REPUBLIC OF KENYA
MINISTRY OF HEALTH

PREVENTION, DIAGNOSIS AND TREATMENT OF VISCERAL LEISHMANIASIS (KALA-AZAR) IN KENYA

NATIONAL GUIDELINES FOR HEALTH WORKERS

Sponsored by:

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DNDi
Drugs for Neglected Diseases *initiative*

MEDECINS SANS FRONTIERES

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FOREWORD

These guidelines on prevention, diagnosis and treatment of visceral leishmaniasis (kala-azar) are indeed a milestone for control of the disease in Kenya. Their publication accords with the recommendation of the WHO consultative bi-regional meeting on the status of implementing visceral leishmaniasis control strategies held on 9–11 March 2015 in Addis Ababa, Ethiopia.

The diagnosis and treatment of visceral leishmaniasis face some important challenges. For a long time case diagnosis has relied on splenic/bone marrow aspirates, which can be carried out by only skilled health workers. The development of rapid diagnostic test kits for use by health workers with minimal training will help in case diagnosis even at the lowest level of health facilities.

Treatment of kala-azar has been by use of pentavalent antimonials, mainly sodium stibogluconate (Pentostam) and meglumine antimoniate (Glucantime). These medicines can only be administered through injection. They are toxic, with many side-effects and the treatment is given over a period of 30 days. To overcome some of these challenges, WHO recommends the use of new rapid diagnostic test kits that are easy to use and combination therapy that has lower doses, shorter treatment and hospitalization (17 days). The Ministry of Health now recommends the use of combination therapy (sodium stibogluconate plus paromomycin) as the first-line regimen for treatment of visceral leishmaniasis.

Prevention and control of vectors are an essential component of leishmaniasis control. To strengthen prevention of the disease, these guidelines have included various measures that can be used by health workers and community members to prevent and control the disease.

The Ministry of Health will continue to improve the conditions of patients suffering from kala-azar through adoption of new diagnostic techniques and improved treatment regimens.

The revised guidelines will play an important role in guiding health workers and other health development partners in prevention, diagnosis and treatment of kala-azar in endemic areas.

Dr. Kioko Jackson K., OGW

Director of Medical Services

PREFACE

Treatment of visceral leishmaniasis (kala-azar) patients in Kenya has been by use of pentavalent antimonial drugs, mainly sodium stibogluconate (Pentostam) and meglumine antimoniate (Glucantime). These medicines are administered intramuscularly / intravenously at a dose of 20 mg / kg per day for 30 days. Use of antimonials is associated with intense local pain and systemic adverse effects. To overcome some problems associated with these medicines and to prevent the emergence of drug resistance, drug combination therapies have been recommended for use by WHO.

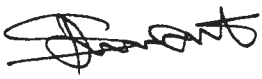
One of the combination therapies that has proven successful in East Africa is sodium stibogluconate and paromomycin). Clinical trials carried out in Kenya at the Kenya Medical Research Institute (KEMRI) and in other countries funded by the Drugs for Neglected Diseases *initiative* (DND*i*) have shown that compared with sodium stibogluconate alone, which requires 30 days treatment, the sodium stibogluconate and paromomycin combination requires only 17 days of treatment and is associated with similar efficacy but fewer complications during treatment.

The review of the old treatment guidelines (2012 edition) was necessitated by the development of the new combination therapy and the need to improve and standardize the diagnosis and treatment procedure in the country.

The guidelines provide information on new rapid diagnostics tests as well as the standard technique of microscopic examination; they also include the use of combination therapy (sodium stibogluconate + paromomycin) for 17 days as a first-line treatment. The second-line drugs such as liposomal amphotericin B (AmBisome) that may be used to treat patients with special needs have also been incorporated. Annexes are included for standard operating procedures.

The incorporation of surveillance and epidemic response and prevention and control of kala-azar will go a long way towards enhancing health workers' knowledge on how to collect data, report and make informed decisions on disease trends. It will also enable them to select the best control measures for vectors as well as to advise community members on which measure is appropriate for their local situation.

The health workers in the Ministry of Health and partners will use the document to enhance prevention, diagnosis and treatment of kala-azar in Kenya.



Dr. David Soti

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Special thanks go to the Innovative and Intensified Disease Management manager at WHO – Daniel Argaw Dagne, the Leishmaniasis Control Program manager at WHO – José Antonio Ruiz Postigo, the DPC at WHO Kenya Country office – Joyce Onsongo, the Visceral Leishmaniasis leader at DNDi Geneva – Fabiana Alvez and the Director DNDi Africa regional office – Monique Wasunna.

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Dr. Sultani Hadley Matendechero

Head, Neglected Tropical Diseases Program

ABBREVIATIONS

AIDS	acquired immunodeficiency syndrome
ART	antiretroviral therapy
BM	Bone marrow
CD4	"T" helper lymphocytes
DAT	direct agglutination test
DND*i*	Drugs for Neglected Diseases ***initiative***
ETWG	Epidemic Technical Working Group
HIV	Human Immunodeficiency Virus
HMIS	Health Management Information System
IDSR	Integrated Disease Surveillance and Response
IRS	indoor residual spraying
ITM	insecticide-treated material
IVM	integrated vector management
LN	Lymph node
LLIN	long lasting insecticide-treated net
KA	kala-azar
KEMRI	Kenya Medical Research Institute
mg	milligram
MSF OCG	Médecins Sans Frontières – Operational Centre Geneva
NNN	Novy-MacNeal-Nicolle medium
NPHLS	National Public Health Laboratory Services
PKDL	post-kala-azar dermal leishmaniasis
RDT	rapid diagnostic test
RPMI	Roswell Park Memorial Institute medium
SP	Spleen
SSG	sodium stibogluconate
TB	tuberculosis
TLC	total lymphocyte count
TOC	test of cure
TSS	tropical splenomegaly syndrome
TWG	Technical Working Group
VBDC	Vector Borne Diseases Control Unit
VL	visceral leishmaniasis
WBC	White blood cells
WHO	World Health Organization
ZIPP	zinc iodoform paraffin paste

CHAPTER 1. INTRODUCTION

Leishmaniasis remains a public health problem in about 30 sub-counties in Kenya. The disease is caused by protozoan parasites of the genus ***Leishmania*** and transmitted by sandflies of the genus ***Phlebotomus***. Globally, it occurs in 88 countries with 500 000 cases of visceral leishmaniasis estimated annually; 556 million people are at risk of acquiring the infection. Six countries (Brazil, Ethiopia, India, Somalia, South Sudan and Sudan) account for more than 90% of global cases. The disease affects socially marginalized and poor communities in semi-arid and arid areas. It is fatal if not treated.

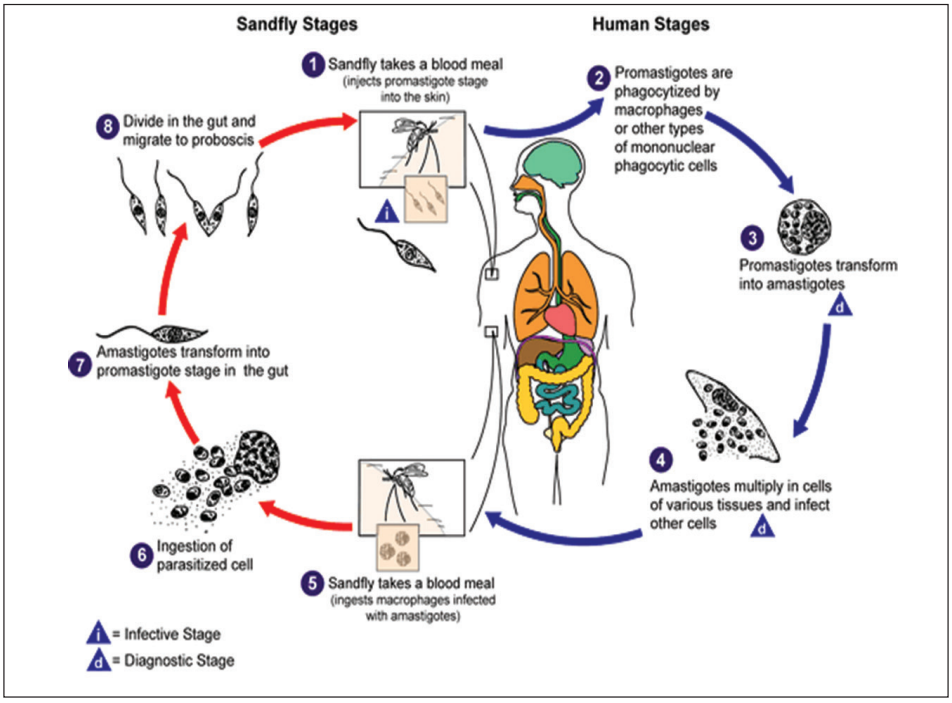
In Kenya, leishmaniasis occurs in two forms: visceral leishmaniasis (kala-azar) and cutaneous leishmaniasis (Oriental sore). Although the disease is curable, it still causes high morbidity and sometimes death due to its low index of suspicion by health care providers, late diagnosis and case management. If not treated, patients with kala-azar will die. Treatment is limited to hospitals in counties and sub-counties because available treatments are injectable and have toxic side-effects. Moreover, current treatment for leishmaniasis is not readily available in most health facilities as the medicines are expensive. There is inadequate information on the prevalence, burden and spatial distribution of the disease, which is distributed mainly in arid and semi-arid regions. Visceral leishmaniasis is endemic in the Rift Valley and Eastern regions, with small foci in North Eastern. In the Eastern Region, foci have been documented in Isiolo, Kitui, Machakos, Makueni, Marsabit, Mwingi and Tharaka counties (Wijers, 1971 Pelinzzi et al., 2006; Herrero, 2008). In Rift Valley, the disease is more common and is found in Baringo, Pokot, Turkana, Samburu, Kajiado and Laikipia sub-counties (Mebrahtu et al., 1987; Mebratu et al., 1988). The exact status of the problem in North Eastern region and the northern parts of the country is not well understood due to inaccessibility and problems associated with diagnosis. However, the disease has been reported sporadically in Mandera and Wajir counties in North Eastern region. The disease occurs also along the Kenya–Uganda and Sudan border; little is known about its distribution, vectors species and reservoir hosts due to the expansive area.

1.1 *LEISHMANIA* LIFE-CYCLE AND TRANSMISSION

The life-cycle of ***Leishmania*** starts when a female phlebotomine sandfly gets infected with the amastigote stage of the parasite through a blood meal of an infected person (Figure 1). The parasites develop from amastigotes to motile flagellated promastigotes that undergo a complex development in the gut of the sandfly. The final phase of development occurs between the anterior midgut and the foregut of the sandfly, at the stomodeal valve, where it transforms into the infective metacyclic form. The parasites are then transmitted during a subsequent blood meal taken by the female sandfly when it injects infective promastigotes into the next human victim. The promastigotes are taken up by macrophages, where they develop into amastigotes and continue to multiply, rupturing the macrophages and infecting the reticulo-endothelial system organs e.g. spleen, liver and bone marrow.

In Kenya, the causative agent of visceral leishmaniasis is ***Leishmania donovani***, which is transmitted by two different sandfly species depending on the region: ***Phlebotomus martini*** and ***P. orientalis***.

FIGURE 1: LIFE-CYCLE OF *LEISHMANIA*



Courtesy of the United States Centers for Disease Control and Prevention

1.2 EPIDEMIOLOGY

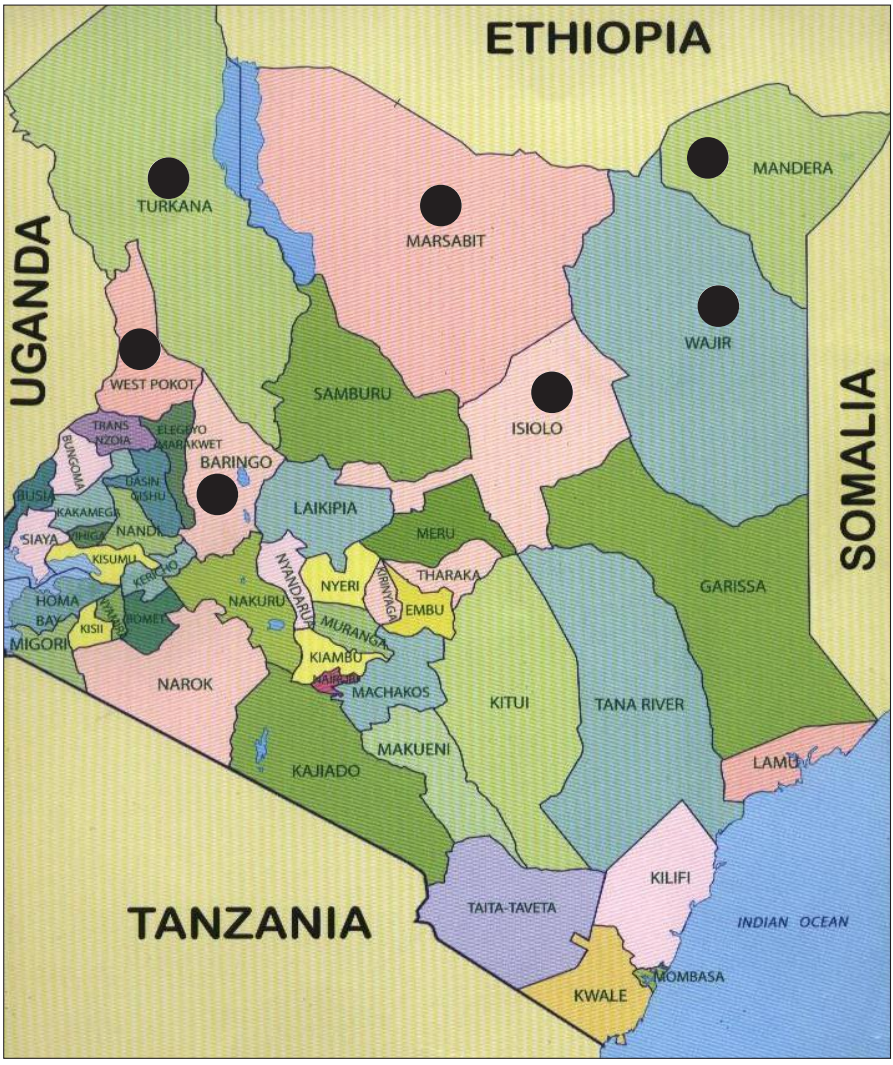
Visceral leishmaniasis is endemic in semi-arid and arid areas of Rift Valley, Eastern and North Eastern regions of Kenya. It is estimated that about 2500 (hospitals record estimates) cases occur annually, the majority of whom are children aged >5 years and young adults; some 6.81 million people are at risk of the infection. The most important transmission foci remain Baringo, Isiolo, Marsabit, Pokot, Turkana and Wajir counties (Figure 2). The disease foci may change to areas previously not known to be endemic as a result of climate change and population movements. There have been several outbreaks of the disease in Kenya; the most recent was confirmed in Isiolo, Marsabit and Wajir counties in, 2008, 2011, 2013 and 2014.

1.3 TRANSMISSION

Infection starts with the bite of an infected female sandfly that injects parasites into a susceptible host. The incubation period ranges from 2 to 6 months. The disease presents with fever, hepatosplenomegaly, general malaise and wasting. However, the incubation period in non-immune hosts could be as short as 2 weeks, which could result in an epidemic.

Some of the exposed persons develop severe disease. Factors that increase the risk of developing disease include: young age, malnutrition, immunosuppressive diseases such as HIV, malignancies and organ transplantation. The case fatality rate approximates 100% if the disease is left untreated. Death is mainly due to secondary bacterial infections.

FIGURE 2: MAP OF KENYA SHOWING DISTRIBUTION OF ENDEMIC COUNTIES



Counties endemic for visceral leishmaniasis

CHAPTER 2. CLINICAL PRESENTATION AND DIAGNOSIS OF VISCERAL LEISHMANIASIS

Visceral leishmaniasis in Kenya mainly affects rural communities, with the majority of cases found in children of the age group 2–15 years. The incubation period is typically 2–6 months but may be shorter or much longer. The onset may be gradual or acute.

