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Human Immunodeficiency Virus Testing Algorithm in Resource Limiting Settings

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1. Introduction

Testing and counseling for human immunodeficiency virus (HIV) is now recognized as a priority in national HIV programs because it is the gateway to HIV/AIDS prevention, care, treatment, and support interventions. In order to ensure access to HIV testing for large populations and to facilitate access to antiretroviral treatment in the context of the World Health Organization's universal access strategy, radical scaling up of HIV testing and counseling services is being advocated globally.

The use of HIV rapid tests will facilitate this in many settings, particularly in services in which the people most likely to benefit from knowing their HIV status can be reached. These Settings include diagnostic and treatment services for tuberculosis and sexually transmitted infections; services linked to the prevention of mother-to-child transmission of HIV; the management of occupational and non-occupational exposures to HIV; at voluntary counseling and testing (VCT) sites; in remote areas where the creation and maintenance of a laboratory infrastructure is not possible; and where hard-to-reach populations have access to HIV testing (PAHO, 2008).

To date, HIV testing strategies has clear objective for diagnosis, surveillance and transfusion safety. The need for appropriate selection of testing platforms and protocol had also varied from setting to setting. In general, four criteria had underpinned the choice of most appropriate test or combination of tests for any given setting and depend on: General goal for testing, Diagnostic indices of sensitivity and specificity, Prevalence of HIV infection in the general population and Cost of testing (WHO, 2004).

HIV testing is the entry point for both care and prevention. In resource limiting settings, this declaration seems more valid than ever given the increase prevalence and incidence of HIV infection in these settings and current efforts at universal access for care and prevention. The aim of this chapter is to provide trend in HIV testing Algorithm- a combination and sequence of specific testing employed in given strategy for the confirmation of HIV status of an individual or sample.

In the evolving Chapter, we shall transit with set-out for HIV testing algorithms (with appropriate sub-themes) from HIV testing evolution and forms of testing to HIV testing strategies and algorithm platforms.

2. HIV testing

2.1. Evolution of HIV testing

HIV screening and diagnostic tests have been developed, and a variety of testing algorithms have come into use. HIV antibody tests have evolved from first generation HIV-1(clade B) viral lysate-based, indirect antibody enzyme immunoassays (EIAs) to third generation antigen-sandwich immunoassays that use synthetic peptide and recombinant DNA derived antigens that represent the immunodominant epitopes from diverse HIV-1 and HIV-2 strains. These third generation enzyme immunoassays have substantially enhanced sensitivity to divergent viral variants and have shortened the infection-to-seroconversion window period by more than 3 weeks compared with first generation tests. Assays have also been developed that detect and quantitate viral antigen (p24) and nucleic acids (HIV RNA or DNA) in blood, and in body fluids and tissues (Branson, 2010; WHO, 2009a).

These assays have seen increasing application in blood and organ donor screening, as well as in clinical diagnosis, prognosis, and therapeutic monitoring; and clinicians now have access to a broad and potentially confusing array of test options, each with its own advantages and limitations. Developing testing algorithms and interpretive criteria appropriate to a particular group of patients—high-risk adults; blood, plasma and organ donors; recently exposed healthcare workers; paediatric patients, and especially in resource limiting settings—poses a challenge, especially as new tests appear with tantalizing claims of enhanced performance (WHO, 2009a/b).

The laboratory diagnosis of the HIV infection is based on a two-stage strategy: a screening analysis followed by a confirmation analysis. A positive screening analysis must always be supplemented by a confirmation analysis on the same sample. An HIV infection can only be confirmed when the result of the confirmation analysis is positive and consistent results are obtained for two separate samples (PAHO, 2008).

Screening tests provide presumptive identification of specimens that contain antibody to HIV. These enzyme immunosorbent assays (EIAs) or simple/rapid immuno-diagnostics are selected for their high sensitivity of detecting antibodies to HIV. Supplemental or confirmatory tests, such as Western blot (WB), can be used to confirm infection in samples that are

initially reactive on conventional EIAs. Alternatively, repetitive testing incorporating EIAs or rapid tests selected for their specificity may be used to confirm whether specimens found to be reactive for HIV antibodies with a particular screening test are specific to HIV. For practical purposes, resource-poor settings depend heavily on EIA and rapid tests for screening and confirmation (WHO, 2004).

