Module 4

HIV Testing Strategies and Algorithms

Purpose	To provide the participants with a basic understanding of how HIV rapid tests are selected for the country's algorithm and how HIV status is determined following the algorithm.
Pre-requisite Modules	Module 1: Overview of HIV Infection
	Module 3: Overview of HIV Testing Technologies
Learning Objectives	At the end of this module, you will be able to:

- Discuss the process for developing a national testing algorithm
- Explain how sensitivity, specificity, positive/negative predictive value relate to development of an HIV rapid testing algorithm
- Explain the HIV rapid testing algorithm approved in your country
- Determine HIV status following a particular algorithm

Content Outline	Testing strategies and algorithms
	Developing national testing algorithm
	Measuring performance of HIV rapid tests
	Interpreting HIV status
Handouts	Exercise #1: <u>Interpreting HIV Status Using Testing Algorithm</u>
	Exercise #2: <u>Interpreting HIV Status Using Testing Algorithm</u>
Notes on Customization	Specify specific tests used in your country algorithm.
	Delete examples of HIV rapid tests not used in your country's algorithm and replace with in-country examples.
	Replace testing algorithm diagram with country-specific algorithm.

Strategies and Algorithms

Strategies are defined as the testing approach used to meet a specific need, such as for blood safety, surveillance, and diagnosis. For a given strategy, multiple algorithms may be used depending on the needs of testing settings.

Algorithms are defined as the combination and sequence of specific tests used in a given strategy. The number of algorithms should be limited.

HIV Testing Strategies

Parallel and serial testing can be part of any testing strategy.

Parallel testing means samples are tested simultaneously by two different tests.

Serial testing means samples tested by a first test. The results of the first test determine whether additional testing is required.

Testing Algorithms Should be Developed at National Level

Before any test is adopted in country for use, a series of key steps must be taken. These steps include:

- Identifying appropriate tests
- Developing an algorithm
- Building consensus
- Developing policy
- Bringing into national scale
- Reviewing testing algorithms annually

Because multiple tests are marketed and available in-country, each country must identify the appropriate tests for use within given environment. A standardized approach to developing an algorithm must be taken. This involved building consensus and developing policy before a test is brought to national scale.

After testing algorithms are adopted and implemented nationally, these algorithms must be reviewed annually to determine if test are performing as expected, and to determine if any changes need to be made to the algorithm.

Timeline for Developing National Testing Algorithm

A number of activities must be accomplished before a test is fully implemented. Tests undergo a series of evaluations before they are adopted for use country-wide. The timeline from beginning of evaluation activities to the time when tests are fully implemented is approximately 9 months to 1 year.

Timeline for Developing National Testing Algorithm

Phases	Key Activities	Timelines
Project Development	Determine Capacity Literature Review Situation Analysis Needs Analysis	1 to 3 months
Test Evaluation / Algorithm (Phase I)	Proposal Ethical Review Procurement Establish Panels Evaluation Analysis of Data Algorithm Decision Publish Findings	3 to 6 months
Development (Phase II)	Site Selection Training of Staff On Site Evaluation Algorithm Approval	6 months
Monitoring (Phase III)	Pilot Manuals Monitor Performance Publish Algorithm	> 3 months

The test evaluation process includes three phases:

Phase I Samples with known HIV results are tested at the laboratory using a number of different kits. The results of the rapid tests are compared with the original laboratory results. Ones that worked the best are then evaluated in phase II.

Phase II Clients are tested at a rapid testing site by the tests under evaluation, and the same sample is tested at the laboratory using laboratory tests. The results are compared, and the rapid tests that worked the best will be used in phase III.

Phase III Rapid tests that have been approved by the MOH are used at rapid testing sites.

Advantages of National Testing Strategies and Algorithms

Nationally adopted testing strategies and algorithms facilitates:

- Country-level standardization of tests used in country - supporting a limited number of tests is more feasible and practical than many different tests.

- Procurement and supply management - using standardized tests allows for bulk procurement which facilitates controlling costs.

- Training –Implementation of a national training program is eased when test sites follow the same testing algorithm. This facilitates pre-planning of workshop, as well as assuring staff who move from one test site to another will not require total re-training.

- Quality Assurance – national oversight of quality of testing operations is easier when test sites use the same tests and have similar operations.

Key Factors in Determining a Country's Algorithm

A number of factors contribute to the selection of specific tests in a country's algorithm. These factors include: test performance in country, test availability in country, program needs, ease of use, type of specimen, cost, and potential need to differentiate between HIV 1 & HIV 2.

Evaluating Test Performance: Basic Terms

One of the factors that determine a country's algorithm is the performance the tests. This performance is based on how close a test under consideration agrees 100% with the result of another test, i.e., reference method or "gold standard", also referred to as the true result or actual HIV status.