2.1 CLINICAL CASE DEFINITION

VL should be suspected in a patient from a VL endemic area who presents with fever for more than 2 weeks and splenomegaly or weight loss in whom malaria has been ruled out or has not shown clinical response to effective antimalarial treatment.

A typical patient will present with several of the following signs and symptoms:

- fever for 2 weeks or longer
- splenomegaly
- weight loss
- anaemia
- cough
- epistaxis
- hepatomegaly
- body weakness.

In rare circumstances, some patients will present with:

- oedema
- jaundice
- vomiting
- joint pains
- abdominal pains
- lymphadenopathy
- diarrhoea.

Once a patient meets the clinical case definition, it is important to know if it is a primary VL case or a relapse VL case, as investigation and patient management will differ.

Primary kala-azar is a patient in whom KA is diagnosed for the first time. The patient has not been treated for KA before.

Initial cure is a patient who successfully completed a course of VL treatment and is discharged with improved clinical condition and no parasites found (negative test of cure).

Relapse case is a patient who successfully completed a course of standard VL treatment, and was discharged with initial cure, who returns later with clinical signs of VL and ***Leishmania*** parasites are found in the parasitological tests. VL relapses are usually observed within 6 months of completing therapy.

2.1.1 DIFFERENTIAL DIAGNOSES

Several diseases that may mimic VL include but are not limited to:

- malaria
- schistosomiasis
- brucellosis
- leptospirosis
- typhoid fever
- tuberculosis
- chronic hepatitis
- liver cirrhosis
- lymphomas and leukaemias
- AIDS
- malnutrition
- hypereactive malarial splenomegaly (HMS) formerly known as tropical splenomegaly syndrome (TSS).

2.2 LABORATORY DIAGNOSIS OF VISCERAL LEISHMANIASIS

A diagnostic algorithm is shown in Annex 7 to provide guidance on the diagnostic tests that should be used in different circumstances, i.e. primary kala-azar or relapses.

The sections below explain the different parasitological and serological tests available to diagnose kala-azar.

2.2.1 PARASITOLOGICAL DIAGNOSIS

A clinically suspected case can be confirmed using spleen or bone marrow aspirate. Splenic aspirates are more sensitive (96%) than aspirates of bone marrow (70–80%). Splenic and bone marrow aspirates are limited to the hospital settings or health facilities where there is adequate equipment and trained staff to manage complications appropriately. Details of the procedure for splenic aspiration and bone marrow aspiration can be found in Annex 1 and 2 respectively.

Parasites can be identified as either amastigote in smears from tissue aspirate stained by one of the Romanowsky stains (Giemsa, Wright or Leishman stains) and examined under oil immersion (See Annex 3 and Annex 4) or promastigotes in culture.

To detect promastigote stages, there is a need to inoculate the tissue aspirate in a culture medium, which requires technical expertise and appropriate infra-structure. Aspirates are inoculated in NNN medium, RPMI 1640 or Schneider's insect medium and incubated at ambient temperature (not more than 26 °C) for up to 2 weeks. Promastigotes can be demonstrated in a wet preparation of the culture observed under microscopy. Cultures have the risk of being contaminated by bacteria and fungi.

Demonstration of parasites in spleen or bone marrow aspirate is proof of VL. Identifying amastigotes under the microscope can be a difficult task, requiring patience, time and focused attention. Inability to find the amastigotes in an aspirate cannot be a reason to exclude VL. In isolated circumstances, repeat aspirates performed one week apart need to be done in patients with a strong suspicion of VL. Examine at least 1000 microscope fields for amastigotes using x100 oil immersion lens.

2.2.2 SEROLOGICAL DIAGNOSIS

These are immunological tests that detect antibodies against ***Leishmania***. Serological tests like DAT and rK39-based rapid diagnostic tests (RDTs) can be used to start treatment provided that a strict VL suspect case definition is followed. If serological tests results are negative or inconclusive then diagnosis may be confirmed by demonstration of amastigotes in splenic/bone marrow aspirates or promastigotes in culture.

2.2.2.1 Direct agglutination test (freeze-dried DAT)

DAT is a sensitive and specific test. It is relatively simple and can be performed under field circumstances. The DAT is technically easy to perform but requires training, cold chain and standardization. The test measures the serological response to surface borne antigens of whole ***Leishmania donovani***.

DAT can be performed using a dried blood spot (on filter paper) or serum. This makes it an excellent test to use at the health centre level. The DAT employs a test antigen that is prepared from formalin-killed promastigote stages of ***L. donovani*** cultures, which have been stained blue for visibility. The test is semi-quantitative, and the antibody titres used at field level range from 1:100 up to 1:51200. The cut-off point for positive DAT is 1:3200 in endemic areas. It requires a well-trained laboratory technical staff to undertake the procedure over 2–3 days. It is a highly sensitive (> 95%) and specific (> 85%) test when performed according to standardized procedures.

If the RDT yields a negative or inconclusive result and there is clinical suspicion of VL, the freeze-dried DAT can be used for diagnosis before performing any parasitological confirmatory test (Annex 5).

2.2.2.2 Rapid diagnostic tests

A rapid test is a simple, point of care test that can be used in all levels of the health care services including the peripheral services to permit prompt diagnosis to initiate treatment. It does not require a laboratory and highly skilled technical staff and the results can be easily read within 30 minutes. A rapid test must also be affordable and possess high sensitivity, specificity, and reliability. Several rapid VL tests for use in field settings have been developed.

- <u>rK39 RDTs</u>

The currently available rK39 RDTs can be performed easily by health personnel at the lowest health facility level with results available within 10–20 minutes (as per manufacturer's instructions). It is a qualitative membrane based immunoassay for detection of antibodies to ***Leishmania*** causing VL. Details on the procedure of performance and interpretation of the rK39 rapid diagnostics test can be found in Annex 6A and 6B.

Currently two commercial rK39 dipstick tests are available, these are: Kalazar Detect (Inbios, Seattle, USA), and IT-LEISH (Bio-Rad, South Africa, formerly from DiaMed AG, Switzerland). Validation studies of various rK39 diagnostic test kits carried out in Kenya by KEMRI, DND*i* and MSF as well as WHO/TDR showed that IT LEISH (DiaMed /Bio-Rad) has the highest sensitivity and specificity in East Africa and hence can be used to initiate treatment in patients with clinical manifestations of VL, following a strict adherence to the VL clinical case definition. Validation results of some of the RDT are shown in Annex 6C.

The Leishmaniasis Control Programme, Ministry of Health, recommends the use of Bio-Rad – IT LEISH as the preferred rapid diagnostic test kit for kala-azar in the country, as it has a higher specificity and sensitivity than other test kits.

Note: DiaMed Company was bought by Bio-Rad. The kits are now called Bio-Rad IT leish.

Advantages and disadvantages of rK39 RDTs

Advantages

- rK39 RDTs enable individual patients to be tested at the bedside.
- Tests are individually packaged and easy to store/transport.
- Little training and no laboratory equipment are needed.
- Results are available in 10–20 minutes.
- Results are clear and easy to read.
- Enables decentralized screening of VL even at community level.
- Easy to use in field setting during active case search or an outbreak.
- Kits can be transported and stored at ambient temperature (up to 30 °C).

Disadvantages

- As any other serological test, they cannot distinguish between active and past symptomatic or asymptomatic infections. Therefore interpretation must always be in combination with clinical case definition, and diagnosis of relapse must rely on parasitology.
- In some cases (around 10–18%) the test will give a negative result even if the patient suffers from VL. In this case, another serological or parasitological test must be performed in VL suspected patients.
- In patients with advanced HIV infection a negative result cannot preclude the diagnosis of VL.

2.2.3 ANTIGEN DETECTION TESTS

2.2.3.1 Latex agglutination test to detect *Leishmania* antigen in urine

Soon after infection, *Leishmania* parasites secrete/excrete antigens that accumulate in the body and then are secreted as waste products in blood and urine. Detection of these antigens may be used as a confirmatory test since the antigens indicate actual infection. The only commercially available antigen detection test is KAtex (Kalon Biological, UK); despite its simplicity (is a latex agglutination test) its widespread use has been limited by a variable sensitivity and specificity obtained in different studies, and the need to boil the urine before testing to avoid false positive results.

The same company has produced a new test for *Leishmania* antigen detection, an ELISA that does not need boiling the urine for testing. This test is currently under evaluation in different countries, but a recent study in Kenya (a collaboration between KEMRI, DND*i*, and FIND) showed a 97% sensitivity and 100% specificity for this test. A test of this type would be useful in the diagnosis of HIV-coinfected patients and, being a marker of actual infection, it could be used for treatment monitoring too.

2.2.4 USE OF DIAGNOSTIC TESTS

In summary, VL testing is administered to clinically VL suspect patients since most people infected with *Leishmania* do not develop the disease (KA). It is crucial to enquire about any previous treatment for KA because serological tests will test positive even after a successful treatment after several years.

The first test to be used in a clinically VL suspect, who has not been previously treated, is the RDT. Treatment should start when the RDT is positive. In case of a negative RDT result, then blood should be tested for DAT.

If the DAT result is positive the patient should be treated. If the DAT result is borderline, the test should be repeated not earlier than one week later, or a parasitological test must be performed. If the DAT result is negative another disease has to be considered.

If a person shows a borderline DAT result and the parasitological test is positive the person has to be treated for KA. If the parasitological test is negative then re-test for DAT or search for another diagnosis. In health facilities where parasitological examination is available, it remains the gold standard for VL diagnosis.

Note: The majority of hospitals in the VL endemic areas do not have capacity to carry out DAT testing. Therefore, if rK39 is negative and the patient fits the clinical definition of VL, the suspect requires a splenic aspirate or bone marrow aspirate. Hence, they should refer the suspect to the next higher hospital level.

2.3 DIAGNOSIS OF RELAPSE

A relapse of kala-azar means that a person has kala-azar but has already been treated before. Relapses usually occur within 6 months after treatment. If a patient presents with fever for more than 2 weeks, and has a palpable spleen, ask if they have been treated for kala-azar before. A serological test cannot diagnose a relapse because it can still be positive for months to 2–3 years after treatment even if a person is feeling well. Therefore, diagnosis investigation in relapse cases should be based on parasitological diagnosis.

Note: The visceral leishmaniasis diagnostic algorithm is illustrated in Annex 7.

2.4 DIAGNOSIS OF PKDL

Post kala-azar dermal leishmaniasis (PKDL) has the following characteristics.

It is a rash that starts on the face. This rash may sometimes spread to the whole body but it always starts on the face. This rash usually starts within 6 months of having kala-azar. Sometimes it starts during or at the end of kala-azar treatment. It is usually seen in patients who have received treatment for kala-azar. Rarely can it be seen in a patient not having suffered yet from kala-azar.

PKDL usually heals by itself. Sometimes it comes and goes for years. Sometimes it gets worse and worse. Sometimes it affects the mucous membranes. The diagnosis of PKDL is made by the history of the patient and clinical signs. Note that people can die with severe PKDL and that PKDL itself may be a reservoir for kala-azar infection.

The lesions of PKDL start on the face as small scattered hyper-pigmented macules and papules. The rash can become nodular and spread to the trunk and limbs. It is symmetrical and non-itching. A grading system is used to describe the spread of the skin lesions:

- **Grade 1**: Scattered macular rash on the face around the mouth with some lesions on the upper chest and upper arms.
- **Grade 2**: Dense macular or nodular rash covering most of the face and extending to the chest, back and upper arms and legs. If extensive or black nodules, it is severe grade 2.
- **Grade 3**: Dense macular rash covering most of the body, including hands and feet. In grade 3 crusting ulcers, scaling and spreading to the mucosa of the lips and the palate occurs (See WHO PKDL Atlas *http://apps.who.int/iris/bitstream/10665/101164/1/9789241504102_eng.pdf).*

PKDL might persist for years (up to 10 years have been reported). It is speculated that PKDL patients could form a reservoir of the parasite in the community. Bed nets should be given to PKDL patients to prevent transmission.

The majority of PKDL cases are self-limiting so treatment is not needed; only severe grade 2 and grade 3 are treated with specific medicines.

CHAPTER 3. TREATMENT OF VISCERAL LEISHMANIASIS

The treatment of visceral leishmaniasis will depend on the patient's age and whether the patient has primary kala-azar, relapse, VL-HIV coinfection or other concomitant medical condition.

3.1 GENERAL PRINCIPLES AND OBJECTIVES OF TREATMENT

The main principle and objectives of VL treatment are to:

1. Clinically cure the patient
2. Minimize drug toxicity
3. Support the patient's nutrition and hydration status
4. Prevent and treat complications
5. Prevent the development of drug resistance
6. Manage and treat concomitant medical condition(s).

The choice of drugs for the treatment of VL in Kenya should be based on:

- efficacy and safety
- age
- concomitant medical conditions
- availability
- cost.

3.2 SUPPORTIVE MANAGEMENT

3.2.1. NUTRITIONAL SUPPORT

Patients should receive adequate nutrition and vitamin supplements where indicated.

3.2.2 TREAT INTER-CURRENT INFECTIONS SUCH AS:

- Pneumonia and otitis media with appropriate antibiotics.
- Maintain oral hygiene to prevent mouth infections (cancrum oris) and rapidly treat cancrum oris, should it occur, with metronidazole and penicillin.
- Maintain skin hygiene and treat skin infections.
- Treat malaria and/or tuberculosis if present.

3.2.3 ANAEMIA

Occasionally, blood transfusion may be required for severe anaemia or bleeding due to thrombocytopenia

3.2.4 OTHER CONDITIONS

Example – In severe epistaxis packing of the nose with gauze with adrenaline or zinc iodoform paraffin paste (ZIPP) is recommended.

3.3 DRUG TREATMENT

3.3.1. PRIMARY VISCERAL LEISHMANIASIS

3.3.1.1 First-line treatment – combination therapy

The Ministry of Health recommends sodium stibogluconate (SSG) and paromomycin (PM) combination therapy as the first-line treatment for primary VL in Kenya unless contraindicated otherwise.

Primary visceral leishmaniasis

Combination therapy: sodium stibogluconate (pentavalent antimonials)/SSG at 20 mg/kg per day intramuscularly or intravenously plus paromomycin 15 mg [11 mg base] per kg body weight per day intramuscularly) for 17 days.

3.3.1.2 Monotherapy treatment

Sodium stibogluconate (SSG) as a monotherapy can still be used in health facilities in endemic areas in situations where paromomycin is not available or is contraindicated (hearing impairment or concomitant renal disease).

The treatment as monotherapy is SSG 20 mg/kg per day intramuscularly or intravenously for 30 days.

The pentavalent antimonial formulations commercially available are:

1. Pentostam (SSG) from GlaxoSmithKline, UK. Concentration of pentavalent antimonials = 100 mg/ml.
2. Generic sodium stibogluconate (SSG) from Albert David, Calcutta, India. Concentration of pentavalent antimonials = 100 mg/ml.
3. Glucantime (meglumine antimoniate) from Sanofi Aventis, France. Concentration of pentavalent antimonials = 81 mg/ml.

Antimonial dosage and administration:

For SSG the dosage is 20 mg/kg per day, intramuscularly or intravenously, as a single daily dose with no upper limit dose of 850 mg as recommended by WHO, unless there is any medical condition that justifies it. If doses are above 10 ml give in two separate intramuscular injections.

For Glucantime the dosage is 20 mg/kg/day, intramuscularly or intravenously, as a single daily dose without upper limit dose of 850 mg unless deemed necessary. Weigh the patient weekly and adjust the dose accordingly.

When used in combination with paromomycin, the treatment duration with pentavalent antimonials is 17 days.

When pentavalent antimonials are used as monotherapy, the treatment duration is 30 days.

Conditions for withdrawal of SSG therapy (when used either as a combination or as monotherapy):

- acute pancreatitis;
- aberrations of creatinine;
- jaundice developing during treatment;
- excessively high LFT values, i.e. > 5x normal values of SGPT/SGOT;

- any evidence of cardiotoxicity (prolonged QT interval, cardiac arrhythmia);
- declining haematological measurements (HCT, total WBC counts) with symptoms suggesting failure of treatment
- uninterrupted vomiting; and
- failure to respond favourably during the first weeks of treatment.