2.2. Enzyme immunsorbent assays

EIAs are the most widely used screening tests because of their suitability for analyzing large numbers of specimens, particularly in blood screening centers. Since 1985, EIAs have progressed considerably from first to fourth generation assays: first generation assays were based on purified HIV whole viral lysates, however, sensitivity and specificity of these assays were poor; second generation assays used HIV-recombinant proteins and/or synthetic peptides, which enabled the production of assays capable of detecting HIV-1 and HIV-2. The assays had improved specificity, although their overall sensitivity was similar to that of first-generation assays. Third-generation assays used the solid phase coated with recombinant antigens and /or peptides and similar recombinant antigens and peptides conjugated to a detection enzyme or hapten that could detect HIV-specific antibodies bound to a solid phase. These assays could detect immunoglobulin M, early antibodies to HIV, in addition to IgG, thus resulting in a reduction of the seroconversion window. Fourth generation assays are very similar to third-generations tests but have the ability to detect simultaneously HIV antibodies and antigens. Typical fourth-generation EIAs incorporate cocktails of HIV-1 group M (HIV-1 p24, HIV-1 gp160), HIV-1 group O, and HIV-2 antigens (HIV-2 env peptide) (WHO, 2009a/b and 2004).

Furthermore, third and fourth-generation assays are able to detect IgM and IgG antibodies to both HIV-1 and HIV-2. These assays may reduce the 2-4 week time period, “window period” of detecting HIV antibodies (WHO, 2009b).

2.3. Rapid/simple assays

Simple, instrument-free assays are also available and are now widely used in Africa. They include agglutination, immunofiltration, and immunochromatographic assays. The appearance of a colored dot or line, or an agglutination pattern indicates a positive result. Most of these tests can be performed in less than 20 minutes, and are therefore called simple/rapid assays. Some simple tests, such as agglutination assays, are less rapid and may require about 30 minutes to 2 hours to be completed. In general, these rapid/simple tests are most suitable for use in settings that have limited facilities and process fewer than 100 samples per day (WHO, 2009b and 2004).

2.3.1. Importance of rapid/simple assays

Although EIA-based serodiagnostic algorithms are highly cost effective, their application in resource-poor settings is limited by several factors. They require well-trained personnel, need a consistent supply of electricity, and maintenance and cost of most equipment. Rapid

assays have high sensitivity and specificity and perform as well as EIAs on specimens from persons seroconverting for non-B HIV-1 subtypes (Koblavi-Dème *et al*, 2001). Rapid enzyme assays circumvent the issue of low rates of return for serologic results associated with EIA-based testing algorithms because results can be delivered on the same day (Puro *et al*, 2004). In addition, their performance has improved considerably, and some do not require reconstitution of reagents or refrigeration; thus, making them very suitable for use in resource limited settings and hard to reach populations (Koblavi-Dème *et al*, 2001). Practical applications for the use of simple/rapid assays are in settings such as Voluntary Counseling and Testing (VCT) and Prevention of Mother to Child Transmission (PMTCT) programs. Studies have shown that using rapid assay testing algorithms result in remarkable increase in the number of HIV-positive women identified as eligible to receive the short-course therapy that reduces mother-to-child transmission of HIV (Sibailly *et al*, 2000).

3. HIV testing strategies and algorithm

3.1. Nature of algorithm/testing strategy

A testing algorithm for serologic diagnosis of HIV-infection is the sequence in which assays are performed to detect HIV antibody in a body fluid. The most common referenced testing algorithm employs an EIA to screen specimens with those found to be positive then confirmed by WB testing. This so-called conventional algorithm has several limitations (PAHO, 2008):

- WB is expensive and requires technical expertise.
- WB often yields indeterminate results with certain types of specimens with uncertain diagnostic significance, e.g., hyperimmunoglobulinemia specimens.
- Both ELISA and WB are time consuming and require a well-equipped laboratory infrastructure.

Various combinations of tests can be used: combinations of HIV EIAs; combinations of rapid tests; or an EIA in conjunction with rapid tests. The choice of strategy and of HIV tests should be determined by the quality of the tests and by the practicality of their implementation, logistics, and the cost-benefit analysis. Figure 1, depicts the WHO/UNAIDS testing strategies which can be adopted in diverse settings

In the WHO/UNAIDS testing strategies I – III, as applicable relative to testing objective (surveillance, blood screening, or diagnosis) or diagnostic indices (sero-prevalence in a given population and the duo of sensitivity and specificity of the test being used). The three HIV testing strategies recommended by WHO and UNAIDS are described below (Figure 1) (WHO, 2009a; UNAID/WHO, 1998).

