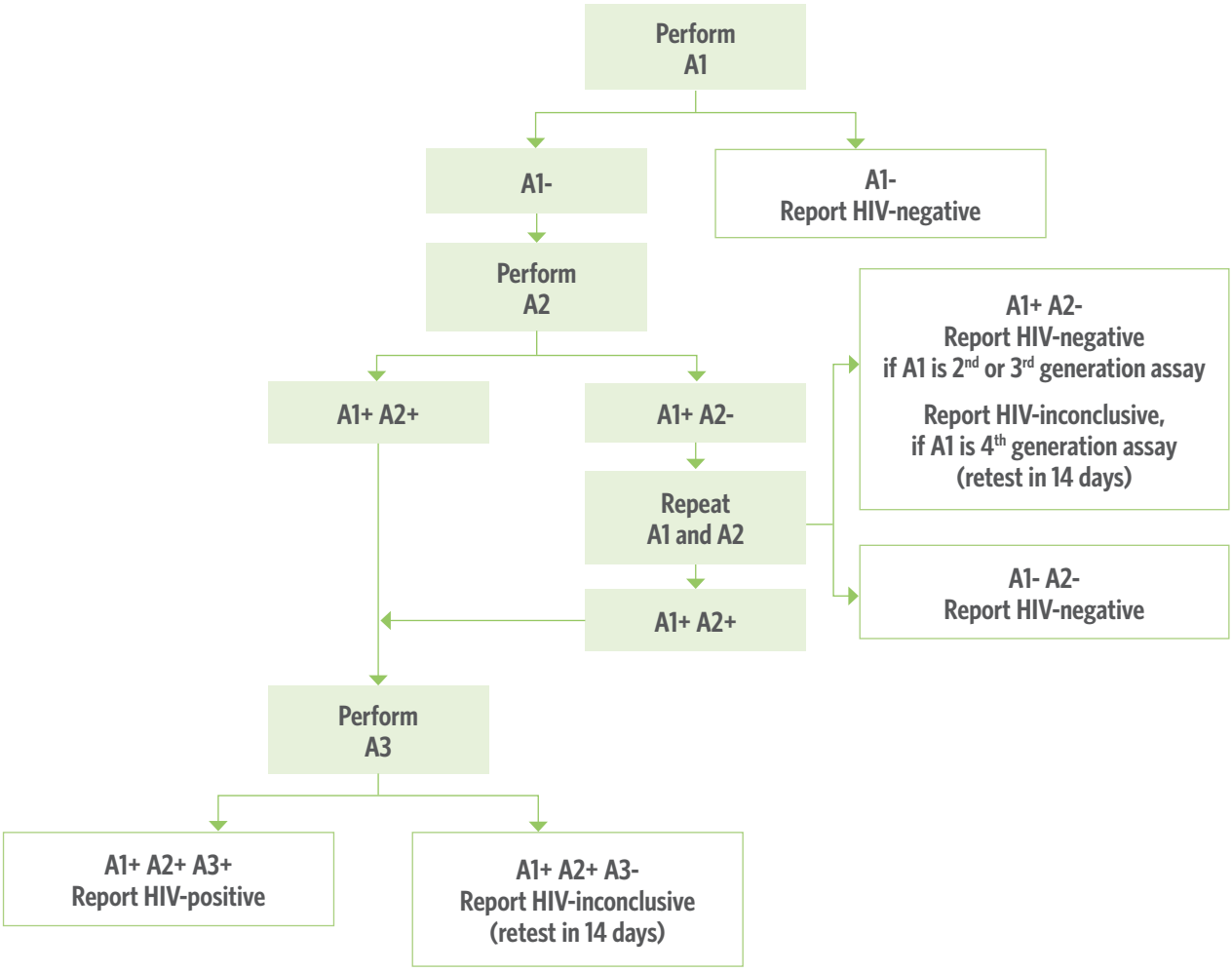
Further information on how to perform HIV testing services can be found in the WHO *Consolidated guidelines on HIV testing services (6)*.

## FIGURE 2. TESTING STRATEGY[1] FOR HIV DIAGNOSIS IN HIGH PREVALENCE SETTINGS




1 Testing strategy generically describes a testing sequence for a specific objective, taking into consideration the presumed HIV prevalence in the population being tested.

## FIGURE 3. TESTING STRATEGY FOR HIV DIAGNOSIS IN LOW PREVALENCE SETTINGS




Once an individual has been initiated on PrEP, HIV testing is suggested every three months and whenever restarting PrEP after a gap in use. Additional HIV testing one month after starting or restarting PrEP may also be beneficial, particularly for programmes that use only serology assays.

It is also suggested that programmes use the low prevalence testing strategy (Fig. 3) for retesting PrEP users. This is because after individuals start PrEP their risk of HIV acquisition will decrease substantially (particularly in those who adhere to their regimen) and the HIV prevalence among PrEP users will be low.