If SSG needs to be withdrawn, then AmBisome can be used as an alternative rescue option.

Contraindications: Patients with known cardiac diseases. Co-administration of quinine or any other medicine known to cause cardiac toxicity.

HOW TO CALCULATE THE SSG DOSE

SSG vials contain 100 mg/ml so it is calculated as follows:

Dose in ml = body weight in kg x 0.2

EXAMPLES:
If your patient weighs 40 kg
40 x 0.2 = 8 — so give 8 ml

If your patient weighs 32 kg
32 x 0.2 = 6.4 — so give 6.4 ml

If your patient weighs 8 kg
8 x 0.2 = 1.6 — but give 2 ml (the lowest dose)

Intravenous injections must be administered very slowly (more than 5 minutes) and preferably through a fine needle to avoid thrombophlebitis, and should be discontinued immediately if coughing, vomiting or substantial pain occurs. Intramuscular injections can be very painful.

The weight of the patient should be taken every week and the daily dose of pentavalent antimonials should be adjusted to the current weight (nearest kg). Patients should be checked regularly for clinical response. The earlier signs of response are the clearance of fever (within 3–7 days) and the improvement of the general condition.

Pentavalent antimonials require monitoring of safety as toxicity and side-effects may occur, especially with longer treatment duration. These include nausea, anorexia, arthralgia, myalgia, pain at the injection site, ECG changes, raised liver enzymes, raised pancreatic enzymes, severe vomiting. Sudden death may occur due to cardiac arrhythmia, intra-cerebral bleeding, anaemia associated heart failure and renal toxicity.

The risk of serious (sometimes fatal) toxicity of pentavalent antimonials is increased in patients who concomitantly have:

- cardiac disease, in particular arrhythmias
- renal failure

- liver disease
- severe malnutrition
- very poor general condition
- HIV coinfection
- pregnancy.

If one of these conditions is present, the patient should be closely monitored or, preferably, be treated with another drug (see below).

Patients with confirmed VL diagnosis should be tested for HIV, as a coinfection will require special case management.

Paromomycin dosage and administration

- You must have 1 ml and 2 ml syringes to give this medicine.
- The recommended dose is 15 mg/kg sulfate (equivalent to 11 mg/kg base); no maximum dose; **monotherapy should not be used.**
- Patients must remain well hydrated because paromomycin can affect the kidneys. Tell patients to drink enough that they pass urine 4 times a day.
- If patients have severe vomiting and diarrhoea, do not give the injections.
- This medicine cannot be given intravenously
- Weigh the patient weekly and recalculate the dose.
- Not recommended during pregnancy.

Common side–effects of paromomycin

The most commonly reported adverse drug reactions are injection site pain, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) elevations, pyrexia, and an abnormal audiogram. These effects are usually mild to moderate and transient or reversible at the end of treatment.

Use the PM dosage table or calculate the dose of paromomycin as shown in the following table:

Paromomycin is 375 mg/ml in a 2 ml vial so it is calculated as follows:
Dose of paromomycin in ml = (weight in kg x 15) divided by 375

If your patient is 8 kg: (8 x 15) / 375 = 120 / 375 = 0.32 ml

If your patient is 15 kg: (15 x 15) / 375 = 225 / 375 = 0.6 ml

If your patient is 45 kg: (45 x 15) / 375 = 675 / 375 = 1.8 ml

Refer to Annex 8. A summary of treatment regimens and Annex 9 for more information on the use of paromomycin.

3.3.2 SECOND-LINE TREATMENT

3.3.2.1 Liposomal amphotericin B (AmBisome)

Liposomal amphotericin B is an efficacious treatment against visceral leishmaniasis with a much improved safety profile as compared to the amphotericin B deoxycholate formulation. Mild infusion reactions (fever, chills and rigor) and back pain may occur in some patients. Transient nephrotoxicity or thrombocytopenia is also occasionally seen. AmBisome comes in vials of 50 mg and needs to be reconstituted and diluted in 5% dextrose and given over a period of 30–60 minutes as an intravenous infusion. The recommended dose in Kenya is 3–5mg/kg body weight per daily dose by infusion given over 6–10 days up to a total dose of 30 mg/kg (Annex 8D).

Liposomal amphotericin B is the first-line treatment for the following conditions:

- pregnant women
- lack of response or relapses after SSG-PM or SSG therapies
- severely ill patients
- children less than 2 years old and adults older than 45 years
- *Leishmania*-HIV coinfected patients
- contraindication to SSG or PM treatment

Note: **Do NOT dilute with saline solutions or mix with other electrolytes or medicines.**

Storage conditions

Before use, AmBisome should be **stored at 2–8 °C and should not be frozen.** It should also be protected from exposure to light.

The reconstituted AmBisome may be stored for 15–24 hours at 2–8 °C before use.

Side–effects

Are rare but the patient may have fever, chills and a low backache if the infusion is given too fast. Anaphylactic reactions have also been observed in some patients.

Hypokalaemia may occur in some patients and should be corrected using potassium chloride.

Contraindications

AmBisome is contraindicated in patients who have experienced previous hypersensitivity reactions.

3.3.2.2 Amphotericin B deoxycholate (Fungizone, Squibb)

Amphotericin B deoxycholate has been used in the past for treatment of visceral leishmaniasis. However, due to its side-effects, it has been replaced by safer liposomal formulations, as described above. A suitable regimen is 0.75–1 mg/kg per day by infusion, daily or on alternate days, for 15–20 doses. The major side-effect of amphotericin B is renal impairment and renal function should preferably be monitored weekly during treatment. Renal impairment can be reduced by pre-hydrating the patient with an infusion of normal saline. If a rise in urea and creatinine occur, the interval between doses should be lengthened. Hypokalaemia and hypomagnesaemia may occur and can be prevented by potassium/magnesium supplementation. Other side-effects are headache, nausea, vomiting, chills, fever, malaise, muscle and joint pain, diarrhoea, gastrointestinal cramps, hypertension, hypotension, cardiac arrhythmias including ventricular fibrillation, skin rashes, anaphylactoid reactions, blurred vision, tinnitus, hearing loss, vertigo, liver disorders,

peripheral neuropathy, convulsions, thrombophlebitis at the injection site and anaemia.

Although cheaper than liposomal amphotericin B (AmBisome), it has many adverse effects that discourage its use in the treatment of VL.

Administration

Amphotericin B is infused in 1 litre of dextrose 5% infusion running over 2–12 hours. The slower infusions decrease infusion related side-effects (chills, fever). Before starting therapy, hydrate the patient and maintain hydration with ORS and, if needed, IV fluids. This is important to decrease the risk of renal toxicity. Give potassium supplementation (1 tablet 3x/day for adults).

Management of fever

Administer paracetamol before infusion or at the onset of symptoms. Avoid gentamicin, streptomycin, paromomycin or other medicines that can cause renal toxicity.

3.3.3 DEFINITIONS OF TREATMENT OUTCOMES

At initial assessment (between 2 and 4 weeks after initiating treatment) these are the outcomes to be recorded:

- **Initial cure**: a full course of drugs has been completed AND the patient has clinically improved. Clinical criteria for initial cure defined as *"no fever + regression of splenomegaly + return of appetite and/or gain in body weight"*.
- **Probable non-response**: signs and symptoms persist or recur during treatment without parasitological confirmation.
- **Confirmed non-response**: signs and symptoms persist or recur during treatment with parasitological confirmation (smear showing parasite density equal to or greater than before treatment).
- **Death**: any death, whether related to VL or not.
- **Default**: the patient does not complete treatment.
- **Lost to initial follow-up**: the patient does not present for assessment after completion of treatment.

At final assessment, 6 months after treatment completion, the outcomes are recorded as follows (but be aware that relapses may occur after 6 months as well):

- **Final (definitive) cure**: a patient who after initial cure remains symptom-free at 6 months after the end of treatment.
- **Relapse**: a patient who experiences recurrence of VL symptoms with parasitological confirmation at any time point after initial cure. VL relapses are usually observed within 6 months of completion therapy.
- **Death**: any death, whether or not related to VL.
- **Loss to follow-up**: a patient who does not present for assessment at 6 months.

Drug–resistant case

A VL patient from which a laboratory confirmed drug resistant parasite is isolated. In this sense, methods for determining drug resistance are needed, which are standardized and usable in endemic countries.

Test of cure

Test of cure (TOC) is performed at the end of treatment when there is no or insufficient clinical improvement and in treatment of relapse for decision to stop treatment. There is no clinical sign that best correlates with a positive test of cure or that predicts an increased risk of relapse. Clinical evaluation should be prioritized over a test of cure for every patient under the currently available invasive procedures. TOC should be reserved for cases where response is in doubt, in the treatment of relapses and for monitoring emergence of drug resistance. In addition, TOC is done to assure that discharge is appropriate for patients who may have difficulty returning for follow-up. Negative TOC is absence of amastigotes in a tissue slide taken from a VL patient. A positive TOC is presence of amastigotes in a tissue slide taken from a VL patient.

There must be two negative TOC results before discharging patients with VL relapse. The tests are done one week apart to ensure that there is at least a week of treatment after the first negative TOC. The likelihood for a positive TOC after treating a relapse is higher than 10% and any further relapses will be more difficult to cure.

Criteria for cure when test of cure is not possible

In health facilities that cannot carry out parasitological test to determine test of cure, the following criteria should be used to decide clinical cure from the disease:

- Return of normal appetite
- No fever
- Regression of spleen
- Improvement in anaemia and a rise in haemoglobin level
- Increase in WBC
- The full course of treatment has been administered
- Increase in body weight

In this case, the patient should be requested to come for a follow up after 60 days or as soon as he/she presents signs of the disease. A patient discharge form is presented in Annex 11.

3.3.4 DRUGS USED IN THE TREATMENT OF RELAPSES AND NON-RESPONSIVENESS OF VISCERAL LEISHMANIASIS.

Drugs which can be used in repeated relapses and unresponsive cases include:

1. Liposomal amphotericin B (AmBisome), total dose 3–5mg/kg per day for 6 to 10 days as an intravenous infusion given slowly for 30–60 minutes.
2. Amphotericin B deoxycholate (Fungizone, Squibb), 0.75–1 mg/kg per day by infusion, daily or on alternate days, for 15–20 doses.

If pentavalent antimonials are the only available drugs, 20 mg/kg per day can be given for a total of 60–90 days. However, this treatment will have to be carefully monitored due to the side-effects associated with long SSG treatments.

3.4 VISCERAL LEISHMANIASIS AND HIV COINFECTION

Since both VL and HIV attack the immune system of the body they produce a profound immune deficiency state. The results and effect of this state is that VL accelerates the onset of full-blown AIDS and shortens the life expectancy of HIV-infected people, while HIV complicates management of VL. WHO also classifies atypical disseminated leishmaniasis as HIV stage 4 defining illness. VL lowers the total lymphocyte count (TLC) and CD4 count to a great extent by depressing the bone marrow and the splenic activities.

The best long-term prospects will exist if a patient with HIV–VL is started on ART after VL treatment. As well as attempting to cure VL, important secondary objectives for HIV/VL coinfected patients are counselling and psychosocial support, relief of symptoms, treatment of secondary infections and prevention/treatment of opportunistic infections.

The special difficulties with VL coinfection include anaemia, bleeding, malnutrition and concurrent illnesses. Patients with HIV can get severe diarrhoea and vomiting. These should be aggressively diagnosed and treated.

Patients with VL–HIV co infection should not be treated with antimonial compounds unless the benefits outweigh the risk. AmBisome is the first-line drug of choice in these patients and may require a higher total dose. If this drug is not available, conventional amphotericin B is a suitable alternative. All VL–HIV patients with atypical disseminated leishmaniasis should be classified as HIV stage 4 and should receive antiretroviral therapy (ART). (WHO Informal Consultative Meeting on HIV–VL coinfection, March 2007, Addis Ababa).

Other concomitant infections such as TB, candidiasis, pneumonia, and diarrhoea should all be diagnosed and treated appropriately. VL relapses and mortality are more common in HIV coinfected patients.

Note that a definitive cure cannot be achieved by any drug, and relapse is almost inevitable. The time to relapse is usually 3–6 months, with successive relapses becoming less typical and less acute, but occurring more frequently.

Patients are less responsive to treatment with each relapse, and eventually may become unresponsive to all drugs used. With repeated courses of antileishmanials, parasite strains become progressively less sensitive to the drug and toxicity may eventually outweigh the benefits. Since VL patient coinfected with HIV requires special care, all patients diagnosed with VL should have an HIV test done.

3.5. POST-KALA-AZAR DERMAL LEISHMANIASIS

3.5.1 PREVALENCE

In Kenya, post-kala-azar dermal leishmaniasis (PKDL) occurs during the first few months after completion of treatment with a prevalence of 2–5% of treated cases. However a few cases have been noted during treatment. PKDL cases are thought to be the main reservoir of infection during inter-epidemic periods and some cases give no history of previous VL disease. So identification of PKDL cases is relevant so as to reduce the human reservoir pool of the disease.

3.5.2 PRESENTATION

The most common presentation of PKDL is hypo-pigmented macules or papules on the face. The lesions can become nodular and spread to the limbs and trunk. The lesions are non-itchy and are symmetrical.

3.5.3 DIAGNOSIS

Suspected PKDL cases should undergo two skin slit smears of the lesions to confirm diagnosis. Staining procedure is same as for splenic aspirate smear. (Annexes 1, 2, 3 and 4). However, most PKDL cases are diagnosed on past history and clinical manifestations.

3.5.4 TREATMENT

The majority of PKDL cases are self-limiting so treatment is not needed; only severe grade 2 and grade 3 are treated with specific medicines. To limit the potential of spreading the parasite, PKDL patients should sleep under an insecticide-treated bednet, as this is also recommended for VL patients in general.

Confirmed PKDL cases should receive the same treatment as for VL. PKDL cases respond well to antimony drugs but require longer duration of treatment. Treatment should continue for 30 days. If there is no parasitological cure (skin slit smears still positive) give additional 30 days of pentavalent antimonials.

Note: All data for patients treated for KA should be entered in the VL case reporting form (Annex 10A) while all cases should be summarized in the monthly report forms (Annex 10C). The data should also be entered in the National database of the Ministry of Health (HIMS).

3.5.5 ANTILEISHMANIAL MEDICINES USED IN OTHER COUNTRIES

Miltefosine (Impavido, Zentaris Pharma, Canada) was initially developed as an anti-cancer drug. Currently it is an oral drug for VL. Miltefosine has some undesirable adverse effects such as teratogenicity, diarrhoea and vomiting, which can be reduced by administering with food. In some cases, it may require anti-emetics and anti-nausea. Miltefosine use is strictly contraindicated in pregnant women or in women who could become pregnant within 3 months after treatment.

3.5.6 DRUGS UNDER CLINICAL EVALUATION

Patients with VL need an oral, safe, effective, low cost, short course treatment. There is also a need to further improve point of care diagnostic tools that are field adapted. Towards this end, the Ministry is collaborating with research institutions and international research organizations e.g. KEMRI, DND*i* and others. Through such collaborations, specialized VL treatment centres that offer specialized care have been established. They offer the community a chance to participate in research in order to improve diagnosis and treatment of VL.

Note: Medicines and reagents use form for kala-azar are presented in Annex 12.

CHAPTER 4. DISEASE SURVEILLANCE AND EPIDEMIC RESPONSE

4.1. DISEASE SURVEILLANCE

Surveillance can be defined as the systematic collection, analysis, and interpretation of health data and includes timely dissemination for action. It is a key component in kala-azar control as it helps to assess the annual trends, disease burden and cost–effectiveness of interventions. Visceral leishmaniasis surveillance includes reporting of all cases of kala-azar and PKDL. To make disease surveillance effective, it is necessary to organize a system of regular reporting. This should be within health facilities as well as with higher authorities to facilitate and rationalize the planning, implementation and evaluation of control measures.