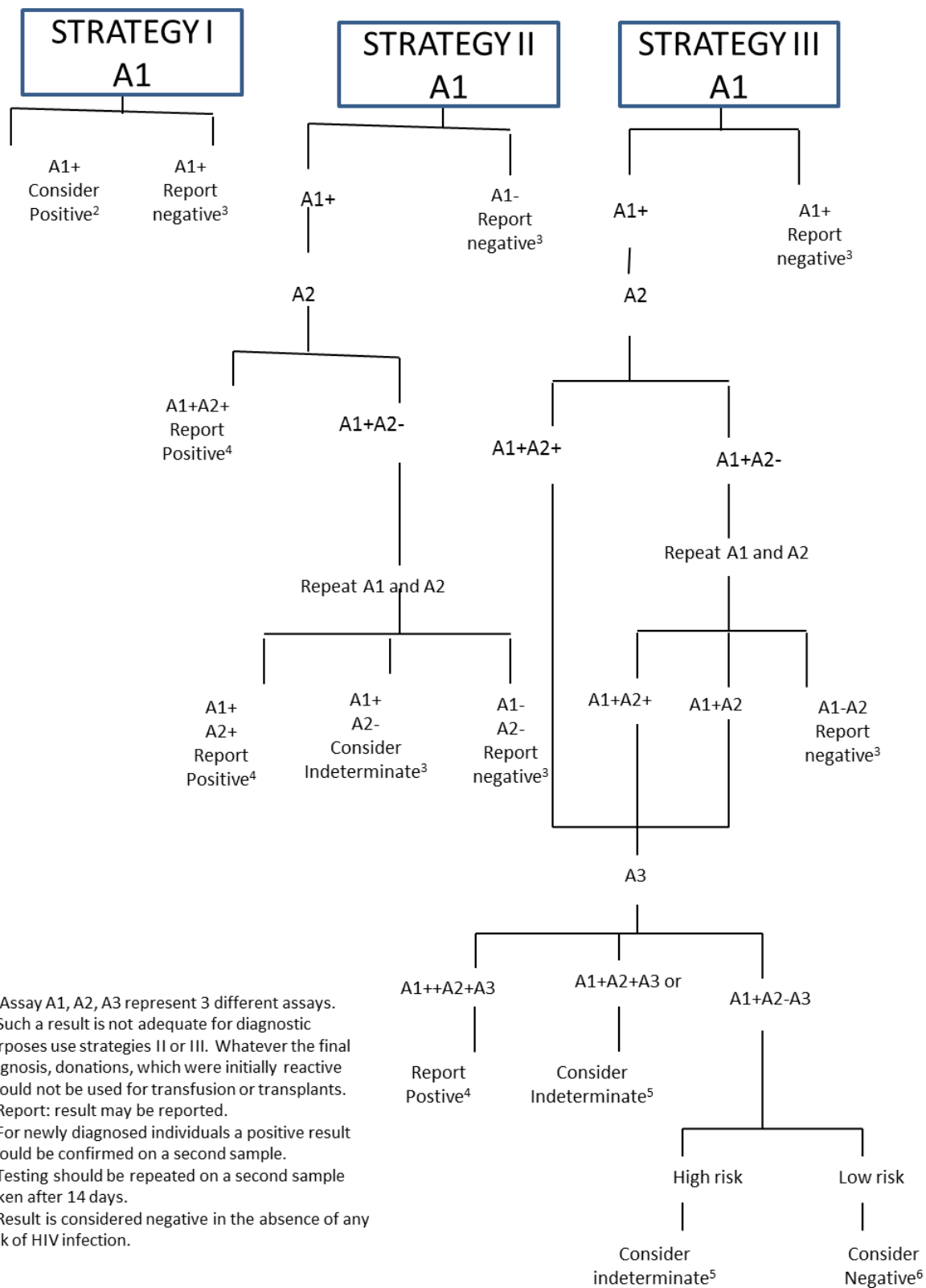


Figure 1. Schematic Representation of the WHO/UNAIDS HIV Testing Strategy(Adapted from WHO, 2009a/b and UN-AID/WHO,1998)

Strategy I:

- Requires one test.
- For use in diagnostic testing in populations with an HIV prevalence $>30\%$ among persons with clinical signs or symptoms of HIV infection.
- For use in blood screening, for all prevalence rates.
- For use in surveillance testing in populations with an HIV prevalence $>10\%$ (example: unlinked anonymous testing for surveillance among pregnant women at antenatal clinics). No results are provided.

