VISCERAL LEISHMANIASIS AND MATERNAL HEALTH IN JONGLEI, SOUTH SUDAN

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Master of International Health
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A thesis submitted in partial fulfilment of the requirement for the degree of

Master of International Health

by

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The Netherlands

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Where other people's work has been used (either from a printed source, internet or any other source) this has been carefully acknowledged and referenced in accordance with departmental requirements.
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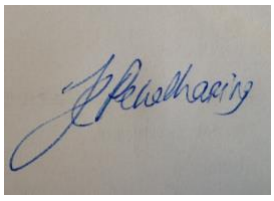
Signature: 

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List of abbreviations

AmBisome	Liposomal amphoceterin B
ANC	Antenatal care
BPHS	Basic Package of Health Services
CHW	Community Health Workers
CPA	Comprehensive Peace Agreement
D&C	Dilatation and curettage
DAT	Direct agglutination test
DNDi	Drugs for Neglected Diseases Initiative
EP-TB	Extra-pulmonary tuberculosis
Hb	Haemoglobin
IMA	Interchurch Medical Assistance
LNA	Lymph node aspirate
LSHTM	London School of Hygiene and Tropical Medicine
MUAC	Mid upper arm circumference
MSF	Médecins Sans Frontières
MVA	Manual vacuum aspiration
MoH	Ministry of Health
NTDs	Neglected tropical diseases
NGO	Non-governmental organization
PM	Paromomycin
PKDL	Post kala azar dermal leishmaniasis
PPH	Postpartum haemorrhage
RDT	Rapid diagnostic test
RPOC	Retained products of conception
RUTF	Ready to use therapeutic food
SPLM	Sudan People's Liberation Movement
SSG	Sodiumstibogluconate
TB	Tuberculosis
ToC	Test of cure
UPT	Urine pregnancy test
VL	Visceral leishmaniasis
WHO	World Health Organisation

Abstract

Introduction: Visceral leishmaniasis (VL) is a parasitic disease transmitted by sandflies, and is usually fatal if untreated. South Sudan has the worlds' second highest disease burden of VL. A significant proportion of cases in South Sudan is reported from Lankien, Jonglei state. There is limited evidence available about clinical aspects and treatment outcomes of VL in pregnancy.

Objectives: To describe determinants, health system response, and characteristics and maternal and pregnancy outcomes of patients with VL in pregnancy; in order to formulate recommendations for improving care for patients with VL in pregnancy in the context of Lankien, South Sudan, and East Africa in general.

Methodology: Literature review and a retrospective analysis of routinely collected data from a VL cohort in Lankien.

Results: Ecological conditions are an important determinant for VL in South Sudan. Epidemics are related to periods with civil unrest, via different determinants. The health system is strongly dependent on NGOs for delivery of VL treatment services. Patients with VL in pregnancy presented with severe anemia, increased need for blood transfusions, and adverse pregnancy outcomes (including premature delivery) in 20% of cases. Nevertheless, cure rates were high (96.5%) and mortality was low (1.8%) in this cohort.

Discussion: This is the largest cohort of patients with VL in pregnancy reported. This study demonstrates that good maternal outcomes are possible in resource-limited settings. Availability of AmBisome treatment, availability of blood transfusion, and BEmONC facilities to manage common complications, are important factors in treatment of patients with VL in pregnancy.

Key words: visceral leishmaniasis, maternal health, South Sudan, neglected tropical diseases

Word count: 11.999

Introduction

My name is Judith Pekelharing. I am a medical doctor from The Netherlands, with a specialisation in Global Health and Tropical Medicine. In 2017 I worked for Médecins sans Frontières (MSF) in South Sudan for nine months.
The topic of Visceral leishmaniasis (VL) - also called Kala azar - in pregnancy was identified by MSF for a research project, because of limited available evidence about management and outcomes of VL in pregnancy. I was motivated to conduct this study because I could relate to the topic from personal experience of caring for patients with VL (in pregnancy) in this setting and my interest in maternal health.
The thesis will focus both on clinical aspects of VL in pregnancy as well as determinants and organisation of care.
The thesis is directed at MSF. The aim is to contribute to improvement of care for patients with VL in pregnancy using the results of this study.
The outcomes of this thesis may also be useful for local health authorities for future strategic planning of the VL response in South Sudan and for other (East African) settings where patients with VL in pregnancy are treated.
The burden of VL is decreasing globally in recent years, thanks to a decline in reported cases in South Asia. However, being the country with the second highest burden of VL in the world, it is an important public health problem in the endemic areas in South Sudan. The available data from the MSF treatment facility in South Sudan provide a valuable source of information to study this topic and ultimately formulate recommendations for improvement of care.