4.2 SUB-COUNTY HOSPITALS AS REPORTING UNITS

All sub-county health facilities and any other health facility in endemic areas that offer kala-azar diagnosis and/or treatment become the reporting units. The lower health facilities should refer suspected cases to sub-county hospitals for treatment. Appropriate data capture tools on kala-azar and PKDL have been developed and all data should be entered in the KA reporting form (Annex 10A, 10B, 10C and 10D). The data managers in the sub-counties should enter the data in the DDSR and the HMIS/DHIS2 data base. A copy of the data should be sent to the county surveillance officer once a month on an agreed date of each month. The county surveillance officer should analyse the data, interpret and transmit them to relevant authorities in the county and national level for action.

In health facilities with online resources the data collection (aggregated or case-based) is entered or uploaded into the DHIS2 (or other) software for validation at the next higher level (sub-county or county) to be then shared with the national level and the WHO Global Leishmaniasis Control and Surveillance Programme.

During suspected outbreaks and where possible, individual data (line-listing or case-based) should be collected and entered into the health management information system to facilitate data analysis and automated reports showing aggregated data.

4.3 REPORT REVIEW AND FEEDBACK

The county surveillance officers after compilation of the report and its review should write their comments on the monthly report and send it to the National Leishmaniasis Control Programme. The reports are reviewed at national level and follow-up action taken. The National Programme should compile the monthly reports from each county and share it with the Technical Working Group (TWG) on a quarterly basis to facilitate early follow-up action on the report. The county surveillance officer also has the responsibility of providing regular feedback to the sub-county and the peripheral health facilities by calling followed by a written advice on the same. Review and feedback should be taken seriously at all levels and any action recommended should be executed. A supervisory visit should be made to mentor and follow-up action.

The advantage of using a dedicated software such as HMIS/DHIS2 is that surveillance officers and authorities at the county and national levels would have access in real time, as soon as data are entered and validated. If data are entered at the health facility level this would allow producing reports/data analysis in a very easy and standardized manner.

4.4 SURVEILLANCE OF KALA-AZAR

Surveillance comprises passive and active surveillance of cases as well as vector surveillance. Integration of pharmacovigilance and treatment outcome monitoring should also be part of the routine surveillance system (see Annex 16).

4.4.1 PASSIVE CASE SURVEILLANCE

This is the main method used and is hospital based. This means timely, regular and accurate reporting of patients who seek diagnosis and treatment in hospitals. Patient cards should be the starting point for passive surveillance. All relevant information in the card should be entered in case and laboratory reporting tools that have been provided by the Programme (Annex 10A, B, C and D). The main disadvantage of passive surveillance is that it is a slow process as one has to wait for the patients to report to the hospital.

4.4.2 ACTIVE CASE SURVEILLANCE

Active surveillance implies active search of cases. Health workers and community health workers/ volunteers are oriented in the process of active case searches through campaigns and house-to-house visits. During active surveillance health workers/community health workers visit the households to detect cases of fever of more than 2 weeks, splenomegaly or abdominal pain and screen them with the rK39 diagnostic test kit and the malaria rapid test. Those who test positive for rK39 and negative for malaria should be referred to the nearest health facilities for treatment of kala-azar. The health facility should ensure that there are adequate materials for the diagnosis and treatment of cases of kala-azar before the exercise starts. The hospital and the team should also organize to provide services or refer patients who may not be suffering from kala-azar. This process is disadvantaged by unavailability of fund to facilitate movement of the health teams.

4.4.3 VECTOR SURVEILLANCE

In most endemic areas, kala-azar is characterized by a patchy distribution with discrete transmission foci. This focal distribution of kala-azar transmission sites is due to micro-ecological conditions that affect vector dynamics (density, parity, infectivity rate, and feeding and resting behaviour). An increase in vector density will directly result in an increase in parasite transmission. Thus, frequent monitoring of vectors will give a trend of their occurrence over a particular period. These activities would allow establishing a vector population density threshold reached above which control measures should be put in place or strengthened in order to reduce transmission.

4.4.3.1 Methods of vector surveillance

Vector surveillance requires sampling of sandflies species frequently using uniform trapping methods as certain species may only appear at certain times of year. Sandfly species densities are influenced by ecological factors such as climatic conditions, land cover, vegetation and rainfall. For sandfly trapping, it is important to use several collection methods to minimize biases in individual techniques as well as to allow sampling of populations with diverse behavioural characteristics from various habitats. Some of the sampling methods used for sandfly collection are: 1) Human-landing catches, 2) Aspirations, 3) Pyrethrum spray catches, 4) Light trap catches, 5) CO_2 baited trap, 6) Sticky paper traps. These methods can be used under different settings that include indoors and outdoors.

4.5. DISEASE OUTBREAK RESPONSE

When more than the expected number of kala-azar cases is reported in a given area, the situation should be investigated and verified. Weekly data should be collected and filled in the right reporting form (Annex 13). An outbreak should be declared and a prompt response should be launched if cases are confirmed. An outbreak may be restricted to one village or location and rarely is the whole sub-county affected. Some endemic foci can erupt into epidemics, or new foci can appear where leishmaniasis has not previously been reported.

4.5.1 DETECTION

Detection and confirmation of an outbreak depend on accurate surveillance data that show an increase in the number of confirmed VL cases more than expected. Outbreaks may be detected by the existence of large numbers of cases, health clinic attendances, admissions to hospital, deaths or media reports.

4.5.2 CONFIRMATION

When an outbreak is suspected:

- A preliminary case investigation must be carried out to confirm the diagnosis, assess the extent of the outbreak and identify the population at risk.
- This is best done by health workers using a standard outbreak form, seeking details on cases (Annex 10A and 14).
- The outbreak is confirmed by comparing the current and previous incidence of the disease, while allowing for seasonal variation, potential changes in completeness of reporting due to alteration to local conditions (e.g. insecurity, affecting access to health care facilities).

4.5.3 RESPONSE

- The health worker, using the outbreak form, should inform the Sub-County Medical Officer of Health who in turn reports to the county and national level.
- An outbreak response team at the county/sub-county level should be constituted to address and implement the various response activities at county level. Similarly an Outbreak Technical Working Group (OTWG) at national level should be constituted to coordinate an outbreak control response by ensuring funds are available for immediate purchase of essential supplies including:
    - Drugs for treatment of leishmaniasis and for management of opportunistic infections in visceral leishmaniasis patients
    - Rapid diagnostic tests
    - Laboratory and parasitological diagnostic equipment and reagents
    - Weekly surveillance
- Health workers in the affected area should be oriented and provided with appropriate training to equip them with the necessary skills to detect, diagnose, manage and report cases.
- Work with peripheral health facilities or community health workers in identifying and referring clinically suspect cases to a VL treatment centre for confirmatory testing and treatment.
- When there is high mortality from VL, active case finding in the areas where the victims came from should be conducted, as a high case-fatality rate is a result of advanced disease and indicates that patients had difficult or delay in accessing treatment.

- Provide information to all levels (health centres, dispensaries, hospitals and local communities) in messages that:
  - contain clear, simple instructions to the population at risk to consult a health centre at an early stage of the disease;
  - the locations of diagnosis and treatment centres; and
  - epidemiological data and practical measures for prevention.
- Mobilize resources, if available, from international technical expertise to assist where needed ensuring multi-sector involvement (WHO, DNDi, KEMRI, UON, ICIPE, UNICEF, MSF, etc.).

4.5.4 POST OUTBREAK

After an outbreak, the OTWG must carry out a thorough evaluation of the following:

- cause of the outbreak;
- surveillance of kala-azar and detection of the outbreak;
- preparedness for the outbreak; and
- management of the outbreak.

The findings of this evaluation should be documented in a written report containing clear recommendations regarding:

- epidemiological characteristics of the outbreak
- surveillance (assess the surveillance system, recommend actions to enhance kala-azar surveillance in the affected areas)
- preparedness / recommend action to improve outbreak response

Ongoing surveillance in endemic sub-counties should be instituted using the VL monthly summary reporting tool (Annex 10C) to detect any change in trends of the disease incidence.

CHAPTER 5. PREVENTION AND CONTROL OF VECTORS

5.1 PREVENTION AND CONTROL OF VECTORS

Vector control is an essential component of any leishmaniasis control activities. However, its value and relevance have not clearly been recognized. Among the factors that hinder the effective use of vector control measures are: lack of an epidemiological basis for intervention, inadequate resources, lack of trained personnel and inappropriate infrastructure. However, there is no single control tool or approach that is appropriate to all situations due to variation in geography, ecology and human behaviour. The main vector control methods available include:

5.1.1 USE OF INSECTICIDE IMPREGNATED BED NETS

Long-lasting insecticide impregnated bed nets are currently used as the most practical method to reduce human–vector contact. Bed nets form a protective barrier around people sleeping under them. However, bed nets treated with an insecticide are much more protective than untreated nets. Insecticides belonging to the pyrethroid family that are used to impregnate bed nets are: permethrin, lambda-cyhalothrin, alpha-cypermethrin and deltamethrin.

These insecticides kill sandflies, as well as mosquitoes and other insects. The pyrethroids also repel sandflies, reducing the number that enter the house and attempt to feed on people inside. In addition, if high community coverage is achieved, the numbers of sandflies, as well as their length of life, will be reduced. When this happens, all members of the community are protected, regardless of whether or not they are using a bed net. To achieve such effects, more than half of the people in a community must use an ITN. The use of impregnated bed nets in malaria control has been reported to reduce leishmaniasis transmission in areas where the two diseases co-exist.

5.1.2 INDOOR RESIDUAL SPRAYING

Insecticides play an important role in control of sandfly vectors, especially in domestic and peridomestic situations. Spraying the internal walls of appropriate houses is a cost–effective way to control endophilic vectors and can have a long-lasting effect, depending on the insecticide used, the surface treated, and the dosage and method of application. However, the spraying coverage has to be high as low coverage may contribute to insecticide resistance. If partly a exophilic or peridomestic vector species is involved outer surfaces of shelter and other potential outdoor resting sites should be sprayed as well. Community participation should be encouraged during such exercise.

5.1.3 PERSONAL PROTECTION

Indoor protection from sandflies bites can be obtained by the use of fine-mesh screens on windows and doors, insecticide-treated curtains, mosquito coils and burning of traditional leaves known to be sandfly repellants. Individual protective measures for outdoor areas include application of repellents, such as diethytoluamide to the skin or clothing to reduce human–vector contact. Wearing of appropriate clothing can minimize areas of exposed skin. Persons living in or travelling to VL endemic areas should wear long-sleeved shirts, long trousers, boots, and hats. Tucking in shirts, tucking trousers into socks, and wearing closed shoes instead of sandals may reduce risk.

5.1.4 ENVIRONMENTAL MANAGEMENT

Modification of the physical environment may have a dramatic effect on the relative abundance of sandflies and on levels of transmission. House structure improvement by sealing open spaces may greatly minimize the entry and resting sites for sandflies. The clearing of vegetation around villages and settlements may effectively reduce or eliminate vector–human contact and disease transmission. Similarly destruction of animal burrows and inactive termite hills near households may also reduce significantly the sandfly population. This can be achieved through community involvement in rural areas.

5.1.5 HEALTH EDUCATION

Health education is an essential component in any disease control programme. In VL control the main targets are the health personnel in the local health facility, community health workers and the local community at risk. The success of the leishmaniasis control programme in any endemic area will depend on the local community who should support and own the control activities for their long-term use and sustainability.

5.1.6 INTEGRATED VECTOR MANAGEMENT

In most situations, no single effective measure to reduce transmission is guaranteed. Integrated vector management (IVM) entails the utilization of all appropriate technological and management techniques to bring about an effective degree of vector suppression in a cost–effective manner. The complementary or synergistic effect of two or more methods always gives a better result. IVM involves the use of a range of locally appropriate and effective vector control interventions, often in combinations, to reduce or interrupt disease transmission. It is important that the selection of control methods is based on knowledge of local vector biology, disease transmission, ecological, environmental, safety and cost–benefit consideration. Integrated vector control has an advantage in that it can be implemented through community participation. Partnership and collaboration with various stakeholders and other vector-borne disease control programmes are key in implementing IVM.

Nevertheless, continuous research is needed to guide the planning and implementation of vector control activities, especially those aimed at IVM.

5.1.7 COMMUNITY AWARENESS AND MOBILIZATION

Communities living in endemic areas should be mobilized and sensitized on the local burden of leishmaniasis. Individuals should be able to recognize disease signs and symptoms as well as prevention and control measures. Communities should be made aware of accessibility and availability of health services for disease prevention, case management and treatment.

5.2 ROLE OF COMMUNITY HEALTH VOLUNTEERS IN PREVENTION AND CONTROL OF LEISHMANIASIS

Community health volunteers can participate in the control of leishmaniasis using the IVM strategy by educating community members to take the following steps::

1. To sleep under insecticide-treated mosquito nets to all communities living in endemic areas so as to prevent human–vector contact with the sandfly.
2. To encourage the use of long sleeved shirts/blouses and trousers when outside in the evening.
3. To support spraying of appropriate houses with insecticide to reduce the sandfly population.
4. To request community members to apply insect repellents on exposed parts of their body.

5. To advise all community members to avoid sandfly breeding and resting sites especially the boys when grazing their animals.
6. To request community members to repair cracks on walls of houses to minimize entry and resting sites for sandflies.
7. To request and support community members to clear vegetation around the homestead to reduce resting sites for sandflies.
8. To request and support community members to destroy inactive termite hills and animal burrows around homesteads to reduce breeding sites for sandflies.
9. To train community members to recognize the early symptoms and sign of the diseases and to seek health services as soon as possible (early diagnosis and treatment).

Before embarking on any control strategy as discussed in this section, it is important to discuss the implications with the community and the leaders. It is also crucial to have baseline data and to monitor and evaluate control interventions to later assess the extent to which they have to be maintained or modified.

5.2.1 ANIMAL RESERVOIRS

Currently, VL in Kenya is considered anthroponotic (human–human transmission) as no animal reservoir has been confirmed.

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ANNEXES

ANNEX 1:
STANDARD OPERATING PROCEDURES FOR SPLENIC ASPIRATION

The following requirements must be met before splenic aspiration can be done:

1. Splenomegaly must be present in a patient clinically suspected of visceral leishmaniasis (VL)
2. Haemoglobin of ≥ 5 gm/dl
3. Platelet count of ≥ 40 000/mm^3
4. White blood cell count of at least ≥ 1.0 x 10^3/mm^3
5. A prothrombin time difference of not more than 5 seconds compared with the normal control.
6. The patient should not have had a splenic aspiration within one week from the date of the current procedure.
7. No active bleeding.
8. No clinical jaundice (a possible marker of liver dysfunction).
9. No pregnancy.
10. Given the potential risk of this approach, the center on which spleen aspirate is performed should have access to blood supplies as well as blood transfusion and surgery facilities.

SPLENIC ASPIRATION PROCEDURE

- In patients less than 5 year old, splenic aspiration should be
  - performed only by a clinician fully experienced with the procedure
  - otherwise bone marrow is recommended from the iliac crest.
- A patient is made to lie in the supine position with hands on the sides.
- The edge of the spleen is outlined with a ball pen.
- The area of the spleen is cleaned by the clinician using spirit or any other antiseptic and a green towel (sterile, like the one used for bone marrow aspirates) placed over the splenic area.
- A 21 gauge needle attached to a 5 ml syringe is inserted just under the skin over the middle of the spleen, and as suction is applied (about 1 ml) the needle is rapidly inserted into the spleen and withdrawn, with the needle remaining in the spleen only a fraction of a second. Aim the needle cranially at an angle of 45° to the abdominal wall.
- The small amount of splenic tissue and blood in the needle is expressed into the culture medium (NNN) or Schneider's with 10% overlay of fetal calf serum) and onto slides for the smears.
- The splenic smears are stained with Giemsa or Leishman stain to demonstrate amastigotes.

NB: Bone marrow aspirate may be done but usually bone marrow smears contain fewer amastigotes and parasites are found in only 80–85% of cases.

The procedure should be handled under sterile conditions and therefore this must be observed by the attending clinician.