If a person on PrEP is diagnosed with an HIV infection, PrEP should be changed to a fully suppressive antiretroviral treatment regimen. If possible, before ART is initiated, a blood specimen (dried blood spot or plasma) could be collected along with basic epidemiological information as a form of case-based surveillance for HIV drug resistance and sent to the national reference laboratory.

## HIV self-testing in the context of PrEP

HIV self-testing could be an important demand creation tool that provides a way to reach individuals eligible for PrEP who may not otherwise test or access a health facility. However, a non-reactive self-test result is not sufficient to start PrEP. If an individual has a non-reactive self-test result, he or she should be linked to further testing starting from the beginning of the relevant validated testing algorithm before starting or restarting PrEP.

More information is available in the WHO *Guidelines on HIV self-testing and partner notification services (7)*: http://apps.who.int/iris/bitstream/10665/251655/1/9789241549868-eng.pdf?ua=1.

## Considerations for selecting HIV assays for starting and monitoring PrEP

In the context of PrEP, as with all HIV testing, when constructing a testing algorithm it is important to select a highly sensitive first-line assay that will reduce the risk of false negative results and help ensure persons initiated on PrEP are truly HIV-negative. Following this, highly specific second- and third-line assays are used to reduce the risk of false reactive test results and rule in HIV-positive diagnoses. When selecting assays, testing services should also consider geographical or population variables that may also cause or contribute to false reactive or false non-reactive test results.

Serology assays when selected appropriately and used in combination, as recommended by WHO, can provide a highly accurate diagnosis, often on the same day, in the context of starting PrEP or retesting PrEP users.

By following these guiding principles and using WHO prequalified serology assays within a validated testing algorithm, programmes can provide a highly accurate HIV diagnosis and, thereby, direct those who are HIV-negative to PrEP and other relevant HIV prevention methods and those who are HIV-positive to treatment services.

## Antiretroviral medicines for prevention and serology testing

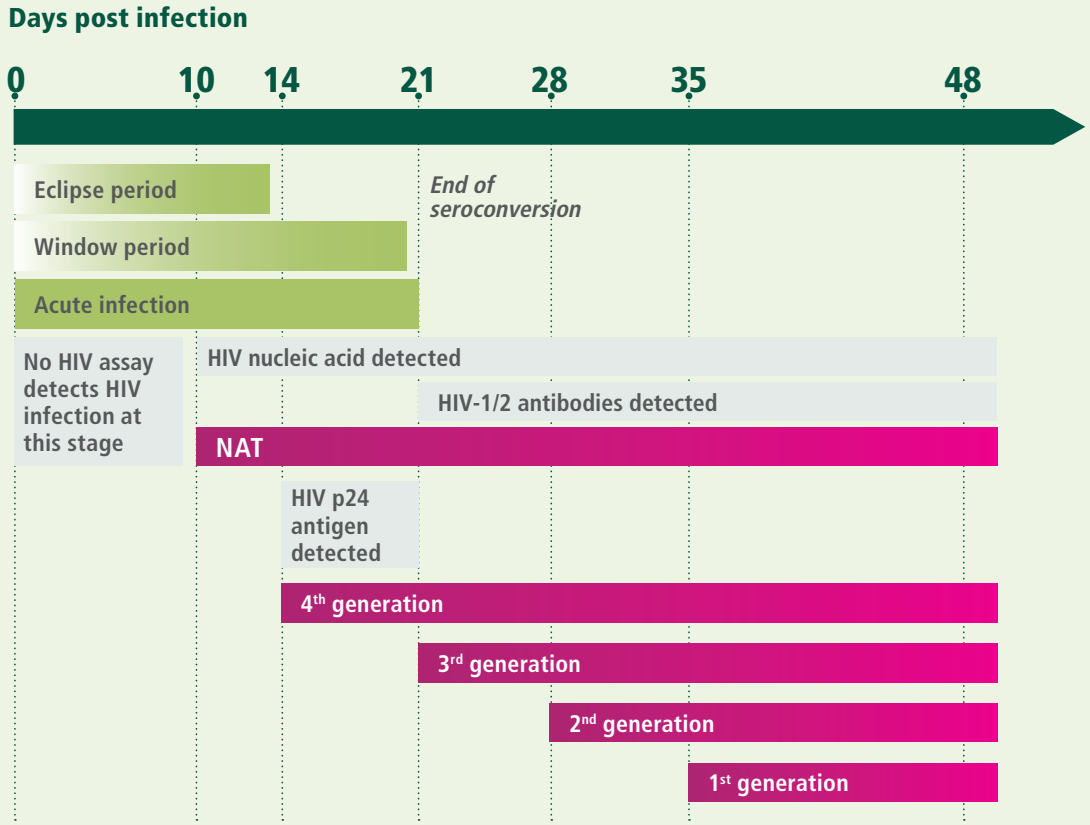
It is possible that people using PrEP, who become HIV-infected, may develop a delayed antibody response that can lengthen the window period (the period when HIV testing cannot detect HIV infection). This is because taking antiretroviral drugs could decrease or delay the production of antibodies. While current evidence is limited, two PrEP trials that used a series of 3rd generation serology assays did not observe suboptimal sensitivity due to PrEP *(1, 2)*. WHO is reviewing additional evidence on this issue and will provide further guidance in 2018.

