

# Visceral Leishmaniasis Rapid Diagnostic Tests



Special Programme for Research & Training  
in Tropical Diseases (TDR) sponsored by  
UNICEF/UNDP/World Bank/WHO



# The Use of Visceral Leishmaniasis Rapid Diagnostic Tests



**World Health  
Organization**



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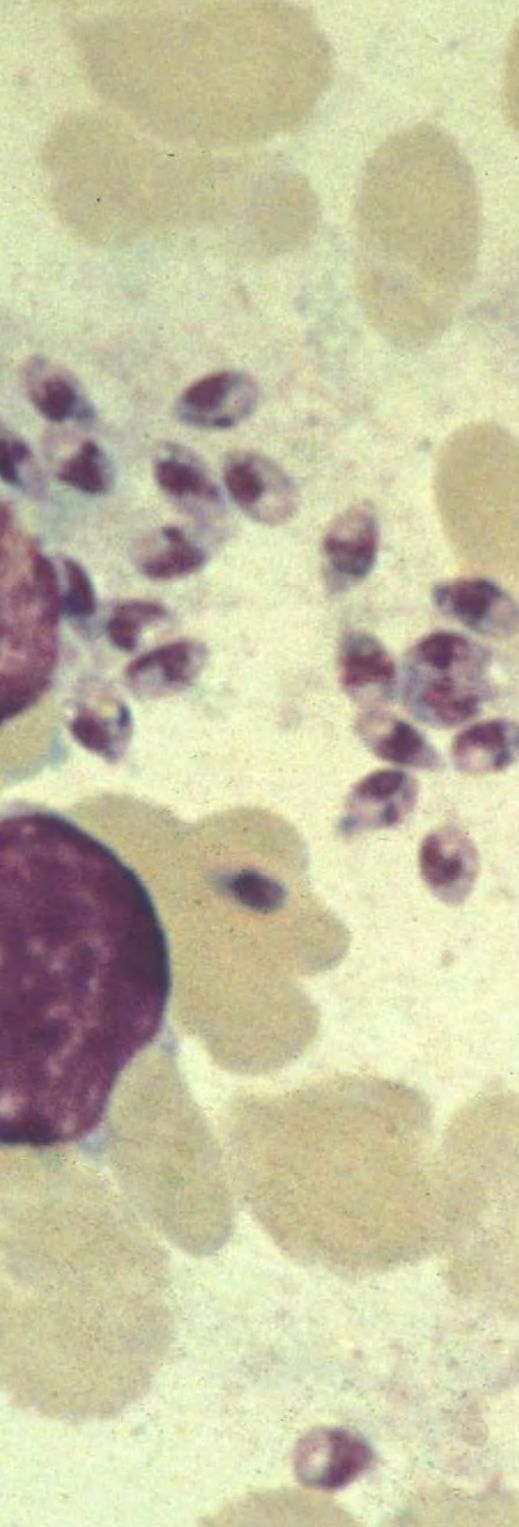
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## Introduction

A reliable diagnosis is critical in the management of visceral leishmaniasis (VL). Early case detection and treatment improve prognosis for the patient and can reduce transmission, especially in *Leishmania donovani* areas as there is no animal reservoir.

Rapid diagnostic tests (RDTs) for VL are amongst the most important innovations in the control of VL. These tests allow for patients to be diagnosed closer to their homes. The demand for RDTs was such that counterfeit products began circulating in the Indian subcontinent soon after they were adopted in the VL elimination initiative.

This user guide provides general information on RDTs for VL but is not a manual for patient management. We hope it will facilitate proper use of RDTs and improve the quality of VL care. Though it was developed with the Indian subcontinent in mind, this guide can, with some minor local adaptations, be useful in other settings.

# I. What is visceral leishmaniasis (VL) and why is it important?

Visceral leishmaniasis (VL), also known as kala-azar, is an infection transmitted by sand flies and caused by parasites of the genus *Leishmania*. An estimated 500 000 people acquire this disease each year, 90% of whom live in India, Nepal, Bangladesh, Sudan and Brazil. VL is predominantly a disease of the poor living in remote communities with few health care facilities.