INSTRUCTIONS AFTER THE SPLENIC ASPIRATE

1. Patient to stay in bed strictly for 12 hours.
2. Observe blood pressure, pulse, temperature, and respiratory rate immediately after the aspiration then ½ hourly for 2 hours, 1 hourly for 4 hours then 4 hourly.
3. Suspect bleeding if there is falling blood pressure, rising pulse an normal or falling temperature; fix an IV line immediately of 5% dextrose alternating with normal saline. Take blood for grouping and cross matching immediately. Usually the majority of patients settle with IV fluids infusion within 12 hours.
4. Repeat aspiration should only be done after one week and not earlier.

ANNEX 2:
STANDARD OPERATING PROCEDURES FOR BONE MARROW ASPIRATION

1. Place the patient in a right or left lateral decubitus position with the back comfortably flexed and the top knee drawn toward the chest.
2. Locate the posterior iliac spine and mark with ink or thumb nail pressure.
3. Using sterile technique, prepare the skin with antiseptic and drape.
4. Using sterile syringe, apply/infiltrate the marked area with anaesthetic especially the periosteum.
5. Make a 3-mm skin incision with a scalpel blade over the marked area.
6. Hold the needle with the proximal end in the palm and the index finger against the shaft near the tip.
7. With the stylet locked in place, introduce the needle through the incision pointing toward the anterior superior iliac spine and bring it into contact with the posterior iliac spine.
8. Using gentle but firm pressure, advance the needle to bore through the iliac spine.
9. Rotate the needle in an alternating clock-wise and counter-clockwise motion. Entrance into the marrow cavity is generally detected by decreased resistance.
10. Remove the stylet, and check for presence/absence of marrow material. If not, proceed gently to bore until marrow is found at the tip of the stylet.
11. Using a 10cc syringe, locked into the proximal portion of the bone marrow needle aspirate for bone marrow material.
12. The material can then be expelled onto a clean slide. Presence of bone marrow material can be detected as granules on a glass slide.

ANNEX 3:
PREPARATION AND STAINING OF ASPIRATES

MATERIALS NEEDED

Slides rack, staining rack or staining trough, 100% methanol, buffered solution (pH 7.2), filtered stock of Giemsa stain and tap water (filtered water preferred).

FIXATION

- Place the slides horizontally on the slide rack and leave to air dry.
- Fix the slides by dipping them in 100% methanol for 1 minute. The methanol must be stored in a tightly closed bottle to prevent absorption of water.

STAINING

- Stain the slides with Giemsa stain 1:10 concentration; 1 ml of stock Giemsa stain to 9ml buffer solution pH 7.2. In the absence of buffer solution, filtered water can be used provided the pH is 7.2. The slides can either be stained in a staining trough or on a staining rack. When the stain concentration is 1:10 the staining time is 20 minutes.
- At the end of the staining, rinse the slides briefly with tap water or filtered water and place them in vertical position on a slides rack to dry.

READING SLIDES

- Examine at least 1000 microscope fields for amastigotes using x100 oil immersion lens. An artefact is more likely to be mistaken for a parasite if the microscopists are overloaded (more than 4 hours of microscopy per day), have poor light for the microscopes, or if dirty (unfiltered) Giemsa is used.

ANNEX 4:
GRADING OF SPLENIC/BONE MARROW ASPIRATE SMEARS FOR LEISHMANIA AMASTIGOTES

Grading of the number of ***Leishmania*** amastigotes in splenic or bone marrow aspirate smears.

Grade	Number of parasites	Microscopic Fields
0	0	1000
1+	1–10	1000
2+	1–10	100
3+	1–10	10
4+	1–10	1
5+	10–100	1
6+	> 100	1

PLATE A: Splenic aspirate smear showing ***Leishmania donovani*** amastigotes

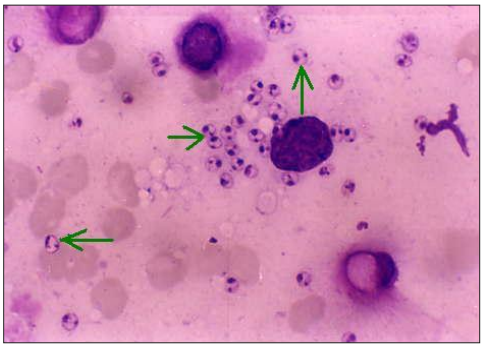
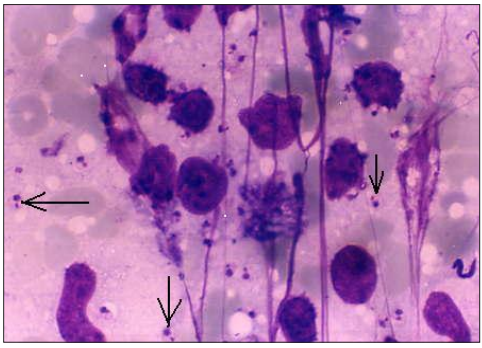


PLATE B: Splenic aspirate smear showing ***Leishmania donovani*** amastigotes.



ANNEX 5:
DIRECT AGGLUTINATION TEST (DAT)

Blood can be collected from the finger to blot on to filter paper (Whatman No. 3) or from the vein to obtain serum or plasma. Serial dilutions of the patient's blood sample eluted from filter paper, or directly from serum, are incubated with ***Leishmania*** antigen in V-shaped microtitre plates. The plates are incubated at room temperature for 8–12 hours and then read visually. If no anti-***Leishmania*** antibodies are present, the antigen will sediment to the bottom of the well and form a small sharp blue dot. If anti-***Leishmania*** antibodies are present in the blood, they will react with the antigen and the agglutination will be visible as a blue mat, a dot with frayed edges, or an enlarged dot.

By diluting the serum 2-fold in each well starting at 100x dilution, the titre (quantity of antibody) can be measured.

These procedures are for freeze-dried presentation of DAT.

COLLECTION OF BLOOD SPECIMEN FOR DAT

Collect capillary blood from the finger or the toe or heel in infants.

METHOD

REQUIREMENTS

- DAT request form
- DAT registration book
- Whatman No. 3 filter paper
- Sterile lancet
- Disinfectant e.g. iodine, alcohol, etc.
- Cotton wool
- Scissors
- Plastic bag
- Pen (ball point)
- Paper clips.

PROCEDURE

- Cut the circular filter paper into 8–16 segments depending on the size. Each segment can be used for one patient's test only.
- Draw a circle of approximately 1cm in radius on the segment of the filter paper.
- Record the patient's details in the laboratory registration book (Annex 10B).
- Write the DAT number on the patient's request form and also write this number on the segment.
- Soak a piece cotton wool in iodine or alcohol and disinfect finger, toe or heel thoroughly. Allow the skin to dry.
- Using the sterile lancet, prick the finger firmly so that blood flows freely without excessive squeezing.
- Wipe the first drop of blood with a plug of dry cotton wool. The first drop of blood is normally contaminated with dirt and tissue fluid.
- Squeeze the finger gently and collect the next drop of blood into the circle on the segment of the filter paper. Check the DAT number on the filter paper before collecting the blood.
- Make sure the blood soaks through both sides of the filter paper and fills the circle
- Allow the filter paper to dry.
- Apply pressure to the finger prick with dry cotton wool.
- Discard the used cotton wool into the waste bucket and the lancet into the sharps container.
- When dry, very dry, clip the filter paper with the request form and put into a plastic bag.
- Store in a fridge or cooler box until ready to send for testing or until ready for performing the test..

ELUTION OF SAMPLES – DAY 1

Requirements

- Laboratory register
- Microtitre plates (V-shaped)
- Sample (dry in filter paper)
- Micropipette to measure 125 µl
- Micropipette tips
- Normal saline
- Paper punch (5mm)
- Scissors
- Marker (permanent)
- Forceps
- Refrigerator

Procedure

- Write the number of the samples in order in the laboratory register. The list should be labelled to show which row of which microtitre plate corresponds to which sample. e.g. the list can be labelled A, B, C, D, E, F, G, and H in order.
- The samples need to be grouped by eight samples in each group or less. Group one is called Plate I, group two is called Plate II and so on.
- Label the microtitre plates to correspond with the laboratory register. i.e. Get out the microtitre plates and write the plate number on the plate itself. The first one is plate I.
- Using the paper punch, punch out a sample of filter-paper blood.
- Using the forceps, put the punched sample of filter-paper blood into the well of the first column of the microtitre plates corresponding to the position recorded on the patient laboratory register. Ensure that the punched filter paper blood is properly inserted in the well. e.g. the sample listed as A should go in the first row labelled A. The sample listed as B should go in the second row labelled B, and so on.
- Take the micropipette and adjust it to measure 125 µl, fix the pipette tip firmly and pipette 125 µl of normal saline. Add the 125 µl of normal saline to each well with a sample paper. Make sure that the punched filter paper blood is completely immersed in the saline.
- Cover the plates with another microtitre plate incubate in the fridge (at 4 °C) overnight for at least 8 hours.

DILUTION AND TITRATION – DAY 2

Requirements

- Measuring cylinder
- 50 ml container (plastic or glass bottle or conical tubes)
- Research (Repetitive) pipette 100–1000 µl, adjustable; brand Handy-Step or Eppendorf with volume display, combitip ejection.
- Multipipette 100–1000 µl Eppendorf or Handy-Step adjustable with volume display and tip ejection.
- Multichannel pipette, 8 channels, 5–50 µl Eppendorf, adjustable volume and tip ejection.
- Micropipette tips (yellow tips for 100 µl Multipette and the Multichannel pipette, blue tips for up to 1000 µl Research pipette, combitips standard 1.25 ml and combitips plus 2.5 ml)
- 5–10 ml syringe
- 2-mercaptoethanol (2-ME)
- Normal saline
- DAT antigen (freeze-dried antigen OR liquid antigen)
- Freeze-dried control sera

PREPARATION OF DILUENT

1. To be used with freeze-dried antigen (FDA)

- Measure 50 ml of normal saline and place in the container
- Adjust the multipipette to measure 390 µl, pipette 390 µl of 2-ME and add to the normal saline then mix gently.

RECONSTITUTION OF THE FREEZE-DRIED ANTIGEN (FDA)

1. To be used with freeze-dried antigen (FDA)

- Add 5 ml of fresh normal saline to the vial of the antigen.
- Mix gently by rotating and tilting the vial. Do not shake.
- Let it stand for about 10 minutes before use.

Freeze-dried antigen is kept at room temperature.

RECONSTITUTION OF THE FREEZE-DRIED CONTROL

Use a new set of control sera with every new batch of DAT antigen. Make sure all the freeze-dried powder is on the bottom of the vial. (The control kits made in Amsterdam contain 2 ml of serum each.)

Strictly follow the manufacturers' instructions on the procedure for reconstitution, especially the amount of normal saline or diluent to be added to the vial.

- Either add 100 ml or 200 ml of normal saline or diluent to the vial of the control sera depending on the manufacturers' instructions.
- Mix gently by rotating.
- Let it stand for at least 10 minutes before use.

DILUTION OF SAMPLES

FILTER PAPER BLOOD

Take the microtitre plates with the eluted blood out of the fridge and allow it to reach room temperature (serum dilution in column 1 is 1:50).

RECONSTITUTED CONTROL SERA

Fill the control well(s) in column 1 with 100 µl of reconstituted control serum. This is a 1:50 dilution.

- Adjust the pipette to measure 50 µl.
- Fill the wells from columns 2 to 12 with 50 µl diluent.
- Adjust the multichannel pipette to measure 50 µl.
- Place eight standard tips (yellow tips) on the multichannel pipette, making sure they are firmly fixed to avoid pipetting errors. If the multichannel pipette is not available, you may use a single channel pipette and pipette each row separately.

Mix the contents in column 1 by pipetting in and out at least five times. Avoid forming bubbles by expelling air prior to inserting the pipette tips into the wells and using a slow action.

Pipette 50 µl from column 1 and transfer to column 2. Continue this mixing and transferring until column 11. Discard the last 50 µl from column 11. Do not add to column 12. (Serial dilution). Column 12 is the negative control.

ADDING ANTIGEN

Gently rotate the antigen bottle to mix it. Do not shake the bottle as this may destroy the antigen.

Adjust the pipette to measure 50 µl and fit the pipette tips.

Add 50 µl antigen to every well except wells in column 1. It is advisable that, to avoid contamination, start with wells in column 12 (negative control) and add row by row, and also change the pipette tip every time the antigen is taken out of the bottle.

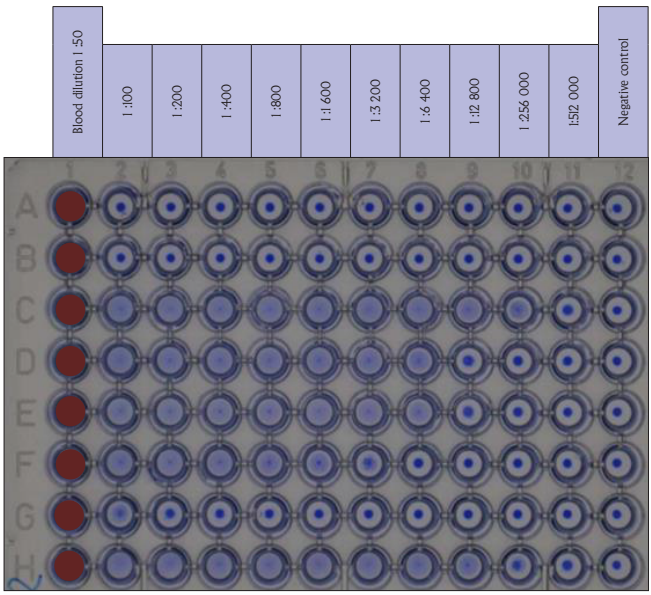
Rotate the plates gently, both clockwise and anticlockwise.

Cover the plates with a spare microtitre plate, leave them on a level surface at room temperature for about 12 to 18 hours.

Well	1	2	3	4	5	6	7	8	9	10	11	12
A	o	o	o	o	o	o	o	o	o	o	o	o
B	o	o	o	o	o	o	o	o	o	o	o	o
C	o	o	o	o	o	o	o	o	o	o	o	o
D	o	o	o	o	o	o	o	o	o	o	o	o
E	o	o	o	o	o	o	o	o	o	o	o	o
F	o	o	o	o	o	o	o	o	o	o	o	o
G	o	o	o	o	o	o	o	o	o	o	o	o
H	o	o	o	o	o	o	o	o	o	o	o	o
Dilution	Blood	1 :100	1 :200	1 :400	1 :800	1 :1600	1 :3200	1 :6400	1:12800	1:256000	1 :512000	Control

READING THE DAT RESULTS – DAY 3

- Put the plates against a white background.
- Estimate the titre by comparing the dots in column 12 (negative control) to those of the samples in the other columns.
- The titre is expressed as the last dilution that shows a difference compared to the negative control. A dark blue dot indicates that the result is negative and no reaction took place whereas a hazy blue mat or cloudy appearance indicates that a reaction took place. The highest titre will be the last dilution that still shows a hazy blue mat or cloud.
- Record the result in the laboratory book by titre and meaning. For example record well 9, 12 800 positive. If you are not sure of the meaning (positive, negative or borderline) simply record the titre. Currently the positive titre is well 7 or 3200 with the FD antigen.
- Report the results in the patients' request form.



Photograph of plate for training purposes. Serum dilution. A,l:100; B, ,l:100; C, .l:51,200; D, 1:25,600; E, 1:25,600; F, 1:6,400; G, 1:800; H, 1:51,200. Modified from doi:10.1371/journal.pntd.0001946.g003

INTERPRETATION OF DAT RESULTS

DAT positive patients (patients with titres of 1:3200 and above) are sent for admission. No need for further parasitological investigations to be carried out on ***Leishmania*** parasites.

DAT negative patients (patients with titres 1:100 or 1:200) are evaluated for other diseases and told to return for repeat DAT after 2–3 weeks depending on the clinical status but not less than a week, if they still feel sick. By then their titre might have risen if they have VL.

DAT borderline patients (patients with titres of 1:400, 1:800 and 1:1600) are either evaluated for other diseases or told to return for repeat DAT after 1–2 weeks, or they are admitted for parasitological investigations.

If the results of two successive splenic or bone marrow aspirates are all negative, they are treated for other diseases.

NB. Due to the batch to batch variations of DAT antigens, it is necessary to make adjustments to the cut-off value. VL control programmes should ensure that DAT antigen of acceptable quality is procured.