## Considerations for using 4th generation assays and NAT technologies for HIV testing in PrEP programmes

Early detection of HIV, including acute infection, allows earlier diagnosis and linkage to treatment, and reduces the risk of developing HIV drug resistance from starting PrEP while acutely infected *(3–5)*.

The risk of acute infection in people who seek PrEP services is expected to range between 1:50 and 1:300 at baseline depending on the underlying HIV incidence in the population *(8)*. Because of this risk and where feasible, there may be benefits to using assays that have the ability to detect HIV earlier, such as 4th generation serology assays that detect HIV-1/2 antibodies and HIV p24 antigen, and NAT technologies (see Fig. 4), for HIV testing prior to starting or restarting PrEP.

## FIGURE 4. DETECTING HIV OVER THE NATURAL HISTORY OF INFECTION *(6, 9)*




*Source*: Rosenberg et al., 2015 *(1)*.

Despite the potential benefits of early HIV detection, however, currently available 4th generation HIV RDTs have been shown to have poorer than expected rates of HIV p24 antigen detection *(10–15)*. Also, detection of p24 antigen may not mean someone is acutely infected, as it could also indicate that an HIV-positive individual has entered the late course of the infection when the immune response wanes, the production of antibodies decrease and, therefore titers of HIV p24 antigen increase. Likewise, although NAT technologies have the ability to detect acute infection (defined as detectable HIV-1 RNA but no detectable antibodies) *(16)*, clinical performance evaluations are needed to validate how best they can be used to diagnose HIV infection (or rule out HIV infection) prior to PrEP initiation.

Key challenges to implementing currently available NAT technologies and 4th generation assays include the cost, requirements for laboratory infrastructure and skilled staff, and the need for venipuncture to collect appropriate specimens, which makes the use of NATs in many low- and middle-income settings not feasible. While these technologies are promising and could be particularly useful in the context of delivering HIV testing within PrEP services, further research is still needed.

### HIV drug resistance testing

While HIV drug resistance testing is not readily available in most low- and middle-income countries and is not recommended by WHO for routine clinical management, WHO recommends countries to establish routine HIV drug resistance surveillance in populations initiating ART, in populations on ART and in programmes scaling up PrEP *(17)*.

HIV drug resistance can be monitored in individuals who become HIV-positive while on PrEP using a plasma specimen or dried blood spot specimen prepared from venous or capillary whole blood. Blood collection should be done before the individual initiates ART and specimens should be handled according to WHO specifications *(18)*.

To date, there have been only two cases reported of acquisition of resistant HIV-1 that appear to have occurred when taking oral PrEP containing TDF and emtricitabine (FTC) despite good adherence; the virus had markers of resistance to TDF, FTC and other antiretroviral medication classes *(19, 20)*. Such infections due to exposure to resistant HIV appear to be rare, yet additional surveillance is warranted.

See WHO guidelines on drug resistance for additional information:
http://who.int/hiv/pub/guidelines/hivdr-guidelines-2017/.

## Kidney function monitoring

### Creatinine testing

It is suggested that serum creatinine testing be done prior to PrEP initiation and throughout the first year (every six months) of taking PrEP. After the first year, testing could be conducted less frequently. The use of PrEP containing TDF is associated in some people with a small decrease in estimated creatinine clearance, which occurs within months after starting PrEP. Based on the available evidence, this decrease does not usually progress during PrEP use and generally reverses after stopping PrEP *(21–23)*. There is limited information about the optimal timing and frequency of creatinine testing.

Individuals taking PrEP who also have conditions affecting the kidney, such as diabetes mellitus or hypertension, are advised to have more frequent creatinine testing, particularly in the first year of taking PrEP. If an individual taking PrEP is under 45 years of age and has baseline estimated creatinine clearance greater than 90 ml/min and weighs more than 55 kg, creatinine testing could be provided less frequently.

People who are on PrEP and have a creatinine clearance lower than 60 ml/min should be retested. After retesting, discontinuing PrEP should be considered if creatinine clearance continues to be less than 60 ml/min. Once PrEP is stopped, creatinine levels can be re-checked one to three months later and PrEP restarted if renal function, as measured by estimated creatinine clearance, has returned to more than 60 ml/min.

Creatinine testing can be conducted using laboratory-based clinical chemistry assays that are used to quantitatively determine the levels of creatinine, typically in serum. Analyzers for use at point of care are also commercially available and may be used in settings where access to laboratory services is lacking.