The disease is characterized by fever, weight loss, enlargement of the liver, spleen and lymph nodes and low blood cell counts, all of which are non-specific signs and not all of which are present in each individual case. A *Leishmania* infection does not always lead to clinical disease as asymptomatic infections outnumber the clinical cases.

Early and accurate laboratory diagnosis is essential before initiating treatment for several reasons:

- i) the clinical features of VL resemble those of several other diseases including malaria or other conditions (infectious and not-infectious).
- ii) effective drugs are available but they need to be administered for a minimum 3 weeks and are potentially toxic and expensive.
- iii) VL is usually fatal if not treated in a timely manner.
- iv) untreated cases are reservoirs of infection and therefore put the community at risk of ongoing transmission.





## II. How is VL diagnosed?

Definitive diagnosis of VL is by culture or microscopic confirmation of the amastigote form of the parasite in tissue aspirates from spleen, bone marrow or lymph nodes (Fig 1) These oval forms are known as Leishman Donovan (LD) bodies. The sensitivity and specificity of splenic aspirate smears is excellent, but this procedure carries a risk of fatal internal bleeding (~1/1000 procedures). Bone marrow and lymph node aspiration are safer but less sensitive. These techniques require technical expertise which is often not available in field settings.

**Figure 1.** Comparative sensitivity of microscopy using different clinical specimens



**Lymph node**  
• Low sensitivity



**Bone marrow**  
• Sensitivity: 70–80%  
• Painful  
• Sterilization needed

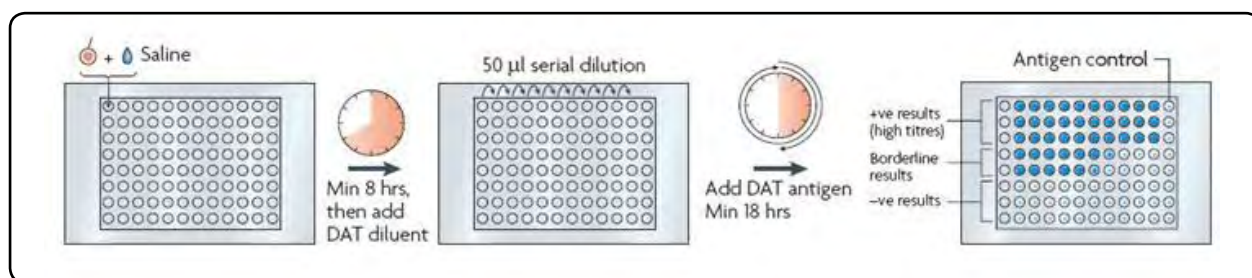


**Spleen**  
• Reference standard  
• Sensitivity ~95%  
• Expertise required  
• Risk of major bleeding

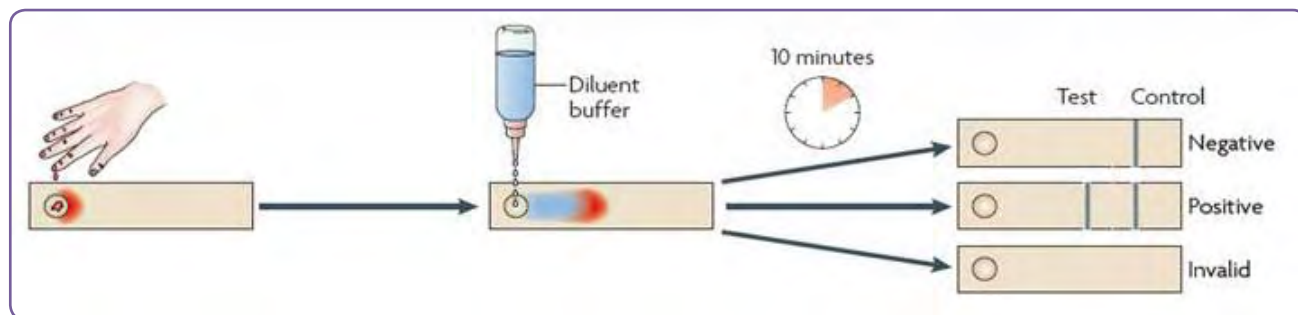
Antibody detection tests, such as the enzyme linked immunosorbent assay (ELISA) and the immunofluorescent antibody test (IFAT) have been developed for the diagnosis of VL. Their utility in the field is limited because they require a well-equipped laboratory and skilled personnel.