IMPORTANT REMINDERS ABOUT THE DAT

The DAT does not distinguish between exposure, previously treated cases of VL and active VL as the antibodies remain in the blood for a number of years (up to 10 or more years) after successful treatment. Therefore, DAT is not useful for diagnosing relapses and is substituted by parasitological test like the splenic aspirates.

ANNEX 6A:

DIAGRAM ILLUSTRATING THE STEPS FOR PERFORMING THE RK39 RAPID DIAGNOSTIC TEST

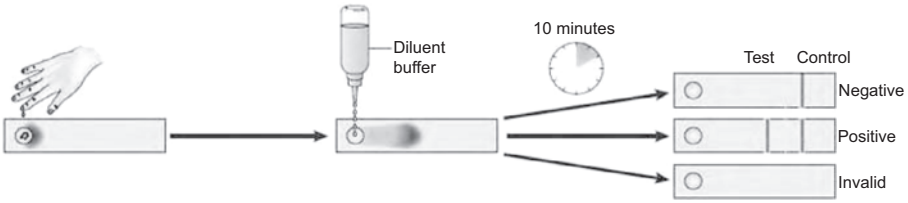


Image adapted from WHO Technical Report series 949

ANNEX 6B:
INTERPRETATION OF RK39 RAPID DIAGNOSTIC TEST RESULTS

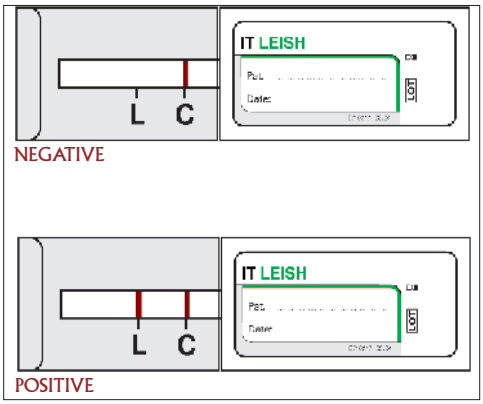


Image from: http://www.bio-rad.com/webroot/web/pdf/cdg/literature/16490_B-IT_LEISH-EN.pdf

TEST READING

POSITIVE RESULT

The test is positive if both the control and test lines appear. It implies that the sample tested has antibodies against **recombinant K39 antigen** of ***Leishmania***. Even a faint line should be considered as a positive result.

NEGATIVE RESULT

The test is considered negative if only the control line appears. **It means there are no antibodies against recombinant K39 antigen of *Leishmania* present in the patient's sample or the level of antibodies is not being detected by the test.**

INVALID RESULT

The test is considered invalid if no control line appears whether the test line appears or not. In such situation, retesting a fresh patient sample with a new strip is recommended.

HOW IS THE TEST INTERPRETED?

The rK39 test stays positive in VL patients for a long time after treatment (past VL), and the dipstick can also be positive in healthy persons from endemic areas who are infected with ***Leishmania*** but not sick. Therefore the test cannot be used as a standalone test. The test can only be interpreted meaningfully in people who are clinically suspect for VL, having a first-time episode.

In some cases the patient may actually suffer from VL but the rapid test is not detecting the antibodies. In that case, it is mandatory to perform another serological (e.g. DAT) or parasitological test.

TO WHOM THE RK39 DIPSTICK SHOULD BE APPLIED

- Persons from endemic areas who are clinically suspect for VL: **fever for more than 2 weeks and enlarged spleen or wasting, and malaria ruled out**.

NB. The rapid diagnostic test should be used to confirm kala-azar when the patient's symptoms match the case definition – not to rule it out.

TO WHOM THE RK39 DIPSTICK SHOULD NOT BE APPLIED

- Persons with past VL history.
- HIV–VL coinfected patients can be tested, but it should be kept in mind that a negative result does not exclude a VL episode.

ANNEX 6C:
SENSITIVITY AND SPECIFICITY OF SOME RAPID DIAGNOSTIC TESTS IN EAST AFRICA

Product	Manufacturer	Sensitivity (95% CI) n=250	Specificity (95% CI) n=250
Crystal KA	Span diagnostic Ltd	36.8 % (31.1–42.9%)	98.0% (95.4–99.1%)
Bio-Rad – IT LEISH	Bio. Rad Lab.	87.2% (82.5–90.8%)	96.4% (93.3–98.1%)
Kala azar Detect	InBios International Inc	67.6% (61.6–73.1%)	90.8% (86.6–93.8%)
Signal – KA	Span diagnostic Ltd	73.2% (67.4–78.3%)	96.4% (93.3–98.1%)

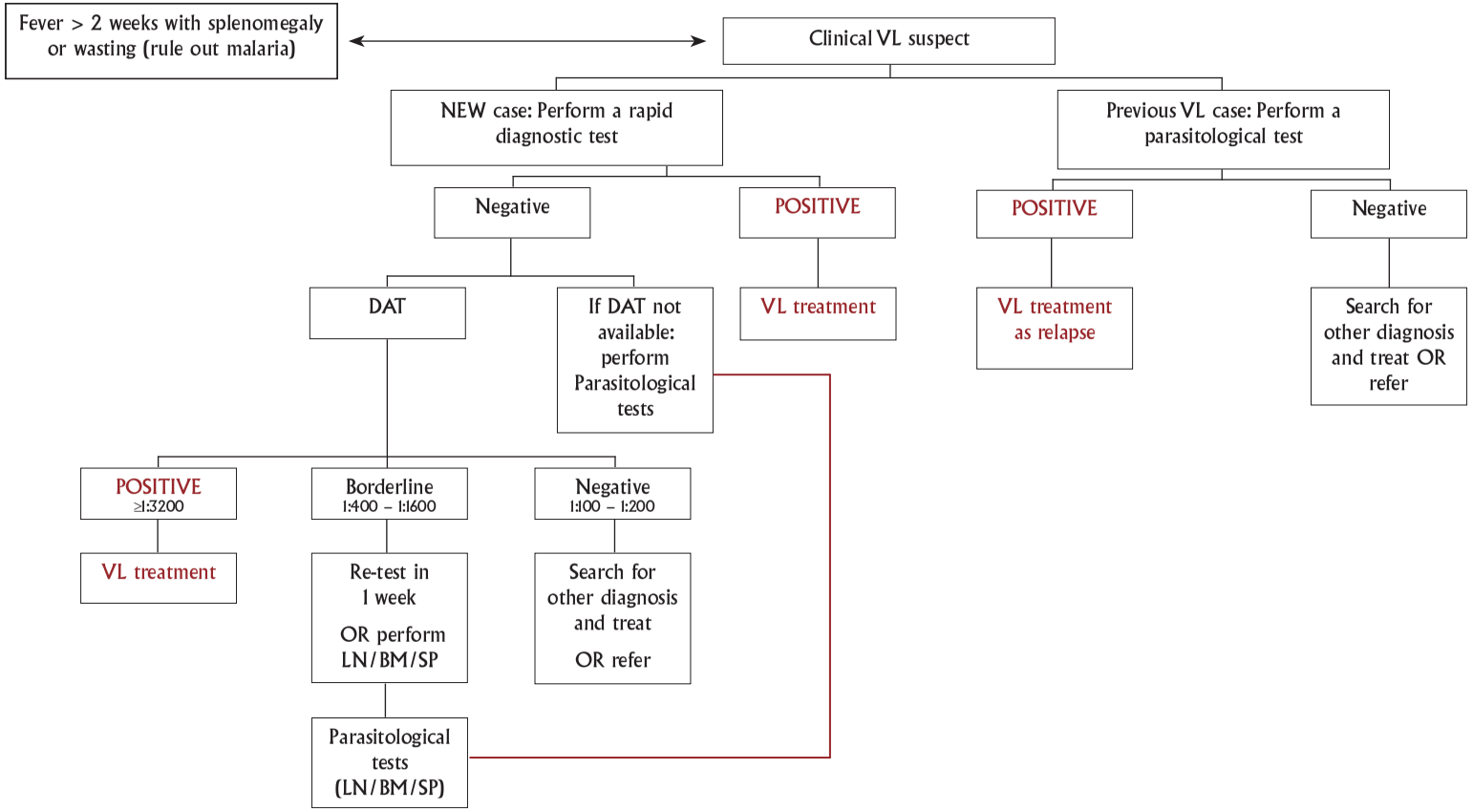
Ref: Diagnostic Evaluation series No. 4: Visceral leishmaniasis rapid diagnostic test performance, page 21

Note: Bio-Rad IT LESH: Specificity – 96.4% Sensitivity: 87.2%

Inbios: Specificity – 90.8% Sensitivity: 67.6%

The Leishmanaiasis Control programme, Ministry of Health, has recommended the use of Bio-Rad IT LEISH as the best rapid diagnostic test kit for kala-azar in the country as it has a higher specificity and sensitivity compared to other test kits.

ANNEX 7:
VISCERAL LEISHMANIASIS DIAGNOSTIC ALGORITHM



LN: Lymph node; BM: Bone Marrow; SP: Spleen

ANNEX 8A:
SUMMARY OF TREATMENT REGIMENS FOR VISCERAL LEISHMANIASIS

	Drug	Dosage	Route of administration	Number of days
First-line treatment	1) Combination SSG + Paromomycin	20 mg/kg per day + [11 mg base] 15 mg/kg body weight per day	Intramuscularly /intravenously Intramuscularly	17
	2) Sodium stibogluconate (SSG), or 3) Meglumine antimoniate	20 mg/kg per day 20 mg/kg per day	Intramuscularly /intravenously Intramuscularly /intravenously	30 30
Second-line treatment **(AmBisome is the first option in certain groups, see section 3.3.2)**	1) Liposomal amphotericin B (AmBisome)	3–5 mg/kg per daily dose (total dose 30 mg/kg)	Infusion	6–10 days
	2) Amphotericin B deoxycholate	0.75–1 mg/kg per day (daily or alternate days) for 15–20 doses	Infusion	Number of days to complete 15–20 doses
Post-kala-azar dermal leishmaniasis (PKDL)				
	1) Sodium stibogluconate (SSG) or 2) Meglumine antimoniate	20 mg/kg per day 20 mg/kg per day	Intramuscularly /intravenously Intramuscularly /intravenously	30–60 days or up to healing 30–60 days
	Amphotericin B (Fungizone, Squibb)	0.75–1 mg/kg per day (daily or alternate days) for 15–20 doses)	Infusion	20 days

ANNEX 8B:
DOSAGE, ADMINISTRATION AND PRECAUTIONS FOR THE USE OF SODIUM STIBOGLUCONATE (SSG)

PRESENTATION

Solution for injection, vials 30 ml.

Contains 33% (= 9.9g/30ml) SSG corresponding to 10% Sb^{5+} which is 100mg Sb^{5+}/1ml or 3000 mg Sb^{5+}/30ml.

TABLE OF SSG VOLUME PER BODY WEIGHT (20 MG SB^{5+}/KG/DAY)

Weight in kg	SSG dose in ml
1	2
1	2
2	2
3	2
4	2
5	2
6	2
7	2
8	2
9	2
10	2
11	2.2
12	2.4
13	2.6
14	2.8
15	3
16	3.2
17	3.4
18	3.6
19	3.8
20	4
21	4.2
22	4.4
23	4.6
24	4.8
25	5
27	5.4
28	5.6
29	5.8
30	6
31	6.2
32	6.4
33	6.6
34	6.8
35	7
36	7.2
37	7.4

Weight in kg	SSG dose in ml
38	7.6
39	7.8
40	8
41	8.2
42	8.4
43	8.6
44	8.8
45	9
46	9.2
47	9.4
48	9.6
49	9.8
50	10
51	10.2
52	10.4
53	10.6
54	10.8
55	11
56	11.2
57	11.4
58	11.6
59	11.8
60	12
61	12.2
62	12.4
63	12.6
64	12.8
65	13
66	13.2
67	13.4
68	13.6
69	13.8
70	14
71	14.2
72	14.4
73	14.6
74	14.8
75	15

Contd.

There are no absolute contraindications to its use – but under ideal circumstances patients with underlying renal, hepatic or cardiac disease should be well monitored. Elderly patients may have age-related decreased kidney function so may be at risk of increased toxicity.

TOXICITY AND SIDE-EFFECTS

PREVENTION OF SSG TOXICITY: The most important way to prevent SSG accumulation between doses is to ensure adequate hydration. SSG is cleared in the urine. Patients should repeatedly be told to drink enough fluids so they pass urine at least four times a day. Babies should pass urine every hour or so while awake.

MINOR SIDE-EFFECTS: Symptoms: nausea, anorexia, arthralgias, myalagias, injection site pain, fatigue, and abdominal pain.

Laboratory toxicity: elevated amylase (biochemical pancreatitis), elevated liver enzymes (biochemical hepatitis), leukopenia/anaemia/thrombocytopenia. Occasionally, renal failure occurs.

Electrocardiograph changes (ST segment and T wave).

Nausea and anorexia are substantial problems where patients are already malnourished and dehydrated. The nausea and anorexia subside somewhat in the later weeks of treatment.

SERIOUS TOXICITY: Severe vomiting and abdominal pain (pancreatitis?): Vomiting is relatively common and should be treated aggressively. Treat with anti-emetic medications, and push sips of fluids. When anti-emetic treatment fails the SSG should be withheld for 2 to 5 days as needed.

If vomiting is associated with other risk factors especially extremes of age, low haemoglobin, severe malnutrition, withholding of SSG is even more imperative.

In hospitals with chemistry available, patients vomiting from known pancreatitis should also have SSG withheld. Note that when the pancreatic enzymes return to normal and the patient is re-challenged with SSG, the amylase may remain normal.

Electrocardiograph abnormalities (QT prolongation), and sudden death (rare): Sudden death occurs rarely; possible explanations are cardiac arrhythmias or intra-cerebral bleeds. ECG changes are common. Sudden death is associated with high doses of SSG (over 30 mg/kg per day). However, cardiotoxicity and sudden deaths are not seen in PKDL patients, so toxicity may be a combination of SSG and a weak individual.

OTHER POINTS OF INTEREST: Blindness is NOT a toxicity of SSG – if a patient complains of loss of vision after treatment then it could be iritis (which can occur in isolation or with PKDL) and this iritis requires further treatment with SSG. Apparently retinal haemorrhages occur with KA (not associated with SSG) as well.

- Injection abscesses from the IM route have been uncommon – but when present need aggressive treatment (antibiotics, drainage of pus).
- Neurological toxicity: not reported elsewhere as a toxic effect of SSG. Before or during treatment some patients have ataxia and severe tremors with or without a headache. Neuropathy, psychosis and epilepsy are other occasional neurological features. It is unclear whether any of these are an effect of SSG in patients with KA (it never occurs in patients undergoing treatment for PKDL), if it is KA itself, or if it represents bleeding into areas of the brain. The ataxia, tremor and neuropathy may all remain for months after cure.

ANNEX 8C:
DOSAGE, ADMINISTRATION AND PRECAUTIONS FOR MEGLUMINE ANTIMONIATE

DOSAGE

Meglumine antimoniate and sodium stibogluconate are the pentavalent antimony (Sb^{5+}) compounds used to treat leishmaniasis;

Meglumine antimoniate is commercialized by Sanofi as a solution for injection in 5 ml ampoules (Glucantime) containing 405 mg of pentavalent antimony (Sb^{5+}), which is 81 mg of Sb^{5+}/1 ml. The dose of meglumine antimoniate is based on the amount of pentavalent antimony; the presentation contains and is 20 mg/kg per day.

Table of meglumine antimoniate volume of injection to give 20 mg/kg per day.

ROUTE OF ADMINISTRATION

Intravenous (IV) or intramuscular (IM)

Sb^{5+} pharmacokinetics are almost identical by either IM or IV routes. The choice of IV or IM depends on the setting. IM administration is most logical in the bush. The medicine may be given by deep intramuscular injection. Consider also the high volume that should be injected (if the volume of injection exceeds 10 ml, it should be divided in two doses: one in each buttock or thigh). During a polio outbreak consider giving all the children less than 3 years of age IV injections (IM injections increase the rate of paralytic disease in those incubating with polio). IV is much less painful. It should be given slowly, over 5–10 minutes or longer, using small butterfly style needles. Another possibility is to dilute the medicine in 5% glucose solution, 500 ml in adults and administer it slowly (30 min–1hour). In children weighing between 10–25 kg body weight use 100 ml, and if less than 10 kg use 50 ml.