Strategy II:

- Requires up to two tests.
- For use in diagnostic testing in populations with an HIV prevalence $\leq 30\%$ among persons with clinical signs or symptoms of HIV infection or $>10\%$ among asymptomatic persons.
- For use in surveillance testing in populations with an HIV prevalence $\leq 10\%$ (example: unlinked anonymous testing for surveillance among patients at antenatal clinics or sexually transmitted infection clinics). No results are provided.

Strategy III:

- Requires up to three tests.
- For use in diagnostic testing in populations with an HIV prevalence $\leq 10\%$ among asymptomatic persons.

Sensitivity and specificity are two important factors that determine a test's accuracy in distinguishing between HIV-infected and uninfected individuals. It is crucial that the HIV tests used in the algorithms all have a sensitivity of at least 99% and a specificity of at least 98% (WHO, 2009a and 1997). There are commercially available HIV EIAs and HIV rapid tests that meet these criteria. When selecting HIV tests to be used in combination, it is important to select tests that do not share the same false positive and same false negative results. This information can be obtained from comparative evaluation studies of HIV test kits, such as those published in international scientific publications and in WHO reports (WHO, 2009a/b). It is recommended that such comparative evaluations of a select number of HIV test kits be conducted at the national and/or regional level prior to the establishment of the national HIV test algorithms. These principles apply to both conventional HIV EIA and HIV rapid tests. The national reference laboratory should validate a select number of test kits for use in the national HIV testing algorithms.

Specific implementation requirements must be considered when selecting tests kits and algorithms. For example, will testing be performed in a laboratory setting, or in a VCT or clinical setting without extensive laboratory facilities? In settings without extensive laboratory facilities or where clients do not return for follow-up visits, algorithms using only rapid tests are preferred. In situations in which patients return at regular intervals (e.g., TB clinics) or in

prenatal clinics where blood specimens are taken for other testing purposes, the set-up may allow for HIV EIA-based algorithms or algorithms combining EIA and rapid tests (Owusu-Ofori et al, 2005; Routet et al, 2004).

Another factor determining the most cost-efficient approach is the volume of specimens to be processed daily or weekly. An EIA test is half the price of a rapid test, so if a particular setting processes 40 specimens a day and the laboratory has the required equipment, it is more cost effective to use EIAs than rapid tests. It is important that the HIV tests and algorithms be chosen carefully and with the aim of optimal integration into the existing health care facilities, minimizing the potential to disrupt their operations or unnecessarily overburden staff.

There are many strategies for HIV testing (Parekh *et al*, 2010; WHO, 2009a/b; Paul *et al*, 2004). WHO, CDC, and the Association of Public Health Laboratories have jointly developed one of the most useful references for HIV testing algorithms. These strategies can be divided into two approaches: serial (or sequential) testing and parallel testing.

3.2. Algorithm platforms

3.2.1. Serial/sequential testing strategy

In a Serial or sequential testing strategy, samples are initially tested with only one, highly sensitive assay. Samples that are reactive in the first assay are then re-tested using a second, highly specific assay. A third test may be performed, depending on the result of the second assay and the objective of the testing. Both the selection of and the order in which the assays are used are of the utmost importance for the final outcome of the tests. If test combinations are not carefully selected, individuals may be incorrectly diagnosed. WHO recommends sequential testing (Figure 2) in most settings because it is more economical, as the second test is required only when the initial test result is positive (Gershy-Damet *et al*, 2010; WHO, 2009a/b; Ferreira *et al*, 2005).

3.2.2. Parallel testing strategy

In a parallel testing strategy (Figure 3), samples are tested using two different assays simultaneously. This approach is rather expensive, as it virtually doubles the cost of testing in low-prevalence settings by requiring two tests at the outset. As with sequential testing, a third test may be performed preferably at the secondary level, where laboratory facilities and experienced staff are available, depending on the result of the assays and the objective of the testing (WHO, 2009a/b).