## Hepatitis B testing

### Hepatitis B surface antigen (HBsAg) testing

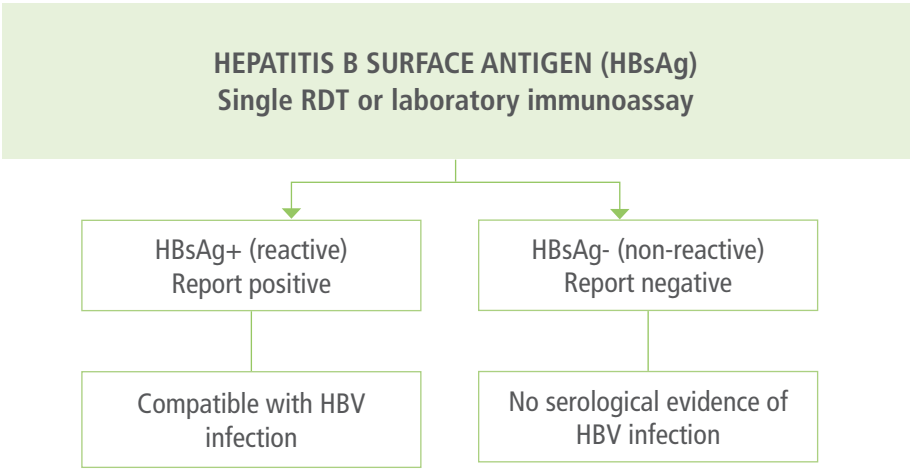
Screening for chronic HBV infection should be considered for people starting or restarting PrEP.

Chronic HBV infection is defined as the persistence of HBsAg for more than six months. Assays for HBsAg may be conducted at the point of care or within a laboratory (see Fig. 5). Testing for HBsAg as a marker of chronic HBV infection is warranted, particularly where there is a high prevalence of HBV infection or poor coverage of HBV immunization.

Starting and stopping PrEP has been found to be safe in people with active HBV infection and no sign of clinical illness *(24, 25)*.

The benefits of HBsAg testing include identification of people who would benefit from HBV treatment (which could include TDF-containing regimens used for PrEP) and identification of sexual partners who would benefit from vaccination for HBV.

## FIGURE 5. SEROLOGY TESTING FOR CHRONIC HBV INFECTION




Source: WHO, 2017 (23)

See WHO Guidelines on hepatitis B and C testing for additional information *(26)*.

### Assays to evaluate treatment indications in individuals with chronic HBV infection

PrEP containing TDF can be used in people with HBV. Not all people with evidence of HBsAg require treatment (see the WHO Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection *(27)*). If HBV treatment is indicated, daily oral PrEP containing TDF can be used for treatment of HBV and HIV prevention concurrently. If PrEP is stopped, consideration should be given to continuing another active HBV treatment (if indicated) to avoid the risk of virological and clinical flare.

## Hepatitis C testing

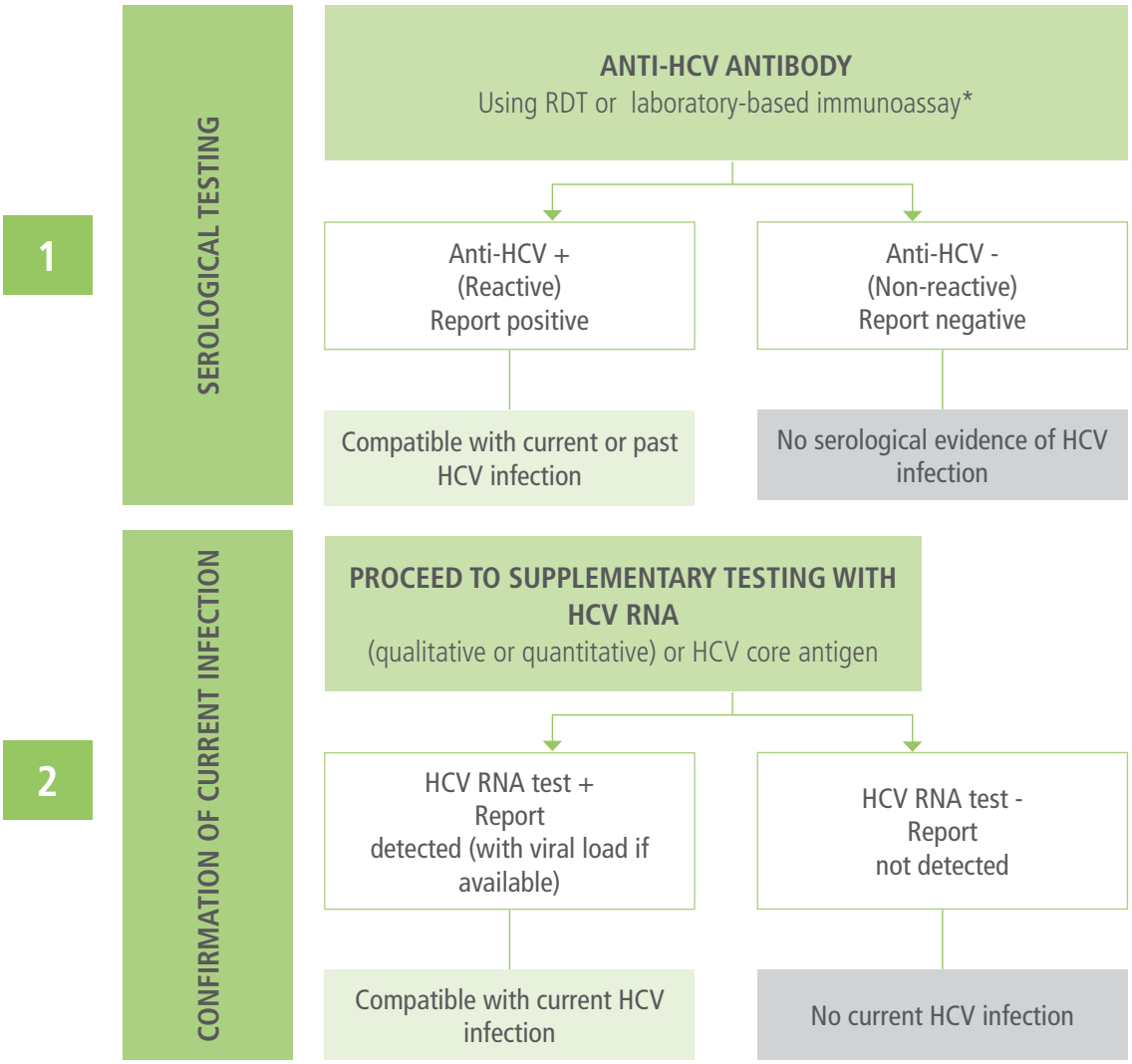
Consideration could be given to testing for evidence of HCV infection in men who have sex with men and people who inject drugs prior to initiation of PrEP and every 12 months thereafter *(23)*.