CONTRAINDICATIONS

Severe cardiac, liver and kidney disorders and breastfeeding.

PRECAUTIONS

The risk of serious, even fatal, toxicity of pentavalent antimonials is increased in patients who concomitantly present with: cardiac disease, in particular arrhythmia; renal failure, liver disease, severe malnutrition/severely impaired general condition; advanced HIV infection; pregnancy. If one of these conditions is present, provide a protein-rich diet and good hydration throughout treatment. If possible, correct iron and other nutritional deficiencies; renal and hepatic impairment; monitor cardiac, renal and hepatic function; treat concomitant infection (for example pneumonia), and check the patient regularly (ECG and renal, liver, pancreatic function). And if possible an alternative medicine should be used.

The minimum dose is 2 ml (162 mg) for children weighing less than 10 kg.

TABLE OF DOSAGE FOR MEGLUMINE ANTIMONIATE

Weight in kg	Meglumine antimoniate dose in ml
< 10	2
10	2.6
11	2.8
12	3.0
13	3.2
14	3.4
15	3.8
16	4.0
17	4.2
18	4.4
19	4.8
20	5.0
21	5.2
22	5.4
23	5.8
24	6.0
25	6.2
26	6.4
27	6.6
28	7.0
29	7.2
30	7.4
31	7.6
32	8.0
33	8.2
34	8.4
35	8.6
36	9.0
37	9.2
38	9.4
39	9.6
40	9.8
41	10.2
42	10.4
43	10.6
44	10.8
45	11.2
46	11.4
47	11.6
48	11.8
49	12.2
50	12.4
51	12.6
52	12.8
53	13.0
54	13.4
55	13.6
56	13.8
57	14.0
58	14.4
59	14.6
60	14.8
61	15.0
62	15.4
63	15.6
64	15.8
65	16.0
66	16.2
67	16.6
68	16.8
69	17.0
70	17.2
71	17.6
72	17.8
73	18.0
74	18.2
75	18.6
76	18.8
77	19.0
78	19.4
79	19.6
80	19.8
>80	20
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Contd.

ANNEX 8D:
DOSAGE, ADMINISTRATION AND PRECAUTIONS FOR THE USE OF AMBISOME

DURATION OF TREATMENT 10 DAYS

IMPORTANT NOTES

1. AMBISOME RECONSTITUTION: Read AmBisome reconstitution instructions carefully. Aseptic techniques must be strictly observed. There is no preservative or bacteriostatic agent in AmBisome. Add 12 ml water for injection to each AmBisome vial, immediately after the addition of water of injection, shake the vials vigorously for 30 seconds to completely disperse the AmBisome. Visually inspect the vial for particulate matter and continue shaking until complete dispersion is obtained.

2. INTRAVENOUS INFUSION 5% DEXTROSE PREPARATION: Further dilute the reconstituted AmBisome in 5% dextrose water. The volume of 5% dextrose infusion solution given over 1–2 hours (i.e. reconstituted AmBisome: 5% dextrose to be in the range 1:1 to 1:19) OR final concentration of 1 to 2 mg/mL prior to administration. Lower concentrations (0.2 to 0.5 mg/mL) may be appropriate for infants and small children to provide sufficient volume for infusion. Range 0.2–2.0mg/ml = ratio of 1:1 to 1:19.

3. PRECAUTIONS: AmBisome is not compatible with normal saline and must not be mixed with other drugs or electrolytes. Flush existing lines with 5% dextrose water prior to AmBisome infusion. If this is not feasible use a separate line.

Patient weight **in kg**	Dose for patient mg/day (calculated at 3 mg/kg/day) **in mg**	Volume of reconstituted AmBisome (4 mg/ml) to be withdrawn (use water for injection to reconstitute AmBisome) **ml**	Volume of 5% dextrose infusion solution given over 1–2 hours **in ml**
4	12	3.0	50
5	15	3.8	50
6	18	4.5	50
7	21	5.3	50
8	24	6.0	100
9	27	6.8	100
10	30	7.5	100
11	33	8.3	100
12	36	9.0	100
13	39	9.8	100

Patient weight **in kg**	Dose for patient mg/day (calculated at 3 mg/kg/day) **in mg**	Volume of reconstituted AmBisome (4 mg/ml) to be withdrawn (use water for injection to reconstitute AmBisome) **ml**	Volume of 5% dextrose infusion solution given over 1–2 hours **in ml**
14	42	10.5	100
15	45	11.3	100
16	48	12.0	100
17	51	12.8	100
18	54	13.5	100
19	57	14.3	100
20	60	15.0	250
21	63	15.8	250
22	66	16.5	250
23	69	17.3	250
24	72	18.0	250
25	75	18.8	250
26	78	19.5	250
27	81	20.3	250
28	84	21.0	250
29	87	21.8	250
30	90	22.5	250
31	93	23.3	250
32	96	24.0	250
33	99	24.8	250
34	102	25.5	250
35	105	26.3	250
36	108	27.0	250
37	111	27.8	250
38	114	28.5	250

Patient weight **in kg**	Dose for patient mg/day (calculated at 3 mg/kg/day) **in mg**	Volume of reconstituted AmBisome (4 mg/ml) to be withdrawn (use water for injection to reconstitute AmBisome) **ml**	Volume of 5% dextrose infusion solution given over 1–2 hours **in ml**
39	117	29.3	250
40	120	30.0	500
41	123	30.8	500
42	126	31.5	500
43	129	32.3	500
44	132	33.0	500
45	135	33.8	500
46	138	34.5	500
47	141	35.3	500
48	144	36.0	500
49	147	36.8	500
50	150	37.5	500
51	153	38.3	500
52	156	39.0	500
53	159	39.8	500
54	162	40.5	500
55	165	41.3	500
56	168	42.0	500
57	171	42.8	500
58	174	43.5	500
59	177	44.3	500
60	180	45.0	500
61	183	45.8	500
62	186	46.5	500
63	189	47.3	500
64	192	48.0	500

Patient weight **in kg**	Dose for patient mg/day (calculated at 3 mg/kg/day) **in mg**	Volume of reconstituted AmBisome (4 mg/ml) to be withdrawn (use water for injection to reconstitute AmBisome) **ml**	Volume of 5% dextrose infusion solution given over 1–2 hours **in ml**
65	195	48.8	500
66	198	49.5	500
67	201	50.3	500
68	204	51.0	500
69	207	51.8	500
70	210	52.5	500
71	213	53.3	500
72	216	54.0	500
73	219	54.8	500
74	222	55.5	500
75	225	56.3	500
76	228	57.0	500
77	231	57.8	500
78	234	58.5	500
79	237	59.3	500
80	240	60.0	500
81	243	60.8	500
82	246	61.5	500
83	249	62.3	500
84	252	63.0	500
85	255	63.8	500
86	258	64.5	500
87	261	65.3	500
88	264	66.0	500
89	267	66.8	500
90	270	67.5	500

ANNEX 9:
DOSAGE, ADMINISTRATION AND PRECAUTIONS FOR THE USE OF PAROMOMYCIN

PAROMOMYCIN INJECTION

Each 2 ml ampoule contains approximately 1 gram paromomycin sulfate equivalent to 750 mg paromomycin (375 mg/ml).

USES

Paromomycin injection is indicated for the treatment of visceral leishmaniasis.

Paromomycin injection has not been studied in patients with post-kala-azar dermal leishmaniasis (PKDL).

DOSAGE

In East Africa region only, paromomycin is administered IM, once a day, for 17 consecutive days in combination with sodium stibogluconate 20 mg/kg per day. The recommended IM dosage for patients (5 kg and above) with normal renal function is 11 mg/kg per day paromomycin (equivalent to approximately 15 mg/kg per day paromomycin sulfate).

Daily doses in ml according to body weight are shown in the table (next page).

PREGNANCY AND BREASTFEEDING

Do not use during pregnancy. Paromomycin crosses the placenta and can cause renal and auditory damage in the unborn child. Paromomycin is excreted in breast milk and adverse effects in the breastfed infant cannot be excluded.

CONTRAINDICATIONS AND WARNINGS

Do not use in patients with hypersensitivity to paromomycin or to other aminoglycoside antibiotics. Discontinue use if an allergic reaction occurs. Paromomycin is contraindicated in patients with renal insufficiency. In cases where paromomycin or the combination of sodium stibogluconate and paromomycin do not lead to a VL cure at or before 6 months, do not repeat therapy. Instead, switch to another antileishmanial drug.

Paromomycin as aminoglycoside has a potential for causing ototoxicity and nephrotoxicity. Neuromuscular blockade and respiratory paralysis have been reported following high doses of aminoglycosides.

Concurrent use of other nephrotoxic drugs, including other aminoglycosides, vancomycin, some of the cephalosporins, cyclosporin, and cisplatin, or potentially ototoxic drugs such as furosemide, may increase the risk of aminoglycoside toxicity. Other factors that may increase patient risk of toxicity are dehydration and advanced age.

WEIGHT IN KG	PM DOSE IN ML
1	--
2	--
3	--
4	--
5	0.2
6	0.2
7	0.3
8	0.3
9	0.4
10	0.4
11	0.4
12	0.5
13	0.5
14	0.6
15	0.6
16	0.6
17	0.7
18	0.7
19	0.8
20	0.8
21	0.8
22	0.9
23	0.9
24	1.0
25	1.0
26	1.0
27	1.1
28	1.1
29	1.2
30	1.2
31	1.2
32	1.3
33	1.3
34	1.4
35	1.4
36	1.4
37	1.5
38	1.5
39	1.6
40	1.6
41	1.6
42	1.7
43	1.7
44	1.8
45	1.8
46	1.8
47	1.9
48	1.9
49	2.0
50	2.0
51	2.0
52	2.1
53	2.1
54	2.2
55	2.2
56	2.2
57	2.3
58	2.3
59	2.4
60	2.4
61	2.4
62	2.5
63	2.5
64	2.6
65	2.6
66	2.6
67	2.7
68	2.7
69	2.8
70	2.8
71	2.8
72	2.9
73	2.9
74	3.0
75	3.0

Contd.

SIDE-EFFECTS

The most commonly reported adverse drug reactions are injection site pain, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) elevations, pyrexia, and an abnormal audiogram. These effects are usually mild to moderate and transient or reversible at the end of treatment. There were no age or gender differences noted in the incidence of adverse events that occurred in patients treated with paromomycin.

In a clinical trial of 500 patients treated at the recommended dosage of paromomycin monotherapy, the following undesirable effects were observed:

- Very common side-effects ≥ 10% of patients: injection site pain.
- Common side-effects 1–10% of patients: AST and ALT elevation, pyrexia, abnormal audiogram.
- Uncommon side-effects 0.1–1% of patients included: vomiting, alkaline phosphatase elevation, blood bilirubin elevation, injection site swelling, ototoxicity, abscess, conductive deafness, proteinuria.
- Nephrotoxicity was not observed in any subjects at the recommended 11 mg/kg per day dose and duration for treating VL.
- Ototoxicity was mild and reversible at the recommended 11 mg/kg per day dose and duration for treating VL.
- In a clinical trial of 381 patients treated at the recommended dosage of paromomycin in combination with sodium stibogluconate, the following undesirable effects were observed:
- Very common side-effects ≥ 10% of patients: injection site pain, AST elevation.
- Common side-effects 1–10% of patients: ALT elevation, abdominal pain, amylase elevation, creatinine elevation, epistaxis, abnormal audiogram, alkaline phosphatase elevation, vomiting, thrombocythaemia, gastroenteritis.
- Uncommon side-effects 0.1–1% of patients included: thrombocytopenia, constipation, diarrhoea, dyspepsia, gastritis, nausea, toothache, injection site swelling, pyrexia, cellulitis, gastroenteritis, hookworm, otitis media, pharymgitis, pneumonia, urinary tract infections, post-kala-azar dermal leishmaniasis, blood urea increased, electrocardiogram changes, total protein elevation, back pain, headache, asthma, cough, rash.
- Nephrotoxicity was observed in 0.5% of subjects at the recommended 11 mg/kg per day dose and duration for treating VL when combined with sodium stibogluconate.
- Ototoxicity was mild and reversible. Mild changes in audiogram were seen in 1.2% patients at end of treatment and remained in 0.4% of patients at 6 months after treatment completion at the recommended 11 mg/kg per day dose and duration for treating VL when combined with sodium stibogluconate.

OVER DOSAGE

Symptoms: Like other aminoglycosides: dizziness, deafness, renal failure.

Treatment: Initial intervention would be to establish an airway and ensure oxygenation and ventilation. Resuscitative measures should be initiated promptly if respiratory paralysis occurs. If neuromuscular blockade occurs, it may be reversed by the IV administration of calcium salts, but mechanical assistance may be necessary. Patients who have received an overdose of aminoglycosides who have normal renal function should be adequately hydrated to maintain a urine output of 3 to 5 ml/kg per hour. Patients whose renal function is abnormal may require more aggressive therapy; haemodialysis may be beneficial.

STORAGE:

Store below 30 °C. Protect from light. Do not freeze.

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ANNEX 10A:
VISCERAL LEISHMANIASIS CASE REPORTING FORM

COUNTY/SUB-COUNTY : _____ CONSTITUENT/DIVISION:_____
CASE NUMBER: _____ DATE RECEIVED: _____

NAME OF PATIENT: _____ PARENT: _____

LOCATION: _____ VILLAGE: _____ NEAREST HEALTH FACILITY:_____

SEX: _____ DATE OF BIRTH: _____/_____/_____ AGE: _____

IF IT IS A WOMAN, IS SHE PREGNANT?: _____

A) HISTORY OF THE DISEASE

1) Date of onset of symptoms:_____/_____/_____

2) Name of the village/sub-county/county where the patient got ill (probable place of infection):_____

3) Did the patient visit a traditional healer before visiting a health facility?_____

4) General condition of patient: Fever? _____ If yes, take temperature_____

5) Abdominal pain:_____ If yes, do spleen and liver palpation

6) Are the organs enlarged? Spleen (cm): _____ , Liver (cm):_____ If yes, perform laboratory diagnostic test

7) Presence of concomitant infection(s)_____ if yes, name them 1)_____ 2)_____

8) Any VL–HIV coinfection observed? HIV positive negative not done. If yes, consult HIV section

B) LABORATORY EXAMINATION

9) Rapid diagnostic test (rK39): Result positive_____ negative_____ If negative, use DAT method; rK39 result inconclusive_____

DAT: Result positive (titre):_____ Result borderline (titre) _____ Result negative (titre)_____ if negative, consult the Clinician and/or perform parasitological test; DAT not done

10) Splenic/bone marrow aspirate: Result positive _____ negative _____ If negative, consult the Clinician; aspirate not done _____

C) HOSPITALIZATION

11) Was the patient admitted to hospital?:_____ Date of admission:_____

12) Ward record number: _____

13) Treatment given:
- Combination (SSG + Paramomycin) Dosage: _____
- Pentostam (SSG) Dosage: _____
- Glucantime Dosage: _____
- Amphotericin B Dosage: _____

14) If it is a pregnant woman treat using second-line drug: Amphotericin B: Dosage_____

15) Number of treatment days: _____

16) Was treatment completed?_____ If no, give reasons_____

17) TREATMENT OUTCOME

a) Initial cure_____ if no, consider using the second line drug
b) Probable non-response
c) Confirmed non-response
d) Death
e) Default
f) Lost to initial follow-up

18) Was there any side-effects of drug used reported?_____ if yes, name them 1) _____ 2)_____ 3)_____

19) Any other condition treated:_____ If yes, name the disease 1) _____ 2)_____

D) FOLLOW UP EXAMINATION

Date of follow up examination: _____/_____/_____

i) Final (definitive) cure
ii) Relapse
iii) Death
iv) Loss to follow-up

20) Any signs and symptom of PKDL: _____ If yes, carry out skin snip microscopic examination: _____ If positive, treat using the same drugs but for a longer period _____