However, two serological tests have been specifically developed for field use and they have been extensively evaluated in both the laboratory and the field settings: the direct agglutination test (DAT) using freeze dried antigen (Fig 2), and the rK39 immunochromatographic test (generally referred to as the 'rK39 RDT') (Fig 3).

**Figure 2.** Direct Agglutination Test (DAT)



**Figure 3.** rK39 RDT



The DAT and rK39 RDT are both based on the detection of antibodies in blood. Due to the persistence of antibodies over long periods, they cannot be used to differentiate between current and past infection. To overcome this limitation, tests are being developed that can detect VL antigen in urine and blood but their performance so far has been suboptimal.

### III. What is a VL Rapid Diagnostic Test (RDT)?

A RDT is a simple test that can be used at all levels of the health care services, it does not require highly skilled laboratory staff and results can be read easily and within 30 minutes. Rapid test results expedite the initiation of treatment.

Field conditions require an RDT to be affordable and to possess high sensitivity, specificity, and reliability. Quality of diagnostics has to be assured along the supply chain. The performance of the RDT in the health services should be monitored on a regular basis through a process called "External Quality Assurance (EQA).

A recent multi-country evaluation sponsored by WHO/TDR showed adequate diagnostic performance of both DAT and rK39 RDT when compared to the gold standard of demonstrating the parasite in tissue aspirates; however the rK39 RDT was found to be more suitable for field use because it is simpler to perform and gives a result in 20 minutes.

Available in dipstick or cassette format, this RDT detects antibodies against a recombinant antigen (rK39) derived from *L. chagasi*. Antibodies against this antigen are present in serum/blood of kala-azar patients and they will bind to the recombinant antigen that is bound to the test strip yielding a visual positive test result. A rK39 RDT is currently the best option for VL diagnosis in the Indian subcontinent, and may also prove useful in East-African settings.



## IV. How is the rK39 RDT performed?

The utility of a VL RDT lies in its simplicity. Several brands of RDTs using rK39 antigen are available. Test operators should always read the package insert carefully, and follow manufacturer's instructions. This is especially important when it comes to the type of specimen used: serum or whole blood. Some brands can only be used with serum, while others can be used with whole blood collected by finger prick.

In general, the test procedure is as follows:

1. Remove the test strip from the pouch and place it on a flat surface.
2. Add a specified amount of patient specimen (serum or finger prick blood) to the absorbent pad on the bottom of the strip.
3. Add the specified amount of buffer provided.
4. Read the result after 10–20 minutes (according to manufacturer's instructions).

Some brands require a slightly different procedure, for example:

1. Take a test tube or a U bottom microtitre plate.
2. Add a specified amount of buffer to the tube or well.
3. Add a specified amount of specimen (blood/serum) to the tube or well and mix.
4. Immerse the test strip into buffer/specimen mixture.
5. Read the results after 10–20 minutes (according to manufacturer's instructions).



### Text Box 1

#### Points to consider for the optimization of RDT use

- Develop a clear management plan to deal with positive and negative results.
- Follow biosafety standards for blood and body fluid precautions.
- Ensure proper storage conditions.
- Do not use damaged or expired tests.
- Adhere strictly to the manufacturers instructions.
- Use test kits within one hour of removal from pouch.
- Read the results within time specified by the manufacturers.
- Do not reuse a test.