Testing for evidence of HCV infection is typically conducted by using a serological assay to detect antibodies to HCV (anti-HCV). However, evidence of anti-HCV alone is not indicative of active HCV infection as 15–45% of HCV infections are spontaneously resolved within six months but anti-HCV may persist for an undetermined period of time. Furthermore, expanded access to antiviral treatment may lead to a subset of individuals with evidence of anti-HCV who have been cured of HCV infection.

To diagnose active HCV infection, individuals with a reactive serology test result should be tested for evidence of HCV RNA or HCV p22 core antigen. Refer to diagram (Fig. 6).

See WHO *Guidelines on hepatitis B and C testing* for additional information *(23)*.

## FIGURE 6. TESTING STRATEGY FOR DIAGNOSIS OF VIRAEMIC HCV INFECTION[2]




Source: WHO, 2017 *(23).*

2 Laboratory-based immunoassays include enzyme immunoassay (EIA), chemoluminescence immunoassay (CLIAs), and electrochemoluminescence assay (ECL).

## Pregnancy testing

Testing for pregnancy can be offered to women (and transgender men) who have signs and symptoms of pregnancy and, where indicated, a referral made to antenatal services. Pregnancy is associated with a higher risk of acquiring HIV infection *(28)*. The acquisition of HIV during pregnancy can result in higher rates of mother-to-child transmission. PrEP can be continued through pregnancy unless the woman chooses to stop.

For more information see WHO technical update on PrEP in pregnancy and breastfeeding: http://who.int/hiv/pub/toolkits/prep-preventing-hiv-during-pregnancy/en/.

## Testing for sexually transmitted infections

PrEP provides an opportunity for regular screening for common STIs, including syphilis, gonorrhoeae and chlamydial infections. Where possible, programmes should expand and implement relevant national guidelines on STI screening among people starting or taking PrEP.

Additional guidance on STI screening can be found in the WHO manual *Laboratory diagnosis of sexually transmitted infections, including human immunodeficiency virus (29).*

## Syphilis testing

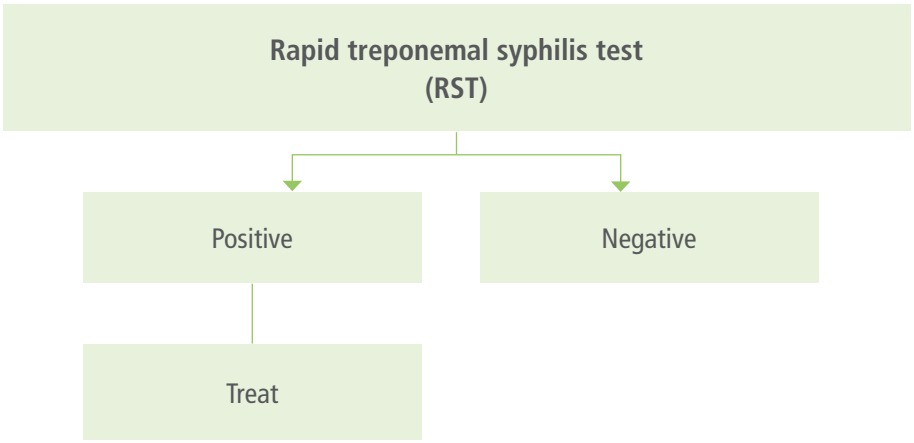
People starting or restarting PrEP will likely benefit from syphilis screening and periodic retesting every three to six months while using PrEP. PrEP programmes should adhere to the relevant national testing procedures and guidelines as conducted within existing health services.