Therefore, the parallel testing strategy is recommended only in situations in which it can add value. Prenatal clinics provide one such example: A woman's first visit to the clinic may be to deliver her child, thus requiring a rapid decision whether an intervention to prevent mother-to-child transmission of HIV is needed. Other emergency situations, such as work accidents, sexual violence, and discordant couples also would benefit from this strategy. In these cases, two rapid tests using whole-blood finger-stick specimens in parallel will pro-

vide the answer in just 10–15 minutes. HIV rapid tests using wholeblood finger-stick specimens have great potential in situations where results need to be known quickly, or where taking a conventional venous sample is difficult (Gersh-Damet *et al*, 2010; WHO, 2009a/b; Ferreira *et al*, 2005).

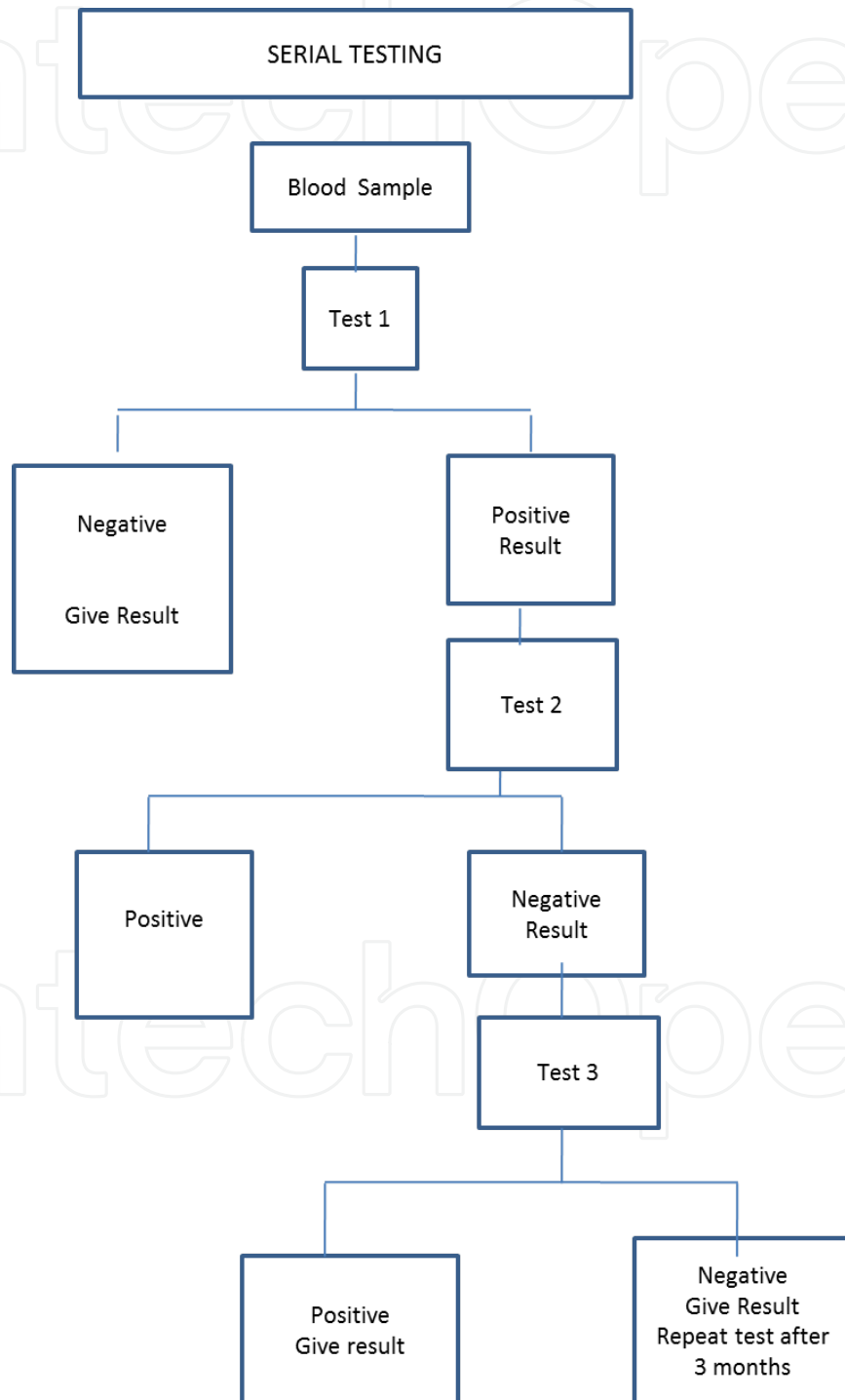


Figure 2. Serial/ Sequential Testing Algorithm (Adapted from WHO, 2009a/b)