## How is the test interpreted?

Test reading:

### Positive result

Both control and test lines appear. The sample tested has antibodies against recombinant K39 antigen of *Leishmania*. Even a faint line should be considered positive.

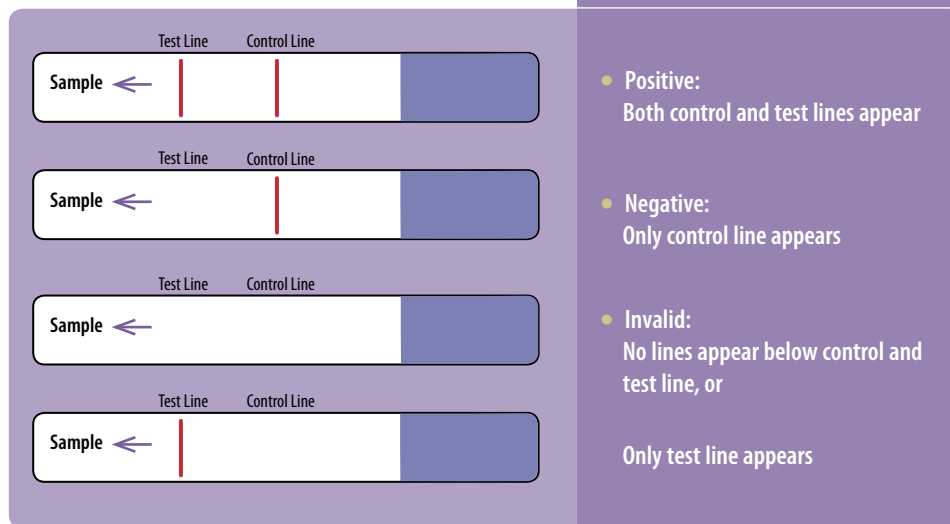
### Negative result

Only the control line appears. There are no antibodies against recombinant K39 antigen of *Leishmania* present in the patient's sample.

### Invalid result

No control line appears. In this situation, retesting a fresh patient sample with a new strip is recommended.

**Figure 4.** How is the rK39 RDT read?



## V. How effective are RDTs in detecting VL?

When used according to the manufacturer's instructions, the rK39 RDT is highly effective in detecting VL. A comprehensive scientific review of published studies estimated its sensitivity to be **93.9% (87.7% – 97.1%) compared to parasitology**.<sup>1</sup> Sensitivity appeared higher and more homogenous in the studies conducted in South-Asia. Its specificity was **90.6% (66.8% – 97.9%)** in studies conducted in the clinical setting, using febrile patients as negative controls.

### Text Box 2

#### Advantages and disadvantages of the rK39 test

Advantages	Disadvantages
<ul style="list-style-type: none"><li>• Simple to perform with minimal training.</li><li>• Does not require a laboratory.</li><li>• Test can be performed using finger prick whole blood, serum or plasma.</li><li>• Kits can be transported and stored at ambient temperature (up to 30°C).</li><li>• Results are available within 10 – 20 minutes.</li></ul>	<ul style="list-style-type: none"><li>• Cannot distinguish between active cases and relapse in previously treated cases. Therefore interpretation must always be in combination with clinical case definition.</li><li>• In patients with advanced HIV infection a negative result cannot rule out the diagnosis of VL.</li></ul>



<sup>1</sup> Microscopic confirmation of *L. donovani* amastigotes in clinical specimens

## VI. When is a RDT useful?

VL commonly affects poor people, living in remote rural areas or suburbs, having limited access to laboratory facilities for the parasitological diagnosis of kala-azar.

The rK39 antibodies remain positive in VL patients for a long time after successful treatment (past VL), and can also be present in healthy persons from endemic areas who were exposed to *Leishmania* but have not developed clinical disease. Therefore, the rK39 RDT cannot be used as a stand-alone, universal diagnostic test. It can only be interpreted with confidence in people who are for the first time clinically suspected of VL.