Depending on which assays are available and utilized in a particular setting, different testing strategies for diagnosis of syphilis can be followed (see examples in Figs. 7 and 8). Where treponemal assays are used, individuals who test positive should receive further testing using a nontreponemal assay to confirm active infection, since treponemal assys do not discriminate between active and past infection. However, given the high risk of an adverse pregnancy outcome with syphilis infection, pregnant women seeking or using PrEP who have a single reactive treponemal test result should be treated for syphilis *(30)*.

While there may be particular benefits of using treponemal assays, it may result in overtreatment in some circumstances. There are now multiplex RDTs for both HIV-1/2 and treponemal antibodies. These could potentially be useful for retesting individuals taking PrEP; however, their clinical utility has yet to be evaluated in this context.

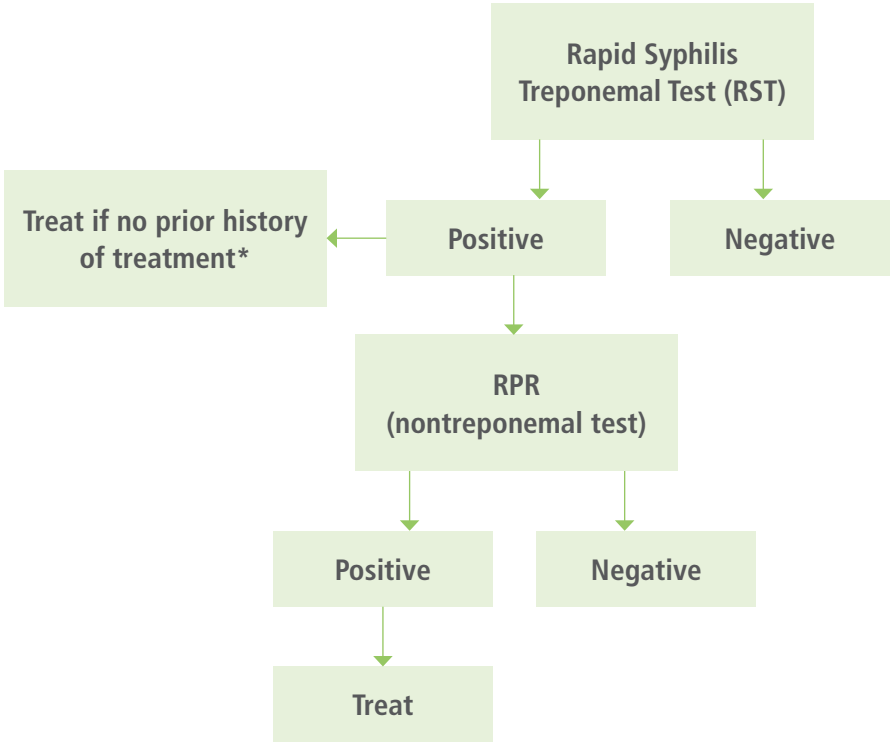
Further guidance on screening for syphilis is available in the WHO manual *Laboratory diagnosis of sexually transmitted infections, including human immunodeficiency virus (29).*

## FIGURE 7. WHO INTERIM RECOMMENDED SYPHILIS TESTING AND TREATMENT STRATEGY FOR LOW SYPHILIS PREVALENCE SETTINGS (BELOW 5%), INCLUDING FOR PREGNANT WOMEN




**Note:**
1. RST does not distinguish between previously adequately treated and untreated syphilis
2. Subsequent testing will likely still be seropositive, therefore, previously RST positive women could be treated without re-testing if the risk of re-infection is considered high. Alternatively perform quantitative RPR testing.

## FIGURE 8. WHO INTERIM RECOMMENDED SYPHILIS TESTING AND TREATMENT STRATEGY FOR HIGH SYPHILIS PREVALENCE SETTINGS (ABOVE 5%)




* Pregnant woman who have tested positive and received treatment during a previous pregnancy should be considered for re-treatment upon receiving a positive syphilis test result in subsequent pregnancies.

### Neisseria gonorrhoeae and Chlamydia trachomatis testing

It is suggested that people starting or restarting PrEP be screened for GC and CT and also receive periodic retesting every three to six months while using PrEP. PrEP programmes should adhere to the relevant national testing procedures and guidelines as conducted within existing health services.

Programmes should use NAT technologies for diagnosing GC and CT because many infections are typically asymptomatic, particularly among women. However, NAT technologies are often unavailable in many low- and middle-income settings. If NAT is not available, PrEP users should be encouraged to attend a clinic for regular STI check-ups. If signs and symptoms of STIs are visible, PrEP users should be treated according to the relevant national STI guidelines.

Guidelines on screening for GC and CT are available in the WHO manual *Laboratory diagnosis of sexually transmitted infections, including human immunodeficiency virus*.