FINAL RECOMMENDATION

_____
_____.

ANNEX 10B:
VISCERAL LEISHMANIASIS LABORATORY REGISTER BOOK

VISCERAL LEISHMANIASIS LABORATORY REGISTER BOOK

COUNTY_____ SUB-COUNTY_____ HEALTH FACILITY: _____ MONTH: _____ YEAR: _____

No.	Date	Name	Age	Sex	Location	Village	Method of diagnosis			Remarks
							rK39	DAT	SA/BM	
							ND	1:3200 (+)	ND	
							(+)	ND	ND	
							(-)	1:800 (bl)	(-)	BM
							Inc	ND	(+)	SA
							(-)	1:200 (-)	(-)	BM, Malaria (+)

NB. SA = splenic aspirate; BM: bone marrow aspirate; ND: not done; (+): positive; (-): Negative: Inc: Inconclusive; (bl): border line

ANNEX 10C:
VISCERAL LEISHMANIASIS TREATMENT SUMMARY REPORTING FORM

COUNTY_____ SUB-COUNTY_____ HEALTH FACILITY: _____ MONTH: _____ YEAR: _____

SEXE	JAN	FEB	MAR	APR	MAY	JUN	JUL	AUG	SEP	OCT	NOV	DEC	TOTAL
Total Number treated													
Total primary VL (PVL) cases													
No. of PVL discharged (initial cure)													
No. of PVL non-responders													
No. of PVL defaulters													
No. of PVL deaths													
No. of relapses cases													
No. of relapses discharged (initial cure)													
No. of relapses defaulters													
No. of relapses deaths													
Total PKDL cases													
No. of PKDL discharged (initial cure)													
No. of PKDL defaulters													
No. of PKDL deaths													
No. of HIV/VL (kala-azar) coinfection													
Discharged (initial cure)													
Defaulters													
Deaths													

ANNEX 10D:
DEMOGRAPHIC CHARACTERISTICS OF POSITIVE KALA-AZAR CASES

COUNTY_____ SUB-COUNTY_____ HEALTH FACILITY: _____ DATE: _____

	JAN	FEB	MAR	APR	MAY	JUN	JUL	AUG	SEP	OCT	NOV	DEC	TOTAL
Sexe													
Male													
Female													
Age group													
< 5 yrs													
5–14 yrs													
15 yrs and above													
Total													

ANNEX II:
KALA-AZAR PATIENT DISCHARGE FORM

NAME: _____ WARD NO_____ ADMISSION DATE_____

AGE: _____ SEX: ___M / F___

CONSTITUENT: _____

LOCATION: _____

VILLAGE _____

DISEASES: PRIMARY KALA-AZAR _____ RELAPSE _____ PKDL _____

TREATMENT GIVEN:
- COMBINATION (SSG + PAROMOMYCIN) _____
- SSG (ALONE) _____
- GLUCANTIME _____
- AMBISOME _____
- OTHER MEDICINES (SPECIFY) _____

DISCHARGE DATE: _____

NEAREST HEALTH FACILITY: _____

DATE OF FOLLOW UP EXAMINATION: _____

WEIGHT: _____ SPLEEN (CM): _____

TOC: POSITIVE NEGATIVE NOT DONE

ANNEX 12:
MEDICINES AND REAGENTS USE FORM FOR KALA-AZAR TREATMENT

COUNTY_____ SUB-COUNTY_____ HEALTH FACILITY: _____ YEAR: _____

	JAN	FEB	MAR	APR	MAY	JUN	JUL	AUG	SEP	OCT	NOV	DEC	TOTAL
SSG													
Expiry dates													
No. of vials at beginning of month													
No. of vials at end of month													
No. of vials consumed													
Paromomycin													
Expiry dates													
No. of vials at beginning of month													
No. of vials at end of month													
No. of vials consumed													
AmBisome													
Expiry dates													
No. of vials at beginning of month													
No. of vials at end of month													
No. of vials consumed													

	JAN	FEB	MAR	APR	MAY	JUN	JUL	AUG	SEP	OCT	NOV	DEC	TOTAL
Glucantime													
Expiry dates													
No. of ampules at beginning of month													
No. of vials at end of month													
No. of vials consumed													
rK39 rapid test kit													
Expiry date													
No. of test devices at beginning of month													
No. of test devices at end of month													
No. of test devices consumed													
DAT test vials													
Expiry date													
No. of test vials at beginning of month													
No. of test vials at end of month													
No. of test vials consumed													
Others													

ANNEX 13:
KALA-AZAR WEEKLY REPORTING FORM (DURING OUTBREAKS)

COUNTY_____ SUB-COUNTY_____ HEALTH FACILITY: _____ YEAR: _____

Epidemiological week	Total no. examined	Total no. primary VL	Total no. relapses	No. PKDL	Male	Female	0–4 yrs	5–14 yrs	15 yrs and above	Death	Remark

ANNEX 14:
KALA-AZAR SCREENING AND DIAGNOSIS ACTIVITIES FORM

COUNTY_____ SUB-COUNTY_____ HEALTH FACILITY: _____ DATE: _____

	JAN	FEB	MAR	APR	MAY	JUN	JUL	AUG	SEP	OCT	NOV	DEC	TOTAL
No. of people screened													
Passive													
Active													

Geographical origin of patients (probable place of infection if known)														
County	Sub-county	Ward / location / village	JAN	FEB	MAR	APR	MAY	JUN	JUL	AUG	SEP	OCT	NOV	DEC	TOTAL

ANNEX 15:
KALA-AZAR TESTS PERFORMED REPORTING FORM

COUNTY_____ SUB-COUNTY_____ HEALTH FACILITY: _____ YEAR: _____

	JAN	FEB	MAR	APR	MAY	JUN	JUL	AUG	SEP	OCT	NOV	DEC	TOTAL
No. of rK39 tests done													
rK39 positive													
rK39 negative													
No. of spleen aspirates done													
No. of spleen aspirates positive													
No. of spleen aspirates negative													
No. of bone marrow aspirates done													
No. of bone marrow aspirates positive													
No. of bone marrow aspirates negative													
No. of DAT tests done													
No. of DAT tests positive													
No. of DAT tests negative													

ANNEX 16:
PHARMACOVIGILANCE REPORTING FORM

LEISHMANIASIS NATIONAL CONTROL PROGRAMME

PHARMACOVIGILANCE FOR ANTILEISHMANIAL MEDICINES

ADVERSE EVENTS TREATMENT REPORT FORM

COUNTY: _____ YEAR: _____ TREATMENT CENTRE: _____

PATIENT INITIALS/ID_____ CODE: _____ AGE: _____ SEX: _____

TREATMENT STARTING DATE: _____ NAME OF THE MEDICINE: _____

Description of the adverse event	Starting date of the adverse event	Duration in days	Intensity 1. Mild 2. Moderate 3. Severe 4. Life-threatening 5. Death	Relationship with the treatment 1. Unrelated 2. Unlikely 3. Possible 4. Probable 5. Certain	Action 1. Treatment continued 2. Treatment suspended (temporary) 3. Treatment stopped (definite)	Outcome 1. Complete recovery 2. Still present 3. Sequelae 4. Death
	__/__/___					

Other drugs use	Date started	Duration in days	Indicate the underlying pathology for which the drug was administered

DATE: _____ REPORTER: _____ QUALIFICATION: _____

INDICATIONS: An adverse event is defined as any unfavorable sign, symptom, or disease temporally associated with the use of a medical treatment that may or may not be considered related to the drug used.

An adverse event form must be filled out for each patient treated with a given medicine or treatment combination that presents with one or more adverse events. If there are more than five adverse events, add another form; also add another form for additional treatments.

The following is a description and classification of the intensity of the adverse events that were most common during the course of antileishmanial therapy. Other adverse events may be observed that are not in this table; their intensity must be determined by the person responsible for filling out this report.

	GRADE				
Adverse event	1	2	3	4	5
Fever (axillary)	37.5 °C – 38.5 °C	> 38.5 °C – 39.5 °C	> 40.0 °C for < 24 hours	> 40.0 °C for > 24 hours	Death
Diarrhoea	Increase of < 4 stools per 24 hours over pre-treatment baseline stools	Increase of 4–6 stools per 24 hours or nocturnal stools	Increase of ≥ 7 stools per 24 hours; or incontinence; or need for IV fluids	Life-threatening consequences that are or require intensive care OR hemodynamic collapse	Death
Abdominal pain	Slight, does not interfere with function	Moderate, does not interfere with activities of daily living	Severe, prevents activities of daily living	Disabling	------
Vomiting	1 episode in 24 hours	2–5 episodes in 24 hours; IV fluids indicated < 24 hours	≥ 6 episodes in 24 hours; or IV fluids indicated > 24 hours	Need for parenteral nutrition; life-threatening consequences leading to intensive care; hemodynamic collapse	------
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition; IV fluids indicated < 24 hours	Inadequate oral caloric or fluid intake; IV fluids, tube feedings, or parenteral nutrition indicated > 24 hours	Life-threatening consequences	Death
Anorexia	Loss of appetite without alteration in eating habits	Oral intake altered without significant weight loss or malnutrition; oral nutritional supplements indicated	Associated with significant weight loss or malnutrition (e.g. inadequate caloric and/or fluid intake); IV fluids, tube feedings or parenteral nutrition indicated	Life-threatening consequences	Death

	GRADE				
Adverse event	1	2	3	4	5
Fever (axillary)	37.5 °C – 38.5 °C	> 38.5 °C – 39.5 °C	> 40.0 °C for < 24 hours	> 40.0 °C for > 24 hours	Death
Hiccups	Slight, does not interfere with function	Moderate, interferes with function but does not interfere with activities of daily living	Severe, significantly interfering with activities of daily living	Disabling	------
Headaches	Slight pain that does not interfere with function	Moderate pain; interferes with function but does not interfere with activities of daily living	Severe pain; interferes in a significant manner with activities of daily living	Disabling	------
Vertigo	Does not interfere with function	Interfering with function, but not interfering with activities of daily living	Interfering with activities of daily living	Bed-ridden/disabling	------
Ataxia	Asymptomatic, but abnormality found during clinical exam	Slight symptoms, interfering with function but not activities of daily living	Moderate symptoms, interfering with activities of daily living	Bed-ridden/disabling	Death
Tremor	Mild and brief or intermittent, but not interfering with function	Moderate tremor interfering with function but not interfering with activities of daily living	Severe tremor interfering with activities of daily living	Disabling	------
Seizures	----	Focal seizure in which consciousness is not altered	Seizure with loss of consciousness	Seizures of any kind which are prolonged, repetitive or difficult to control (status epilepticus)	Death
Confusion	Transient confusion, disorientation or attention deficit that resolves spontaneously without sequela	Confusion, disorientation or attention deficit interfering with function but not interfering with activities of daily living	Confusion or delirium interfering with activities of daily living	Harmful to self or others. Hospitalization indicated.	Death
Level of consciousness	Somnolence or sedation that does not interfere with function	Somnolence or sedation interfering with function, but not interfering with activities of daily living	Obtundation or stupor, difficult to arouse, interfering with activities of daily living	Coma	Death
Insomnia	Occasional difficulty sleeping, not interfering with function	Frequent difficulty sleeping, but not interfering with activities of daily living	Frequent difficulty sleeping interfering with activities of daily living	Disabling	------

	GRADE				
Adverse event	1	2	3	4	5
Fever (axillary)	37.5 °C – 38.5 °C	> 38.5 °C – 39.5 °C	> 40.0 °C for < 24 hours	> 40.0 °C for > 24 hours	Death
Mood alteration – anxiety / agitation	>Mild mood alteration not interfering with function	Moderate mood alteration interfering with function but not interfering with activities of daily living	Severe alteration interfering with activities of daily living	Suicidal ideation or danger to self	Death
Fatigue (asthenia, lethargy, malaise)	Mild fatigue	Moderate fatigue or causing some difficulty in performing activities of daily living	Severe fatigue interfering with activities of daily living	Disabling	------
Musculoskeletal pain	Slight pain that does not interfere with function	Moderate; pain interferes with function but does not interfere with activities of daily living	Severe; pain significantly interfering with activities of daily living	Disabling	------
Arrhythmia	Asymptomatic, no intervention indicated	Symptomatic, non-urgent medical intervention indicated	Symptomatic and incompletely controlled medically	Life-threatening (with congestive heart failure, hypotension, shock, syncope)	Death
Arterial Hypertension	Asymptomatic, transient increase by > 20 mm Hg (diastolic) or to > 150/100 if previously within normal limits, intervention not indicated	Recurrent, persistent or symptomatic increase in BP by > 20 mm Hg (diastolic) or to > 150/100 (if previously within normal limits), intervention not indicated	Drug therapy indicated or dosage of current treatment increased	Life-threatening hypertensive crisis	Death
Arrhythmia	Asymptomatic, no intervention indicated	Symptomatic, non-urgent medical intervention indicated	Symptomatic and incompletely controlled medically	Life-threatening (with congestive heart failure, hypotension, shock, syncope)	Death
Arterial Hypertension	Asymptomatic, transient increase by > 20 mm Hg (diastolic) or to > 150/100 if previously within normal limits, intervention not indicated	Recurrent, persistent or symptomatic increase in BP by > 20 mm Hg (diastolic) or to > 150/100 (if previously within normal limits), intervention not indicated	Drug therapy indicated or dosage of current treatment increased	Life-threatening hypertensive crisis	Death

	GRADE				
Adverse event	1	2	3	4	5
Fever (axillary)	37.5 °C – 38.5 °C	> 38.5 °C – 39.5 °C	> 40.0 °C for < 24 hours	> 40.0 °C for > 24 hours	Death
Edema	Asymptomatic, no treatment required	Symptomatic, treatment indicated	Symptomatic, with functional limitation, not responding to treatment and requiring stoppage of current drugs	Anasarca (severe generalized edema)	Death
Thorax pain	Slight pain that does not interfere with function	Moderate; pain interferes with function but does not interfere with activities of daily living	Severe; pain significantly interfering with activities of daily living	Disabling	------
Cough	Slight	Narcotic antitussive agent indicated	Symptomatic and significantly interfering with sleep or activities of daily living	---	------
Pneumonia	Progression without dyspnea	Progression with dyspnea on exertion	Progression with dyspnea during normal activity	Progression with dyspnea at rest	Death
Injection site reaction	Pain or itching or erythema	Pain or swelling, with inflammation or phlebitis	Ulceration or necrosis that is severe or protracted, or surgical intervention indicated	Disabling	------
Infection at injection site	Slight, non-antibiotic treatment	Moderate, localized infection where local or oral antibiotic treatment is indicated	Severe, systemic infection where IV antibiotic or antifungal treatment is indicated	Sepsis that is life-threatening (septic shock)	Death
Infection in tissues	Slight, non-antibiotic treatment	Moderate, localized infection where local or oral antibiotic treatment is indicated	Severe, systemic infection where IV antibiotic or antifungal treatment is indicated	Sepsis that is life-threatening (septic shock)	Death
Infection (other)	Slight, non-antibiotic treatment	Moderate, localized infection where local or oral [antibiotic] treatment is indicated	Severe, systemic infection where IV antibiotic or antifungal treatment is indicated	Sepsis that is life-threatening (septic shock)	Death

	GRADE				
Adverse event	1	2	3	4	5
Fever (axillary)	37.5 °C – 38.5 °C	> 38.5 °C – 39.5 °C	> 40.0 °C for < 24 hours	> 40.0 °C for > 24 hours	Death
Rash	Macular or papular eruption or erythema without associated symptoms	Macular or papular eruption or erythema with pruritus or other associated symptoms; lesions covering < 50% of the body surface area	Symptomatic, generalized erythema, or macular or papular eruption; lesions covering > 50% of the body surface area	Generalized exfoliative or ulcerative dermatitis	Death
Pruritus/itching	Mild or localized, resolving spontaneously or with local treatment	Intense or widespread, resolving spontaneously or with systemic treatment	Intense or wide-spread, and not being controlled by systemic treatment; interfering with activities of daily living	---	------

This scale is based on the document *Common Terminology Criteria for Adverse Events (CTCAE) version 3.0* (August 9, 2006).