Country guidelines may contain variations of this VL suspect case definition. They can include more signs such as wasting or enlarged lymph nodes, or be more restrictive, such as “only in persons who have not responded to anti-malarials”.

### Text Box 3

#### To whom the rK39 RDT should be applied

- Persons from endemic areas who have clinical symptoms of VL (VL suspects), i.e. fever for more than 2 weeks and an enlarged spleen. Please refer to your national guidelines for definition of VL suspects.

#### The rK39 RDT is not useful in:

- Persons with past history of VL.
- Patients under current VL treatment or recently treated.
- Patients with fever for less than 2 weeks.

#### The rK39 RDT works less well in:

- HIV-VL co-infected persons or those with other immune disorders. The sensitivity of the test will be lower.



## VII. How useful is the rK39 RDT in the VL control program?

At the World Health Assembly in 2005, the governments of India, Nepal and Bangladesh signed an agreement to eliminate VL from these countries by the year 2015. With no available vaccines, early detection and appropriate treatment is one of the key strategies in VL control. The use of a RDT for early diagnosis of VL cases is therefore crucial for the elimination initiative. Based on the results of recent evaluations of RDTs, the rK39 RDT is currently the most useful diagnostic test to guide VL treatment in the Indian subcontinent.

The rK39 RDT can be used effectively for active case detection at community level. It can be a very helpful diagnostic tool in a control program when applied and interpreted appropriately in patients fitting the case definition.

### Text Box 4

#### **rK39 test can be of great value to the VL control program if:**

- The clinical history of the suspected case is known, and the definition of a suspect case is respected.
- A clear case management plan is developed and followed in the case of positive or negative results.
- Effective drugs are made available to patients diagnosed with VL.
- Training and supervision of the healthcare worker is maintained.
- Quality assurance of test performance and reading is implemented.
- Care is taken for proper storage of kits
- Selected test kits are affordable and excellent in terms of performance.



## VIII. What do RDT results mean and when do you treat?

This document does not replace the clinical guidelines for VL management in your country, and you should seek guidance from the appropriate source. **Users of the RDTs should always carefully follow the manufacturer's instructions, and refer to the national guidelines of the VL control program when making treatment decisions.** For example, in areas where malaria is endemic, it is very important to always consider malaria in a febrile person.

In general, a positive rK39 RDT in a person from an endemic area, who for the first time presents with a fever of two weeks or more and an enlarged spleen, indicates that the person is suffering from VL and appropriate drug treatment should be administered.

However, if the person has a past history of VL, a positive RDT will be meaningless, and the case should be referred to a centre where tissue aspiration and microscopy can be performed.