Sensitivity (Se) and *Specificity* (Sp) relate to the performance of the test capacity. Sensitivity of a test is its capacity to correctly identify people who are infected with HIV

Positive and negative predictive value (PPV & NPV) relate to the probability of the individual being infected or not infected when the test yields a positive or negative result

Calculating Sensitivity, Specificity, PPV & NPV

Total Result	Actual HIV Status (Gold Standard)		
	HIV Infected	HIV Uninfected	Total
Positive	A	B	**A+B**
Negative	C	D	**C+D**
Total	**A+C**	**B+D**	

Sensitivity = A ÷ (A+C)   Positive Predictive Value = A ÷ (A+B)

Specificity = D ÷ (B+D)   Negative Predictive Value = D ÷ (C+D)

This table above provides the formulas for calculating Se, Sp, PPV, & NPV.

A = true positives; that is the test under evaluation yields a positive result AND the "gold standard (the reference test method used to compare all other test results to)" yielded a positive result.

C = false negatives; that is the test under evaluation yielded a negative result, while the "gold standard" or true value was positive.

A+C = all people who are truly infected with HIV

B = false positives; that is the test under evaluation yields a positive result, while the "gold standard" or true value was negative

D = true negatives; that is the test under evaluation yields a negative result AND the "gold standard" or true value yielded a negative result

B+D = all people who are truly NOT infected with HIV

Calculating Sensitivity, Specificity, PPV & NPV (Cont'd)

Total Result	Actual HIV Status (Gold Standard)		
	HIV Infected	HIV Uninfected	Total
Positive	A (370)	B (2)	**A+B (372)**
Negative	C (4)	D (624)	**C+D (628)**
Total	**A+C (374)**	**B+D (626)**	1000

Sensitivity = A ÷ (A+C) = 370 ÷ 374 = 98.9%

Specificity = D ÷ (B+D) = 624 ÷ 626 = 99.7%

PPV = A ÷ (A+B) = 370 ÷ 372 = 99.5%

NPV = D ÷ (C+D) = 624 ÷ 628 = 99.4%

The table above illustrates the calculation of Se, Sp, PPV & NPV.

Evaluation of a rapid test on a panel of specimens that have been tested by the gold standard to determine actual HIV status is shown to contain HIV antibodies to 374 samples and no HIV antibodies to 626 samples.

Of the 374 serum samples that were antibody positive, the rapid test classified 370 of the samples as positive.

Of the 626 samples that were HIV antibody negative by the gold standard, 624 were classified by the rapid tests as not containing HIV antibodies.

The results for Se, Sp, PPV, and NPV ranges from 98.9% to 99.7 %. This means:

- The test performance of the HIV rapid test under evaluation is nearly as good as the results of the "gold standard" or true value.
- The HIV test will yield highly accurate results

But, while these results indicated very good performance, you must also keep in mind that the performance is influenced by the makeup of the population.

HIV Rapid Test Performance

As illustrated in the example above, no test is 100% sensitive or 100 % specific when compared to the "gold standard". In other words, no test will yield exactly the same result of the "gold standard" test.

How Prevalence Affects PPV & NPV

If you know the sensitivity and specificity of the kit and the prevalence of HIV in the population, you can theoretically calculate the predictive value of the performed test. The formula for calculating the predictive values of a test is as follows:

$$PPV = \frac{(Prevalence)\,(Se)}{(Prevalence)\,(Se) + (1 - Prevalence)\,(1 - Sp)}$$

$$NPV = \frac{(1 - Prevalence)\,(Sp)}{(1 - Prevalence)\,(Sp + (Prevalence)\,(1 - Se)}$$

PPV for 10 % prevalence population:

$$= \frac{(10/100)\,(98.9/100)}{(10/100)\,(98.9/100) + (1 - 10/100)\,(1 - 99.7/100)} = 97.3\%$$

PPV for 1% prevalence population:

$$= \frac{(1/100)\,(98.9/100)}{(1/100)\,(98.9/100) + (1 - 1/100)\,(1 - 99.7/100)} = 76.9\%$$

In general, the higher the prevalence, the higher the PPV. In this example there is a 97.3 % probability that if a person tests positive then this individual is indeed infected with HIV.

Conversely, the lower the prevalence, the lower the PPV. In the example above, there is a 76.9% probability that if a person tests negative, then this individual is indeed not infected with HIV.

Testing Algorithm Describes the Sequence of Tests to be Performed

Testing Algorithm describes the sequence of tests to be performed. An HIV Positive Status should be based upon the outcome of 2 or more tests.

When two test results disagree (one is reactive, the other non-reactive), the finding is called "*discordant.*" In this case, a third test must be performed.

Always follow the sequence of the tests in the algorithm.

Ideal Algorithm

The ideal algorithm used in one in which tests are highly sensitive and highly specific.

Both tests should not share the same false negatives and false positives, and a third test is performed, if needed.