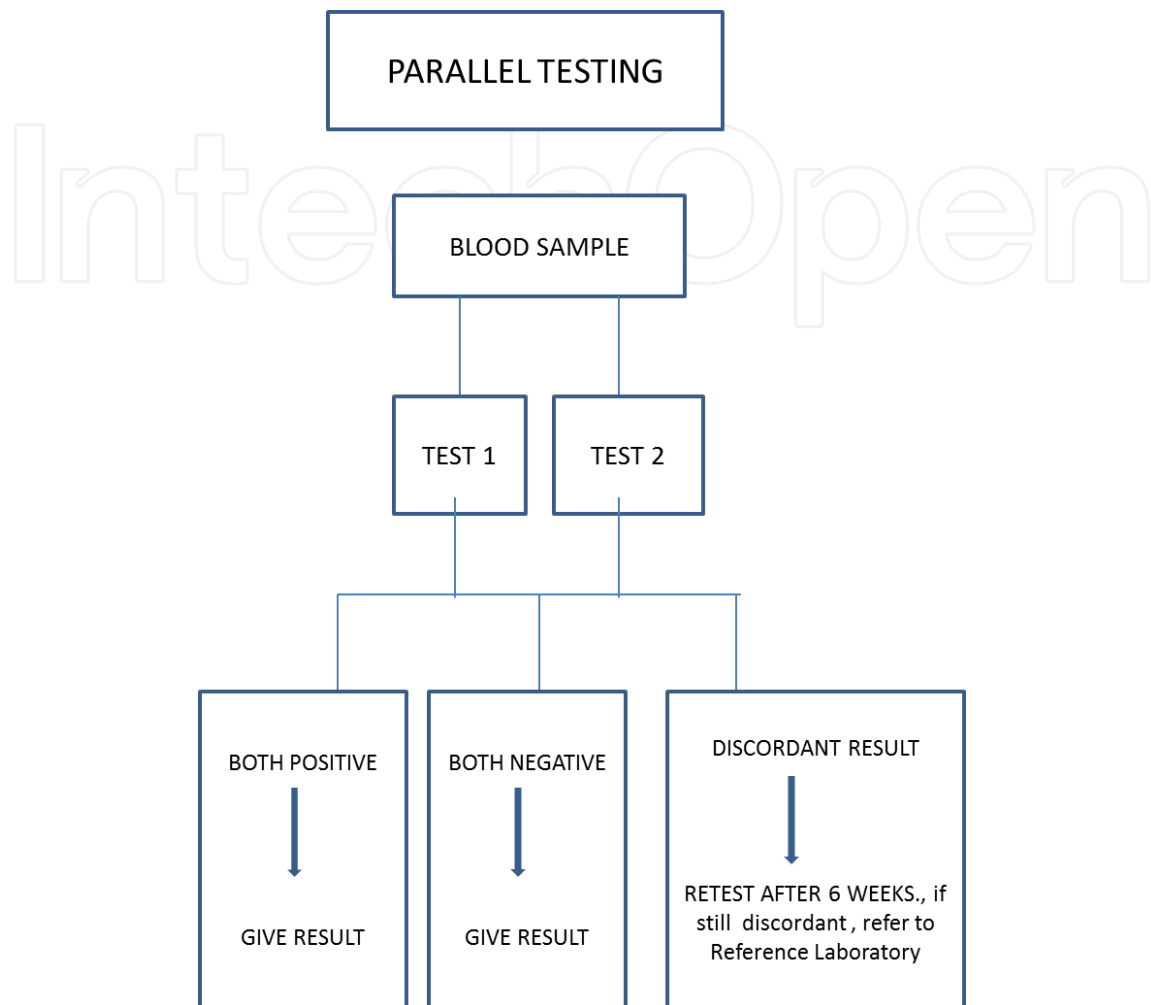


Figure 3. Parallel Testing Algorithm (Adapted from WHO, 2009a/b)

4. Conclusion

HIV testing is the essential entry point for both treatment and prevention. As in all societies, especially in Africa, high degree of genetic diversity exist. One implication for this is the need for each country to have an in-house evaluation of its country –specific testing strategy. The selection of a national algorithm is the responsibility of the country’s Ministry of Health. The choice of sequential or parallel testing should be made after a thorough analysis of the scientific evidence, logistics, test performance requirements, and cost/affordability of the various algorithms.

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