## WHO prequalification assessment and tools for testing providers

Both before an assay is marketed and after it is on the market, its quality, safety and performance must be assured. In vitro diagnostic medical devices (IVDs) are classified by regulatory authorities according to the risk they may pose to public health and individual health, taking into account the potential outcomes and impact if the result is incorrect. Assays for HIV and HBV (and others) usually attract the highest level of scrutiny in their pre-market assessment review, given the high impact of an incorrect result on individual and public health in terms of onward transmission. Assays for creatinine and pregnancy are of a lower risk category and, as such, the independent regulatory review of their safety, quality and performance is less stringent than for HIV and HBV.

WHO Prequalification of In Vitro Diagnostics promotes and facilitates access to safe, appropriate and affordable diagnostics of good quality. The current regulation for IVDs in many countries is less than optimal, both for pre-market assessment and post-market surveillance. Therefore, WHO independently reviews the quality, safety and performance of IVDs that are available in markets in resource-limited settings.

## Pre-market assessment of in vitro diagnostics

WHO conducts the prequalification assessment of IVDs using a standardized procedure to determine if the products meet WHO prequalification requirements. The assessment consists of three key components:

- review of safety, quality and performance of the IVD as presented in a product dossier prepared by the manufacturer;
- desk review of the quality management systems applied during production, followed by a site inspection;
- independent evaluation of performance and operational characteristics of the IVD.

The WHO publication *Overview of the prequalification of in vitro diagnostics assessment* provides further information.

## Post-market surveillance of in vitro diagnostics

Once a product is placed on the market, its quality, safety and performance must be monitored to ensure it continues to meet standards. WHO has established a system for post-market surveillance of IVDs that supplements the obligations of manufacturers, who must also conduct their own post-market evaluation activities. In this context, post-market surveillance consists of:

- proactive post-market surveillance (to identify any problem before use) through in-country lot verification testing, both before and after distribution of test kits to testing sites;
- reactive post-market surveillance (when a problem has been identified during use of the diagnostic) through reporting and evaluation of complaints, including reports of adverse events, and any required actions to correct the problem and prevent recurrence.

For further information, see WHO's *Guidance for post-market surveillance of in vitro diagnostics*:
http://www.who.int/diagnostics_laboratory/postmarket/150210_pms_ivds_guidance.pdf?ua=1.

For the WHO list of prequalified IVD products and related public reports, see
http://www.who.int/diagnostics_laboratory/evaluations/PQ_list/en/.

# References


1. Grant RM, Lama JR, Anderson PL, McMahan V, Liu AY, Vargas L, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. New England Journal of Medicine. 2010;363(27):2587-99.
2. Grant RM, Liegler T, Defechereux P, Kashuba AD, Taylor D, Abdel-Mohsen M, et al. Drug resistance and plasma viral RNA level after ineffective use of oral pre-exposure prophylaxis in women. AIDS. 2015;29(3):331-7.
3. Liegler T, Abdel-Mohsen M, Bentley LG, Atchison R, Schmidt T, Javier J, et al. HIV-1 Drug Resistance in the iPrEx Preexposure Prophylaxis Trial. J Infect Dis. 2014.
4. Grant RM, Liegler T, Defechereux P, Kashuba AD, Taylor D, Abdel-Mohsen M, et al. Drug resistance and plasma viral RNA level after ineffective use of oral pre-exposure prophylaxis in women. AIDS. 2015;29(3):331-7.
5. Lehman DA, Baeten JM, McCoy CO, Weis JF, Peterson D, Mbara G, et al. Risk of drug resistance among persons acquiring HIV within a randomized clinical trial of single- or dual-agent preexposure prophylaxis. J Infect Dis. 2015;211(8):1211-8.
6. Consolidated guidelines on HIV testing services. Geneva: World Health Organization; 2015 (http://apps.who.int/iris/bitstream/10665/179870/1/9789241508926_eng.pdf?ua=1&ua=1).
7. Guidelines on HIV self-testing and partner notification. Geneva: World Health Organization; 2016 (http://apps.who.int/iris/bitstream/10665/251655/1/9789241549868-eng.pdf?ua=1).
8. Marcus JL, Glidden DV, Mayer KH, Liu AY, Buchbinder SP, Amico KR, et al. No evidence of sexual risk compensation in the iPrEx trial of daily oral HIV preexposure prophylaxis. PLoS One. 2013;8(12):e81997.
9. Rosenberg NE, Pilcher CD, Busch MP, Cohen MS. How can we better identify early HIV infections? Curr Opin HIV AIDS. 2015;10(1):61-8.
10. Conway DP, Holt M, McNulty A, Couldwell DL, Smith DE, Davies SC, et al. Multi-centre evaluation of the Determine HIV Combo assay when used for point of care testing in a high risk clinic-based population. PLoS One. 2014;9(4):e94062.
11. Duong YT, Mavengere Y, Patel H, Moore C, Manjengwa J, Sibandze D, et al. Poor performance of the determine HIV-1/2 Ag/Ab combo fourth-generation rapid test for detection of acute infections in a National Household Survey in Swaziland. J Clin Microbiol. 2014;52(10):3743-8.
12. Jones CB, Kuldanek K, Muir D, Phekoo K, Black A, Sacks R, et al. Clinical evaluation of the Determine HIV-1/2 Ag/Ab Combo test. J Infect Dis. 2012;206(12):1947-9; author reply 9-50.
13. Lewis JM, Macpherson P, Adams ER, Ochodo E, Sands A, Taegtmeyer M. Field accuracy of fourth-generation rapid diagnostic tests for acute HIV-1: a systematic review. AIDS. 2015;29(18):2465-71.
14. Rosenberg NE, Kamanga G, Phiri S, Nsona D, Pettifor A, Rutstein SE, et al. Detection of acute HIV infection: a field evaluation of the determine(R) HIV-1/2 Ag/Ab combo test. J Infect Dis. 2012;205(4):528-34.
15. Smallwood M, Vijh R, Nauche B, Lebouche B, Joseph L, Pant Pai N. Evaluation of a Rapid Point of Care Test for Detecting Acute and Established HIV Infection, and Examining the Role of Study Quality on Diagnostic Accuracy: A Bayesian Meta-Analysis. PLoS One. 2016;11(2):e0149592.
16. Guanira JV, Leigler T, Kallas E, Schechter M, Sharma U, Glidden D, et al. Streamlining HIV testing for HIV preexposure prophylaxis. J Clin Microbiol. 2015;53(1):179-83.
17. HIV drug resistance surveillance guidance, 2015 update. Geneva: World Health Organization; 2015 (http://www.who.int/hiv/pub/drugresistance/hiv-drug-resistance-2015-update/en/).
18. WHO manual for HIV drug resistance testing using dried blood spot specimens. Geneva: World Health Organization; 2012 (http://www.who.int/hiv/pub/drugresistance/dried_blood_spots/en/).
19. Knox D, Tan D, Harrigan P, Anderson P. HIV-1 Infection With Multiclass Resistance Despite Preexposure Prophylaxis (PrEP). Presented at: CROI; Boston; 2016.
20. Grossman H et al. Newly Acquired HIV-1 Infection with Multi-Drug Resistant (MDR) HIV-1 in a Patient on TDF/FTC-based PrEP. HIV Research for Prevention (HIVR4P) 2016 conference, Chicago, October 2016, abstract OA03.06LB.
21. Solomon MM, Lama JR, Glidden DV, Mulligan K, McMahan V, Liu AY, et al. Changes in renal function associated with oral emtricitabine/tenofovir disoproxil fumarate use for HIV pre-exposure prophylaxis. AIDS. 2014;28(6):851-9.