Parallel Testing Algorithm

In a parallel testing algorithm, two different tests are performed at the same time. If a 3rd test or tiebreaker is required, this test is different than test 1 or test 2.
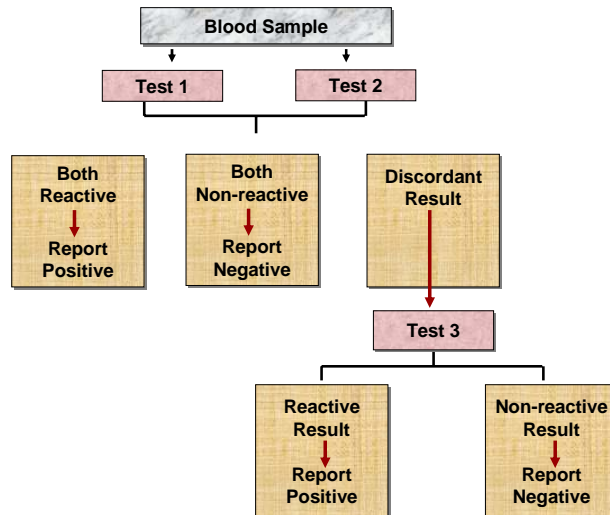
- When both tests are reactive, the final HIV result is positive.

- When both tests are non-reactive, then the final HIV result is negative.

- If one test is reactive and the other is non-reactive, then a third test known as a tiebreaker is performed.

- The tie-breaker determines the final result – if the tiebreaker is reactive, then the final HIV result is positive; if the tiebreaker is non-reactive, then the final HIV result is negative. The test used as the tiebreaker is a different test than test 1 or 2.

Exercises

Interpreting HIV Status Using Testing Algorithm

At the end of this module, you will find two exercise sheets. Read the instructions and write your answers in the space provided.

Possible HIV Test Outcomes: Parallel Testing Algorithm

There are a variety of combinations of outcomes when following a parallel testing algorithm.

Parallel Testing Algorithm

TEST 1	TEST 2	TEST 3	HIV Status
Non-reactive	Non-reactive		Negative
Reactive	Reactive		Positive
Non-reactive	Reactive	Non-reactive	Negative
Reactive	Non-reactive	Non-reactive	Negative
Non-reactive	Reactive	Reactive	Positive
Reactive	Non-reactive	Reactive	Positive

Key message

- Before any test is adopted in country for use, a series of key steps must be taken to evaluate the tests before they are fully adopted for use country-wide.

- The ideal algorithm used in one in which tests are highly sensitive and highly specific.

- No test is 100% sensitive or 100 % specific when compared to the "gold standard".

- Always follow the sequence of the tests in the algorithm.

Module Review

Find out how much you have learned by answering these questions.

Explain the importance of a tests: ' Se, Sp, PPV, NPV

- Se _____

- Sp _____

- PPV _____

- NPV _____

Explain the testing algorithm adopted by MOH. What rapid tests are used and in what order?
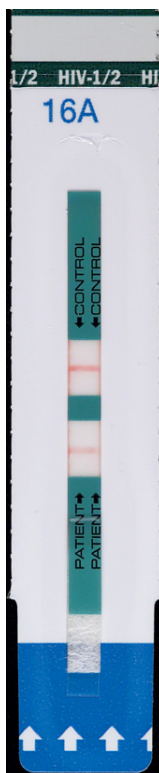
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Exercise #1: Interpreting HIV Status Using Parallel Algorithm

A client has come in for an HIV Rapid Test. Following the parallel algorithm, you conducted three tests. The results are shown below.
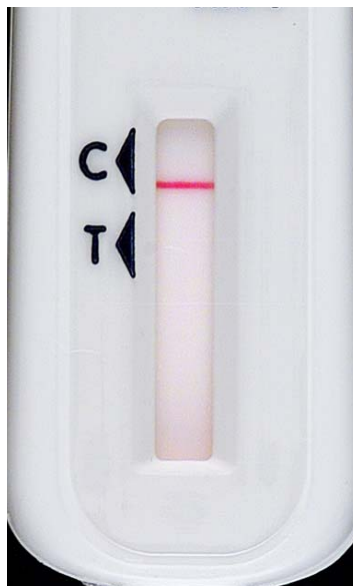
- Interpret the HIV Rapid Test results for Test #1, Test #2, and Test #3
- Decide HIV Status

Test #1   **Test #2**   **Test #3**

Result: _____   Result: _____   Result: _____
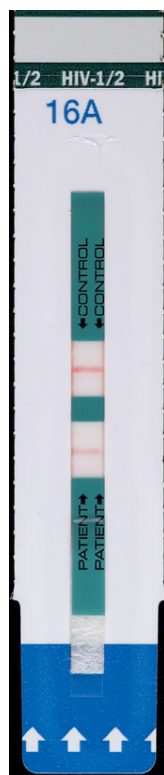

Final HIV Status_____

Exercise #2: Interpreting HIV Status Using Serial Algorithm

A client came in for an HIV Rapid Test. Following the serial algorithm, you conducted two tests. The results are shown below.

- Interpret the HIV Rapid Test results for Test #1 and Test #2.
- Decide if a third test is needed. If not, what is the client's HIV status?

Test #1

Test #2

Result: _____   **Result: _____**

Is a third test needed? ___Yes   ___No

If no, what is the HIV Status? _____