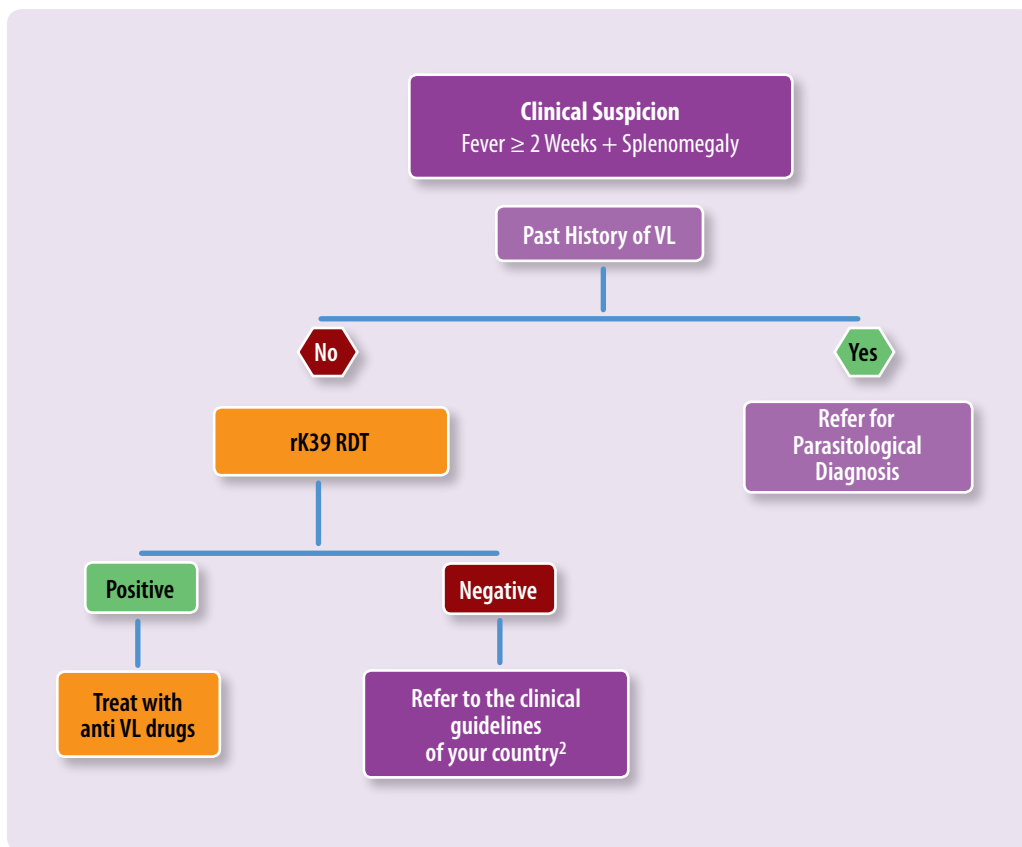
In healthy persons living in the endemic area, a positive rK39 RDT is an incidental finding, suggesting infection only and no treatment is required.

If a person is sick and has a negative rK39 RDT, several courses of actions could reasonably be taken including:

1. Referral to a centre for parasitological diagnosis.
2. Search for an alternative diagnosis, treat and evaluate response.
3. Re-test with the rK39 RDT two to four weeks later.

Remember that a negative RDT may be observed more commonly in VL cases with HIV co-infection.

**Figure 5.** When do you treat?



<sup>2</sup> *The Diagnosis and Treatment of Visceral Leishmaniasis in Ethiopia: Guideline for clinicians and health workers*. 1st Edition. Diseases Prevention & Control Department, Federal Ministry of Health, FDR of Ethiopia, 2006.

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*Guidelines on Use of rK39*. Department of National Vector Borne Disease Control Programme. Delhi, Government of India. <http://www.nvbdcpcp.gov.in/iec.html>

## IX. What should you consider when purchasing RDTs for VL?

RDT selection should be based on the following considerations:

### **Performance:**

A missed diagnosis is dangerous however; over-diagnosis may expose a person to potentially harmful drug effects. Selecting a test with high sensitivity and specificity is important. Performance varies across geographical areas, therefore, try to access regionally relevant information on test performance.

### **Ease of use:**

Kits that require fewer processing steps and use whole blood as a specimen are preferred.

### **Conditions of use:**

Selecting RDTs which are individually packaged in moisture proof pouches is strongly recommended.

### **Storage conditions:**

Most RDT manufacturers specify a storage temperature of  $\leq 30^{\circ}\text{C}$ . If, at the place of test use, the temperature exceeds  $30^{\circ}\text{C}$ , periodic testing is recommended.

### **Shelf life:**

Preference should be given to the kits with longer shelf life. A minimum of 18 months from the time of purchase is recommended.

### **Cost:**

Transportation and training costs required to perform the test should also be considered.



## Tendering and availability of product information

In East-Africa, contrary to the Indian subcontinent, not all brands of rK39 RDTs perform equally well; national authorities should carefully evaluate available data.

The quality of the manufacturing process, long term viability of a company and consistency of production are important considerations when deciding what to purchase. Long term supply of a product by the manufacturer is important to reduce the need for re-training.