22. Mandala J, Nanda K, Wang M, De Baetselier I, Deese J, Lombaard J, et al. Liver and renal safety of tenofovir disoproxil fumarate in combination with emtricitabine among African women in a pre-exposure prophylaxis trial. BMC Pharmacol Toxicol. 2014;15(1):77.

23. Mugwanya KK, Wyatt C, Celum C, Donnell D, Kiarie J, Ronald A, et al. Reversibility of Glomerular Renal Function Decline in HIV-Uninfected Men and Women Discontinuing Emtricitabine-Tenofovir Disoproxil Fumarate Pre-Exposure Prophylaxis. J Acquir Immune Defic Syndr. 2016;71(4):374-80.

24. Peterson L, Taylor D, Roddy R, Belai G, Phillips P, Nanda K, et al. Tenofovir disoproxil fumarate for prevention of HIV infection in women: a phase 2, double-blind, randomized, placebo-controlled trial. PLoS Clin Trials. 2007;2(5):e27.

25. Solomon MM, Schechter M, Liu AY, McManhan VM, Guanira JV, Hance RJ, et al. The Safety of Tenofovir-Emtricitabine for HIV Pre-Exposure Prophylaxis (PrEP) in Individuals With Active Hepatitis B. J Acquir Immune Defic Syndr. 2016;71(3):281-6.

26. Guidelines on hepatitis B and C testing. Geneva: World Health Organization; 2017 http://apps.who.int/iris/bitstream/10665/254621/1/9789241549981-eng.pdf?ua=1.

27. Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection. Geneva: World Health Organization; 2015 http://apps.who.int/iris/bitstream/10665/154590/1/9789241549059_eng.pdf

28. Mugo NR, Heffron R, Donnell D, Wald A, Were EO, Rees H, et al. Increased risk of HIV-1 transmission in pregnancy: a prospective study among African HIV-1-serodiscordant couples. AIDS. 2011;25(15):1887-95.

29. Laboratory diagnosis of sexually transmitted infections, including human immunodeficiency virus. Geneva: World Health Organization; 2013 (http://apps.who.int/iris/bitstream/10665/85343/1/9789241505840_eng.pdf?ua=1).

30. WHO guidelines for the treatment of Treponema pallidum (syphilis). Geneva: World Health Organization; 2016 http://apps.who.int/iris/bitstream/10665/249572/1/9789241549806-eng.pdf?ua=1.

# Notes

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