### Text Box 5

**During the tendering process, the following information should be obtained from the manufacturers:**

1. Real time temperature stability data on the product and accelerated data on the purchased lot.
2. Evidence of successful operational use or good quality field data on the product.
3. Long term viability of the manufacturer to ensure continuity of supply.
4. Availability of product support.
5. Provision of sample products for assessment and testing ease of use
6. Agreement to replace products that fail to meet agreed quality control procedures.
7. Availability of products in box sizes appropriate to rate of use in the intended area, in order to minimize storage time in poor conditions and limit the need to split boxes.
8. Evidence of good manufacturing practices (e.g. GMP or ISO certification; ISO13485:2003 is a standard specific for medical devices).
9. Clarity of product packaging which enables identification of product type, production lots and expiry date.
10. The place of RDT manufacturing should be disclosed to the purchaser if RDTs are re-labeled.

## X. How do you transport and store RDTs?

During transfer from the manufacturer and transport, the product may be exposed to high temperatures which can affect test performance. Recommended storage temperature of the RDTs is 4-30°C. Expiry dates are set according to these conditions. If storage temperature is higher than recommended, shelf life may be reduced resulting in loss of sensitivity before the expiry date.

Similarly, exposure to high humidity, especially if pouch is kept open for a long time or if the envelope is damaged, can rapidly degrade the test.

Transport of the RDTs should be monitored as follows:

### Shipping from the manufacturer

1. Before shipping, manufacturer should contact consignees with the details; airway bill numbers, airline carrier, flight number, number of container, time and date of departure and expected arrival time. This information should be sent by email and followed up by facsimile.
2. The shipper (air carrier) is notified of temperature storage requirements by the manufacturer in writing and by clear markings on container and related documents. Storage of the shipment close to walls of some aircrafts may result in freezing.
3. Shipment should be initiated only after confirmation of receipt of shipping notification by the consignee.
4. Arrangements should be made by the consignee for customs clearance and immediate collection of the material at the receiving airport. Shipments are then moved immediately to moderate temperature storage (less than 30°C, if possible). Care should be taken not to leave the materials on airport tarmacs, in customs sheds or in vehicles.



## Ground transportation

5. Ground transport during any stage of delivery is carried out without delay and with attention to ambient temperature while the vehicle is moving or parked. Avoid leaving RDTs in vehicles parked in the sun.

## Storage

6. Storage at central and final field facilities should be according to manufacturer specifications, preferably below 30°C.
7. Maximize the time of storage in centralized, controlled conditions. Uncontrolled storage in peripheral areas should be minimized. Smaller box sizes may help.
8. Select a cool peripheral storage location; thatch roofing may be cooler than iron, maximize shade, consider evaporative cooling cabinets.

In a tropical climate and at the place of end use, transport and storage above 30°C is sometimes unavoidable. Monitoring the sensitivity of RDTs at appropriate intervals is essential.

## XI. How do you evaluate the quality of your testing program?

The quality of the testing program depends on the quality of the test kits and the proficiency of the end users whom perform them. A number of steps should be considered in the evaluation of the testing program.

### **Quality control on validity of test kits**

Test sensitivity should be checked by the quality control panel of a central laboratory upon receipt from the manufacturer, and periodically throughout the recommended product shelf life. In case of test quality depreciation, users at peripheral health services should be alerted. When distributing tests to the site of use, centers should follow a system, informing the peripheral staff to collect the kits at a specified date and time.

### **Proficiency of users**

Adequate training and supervision of end users of RDTs should be integrated as far as possible into existing health care worker training and quality assurance schemes.

A concise, clear Standard Operating Procedure (SOP) should be prepared in the local language(s) for health workers trained to perform the test. Instructions for processing and interpretation as well as the practice of standard precautions while obtaining and handling blood should be clear.

In addition, health care workers using the tests should be trained, assessed and systematically monitored on test processing and interpretation. They should also maintain a log book where batch number, date of manufacture and kit expiry date are clearly recorded.



## Further readings

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