Acknowledgements

I would like to thank colleagues from MSF Amsterdam and the MSF field teams in Nairobi, Lokichoggio, Juba and Lankien, for their cooperation and support.

Chapter 1
Background information

This chapter provides background information about South Sudan, including health indicators and the health system, followed by an introduction about the disease visceral leishmaniasis.

South Sudan - Introduction

South Sudan is a land-locked country of 640,000 square km in East-Central Africa. The geography consists of plains in the north and centre, and highlands along the border with Uganda and Kenya. The climate is equatorial with a rainy season between April and November. There are many different ethnic groups and more than hundred local languages, the largest ethnic groups being Dinka (35.8%) and Nuer (15.6%). Communities traditionally engage in pastoralism, fishing and farming. The country has fertile soils, abundant water supplies and is rich in oil(1). However, South Sudan is the most oil-dependent country in the world and is experiencing a macro-economic crisis at the moment. The population was estimated at 12.6 million in 2017 with a growth rate of 2.8%. 18% of the population lives in urban areas(2). Fifty-five percent (55%) of the population has access to improved water sources, and 7% uses improved sanitation. Illiteracy rates are 88% for women and 63% for men(3). South Sudan was the most fragile state in the world in the 'Fragile State Index' in 2014,2015,2017 and 2018(4).

Lankien is a town in Nyirol country, previously part of Jonglei state, in the north eastern part of the country. Since the establishment of 28 states in 2015 (in place of the 10 previously established states) it is part of (Eastern) Bieh state(5). MSF has been working in southern Sudan, now South Sudan, since 1983 and in Jonglei state since 1993(6). The population in the area is Nuer, a pastoralist population who practice cattle husbandry and agriculture. During the rainy season they live in villages on slightly elevated ground, and engage in cultivation. The land between the villages is more or less flooded during the rainy season. At the end of the rains, people move from the villages to reside in riverside cattle camps during the dry season(7). Violence (between armed groups, cattle raiding and inter-communal violence), displacement, food security and difficulty in accessing health care and education are among the problems affecting the region(8).

South Sudan – Historical background and political context

What is now South Sudan has been a transition area between northern and sub-Saharan Africa for many years. The original Nubian area was alternately occupied by Egypt and Arab Muslims from the north, and multiple African groups from the south(9).
The area was under Anglo-Egyptian rule from 1898 until Sudan became independent in 1956. After independence, Southern Sudan fought against the Khartoum government for more participation in the political system, which resulted in two prolonged civil wars (1955-1972 and 1983-2005). A six-year peace process began in 2005 by signing the Comprehensive Peace Agreement (CPA) between the Government of Sudan and the Sudan People's Liberation Movement (SPLM). A referendum was held in 2011 to determine the status of Southern Sudan and the vast majority of participants voted for independence. The Republic of South Sudan was born in July 2011. The post-independence period was characterised by on-going tensions with Sudan, and rising tensions within the country. The nature of the current conflict is complex, and runs partly along ethnic lines. In December 2013 a civil war erupted in the worlds' youngest nation. A famine was declared in the country in 2017, in what the UN described as 'a man-made catastrophe caused by civil war and economic collapse' (10,11). In 2017, nearly 4.3 million people were displaced (one in three South Sudanese), including 2.5 million refugees in neighbouring countries and 1.8 million internally displaced(12). Since 2013 several ceasefires were signed and violated, but recently, in September 2018, the Revitalized Agreement to Resolve Conflict in South Sudan was signed by the president and opposition groups in a renewed bid to end the civil war(10,13).

South Sudan - Health indicators

Some general health indicators and health indicators related to neglected tropical diseases and maternal health are presented here.

Communicable diseases remain the leading causes of death. Major causes for morbidity and mortality are malaria, diarrhoea and pneumonia, and maternal deaths. Estimated tuberculosis (TB) prevalence is 146 per 100.000 and HIV/AIDS prevalence is estimated at 2.6%(3). This is lower than the average of the World Health Organisation (WHO) African Region, which has an estimated HIV prevalence of 4.6% and TB prevalence of 330 per 100.000 population(14). Most neglected tropical diseases (NTDs) are endemic, including visceral leishmaniasis (VL), trypanosomiasis, onchocerciasis, trachoma, lymphatic filariasis, guinea worm and schistosomiasis(3). In some areas VL constitutes a large burden of disease, the epidemic fuelled by on-going conflict(15).

Maternal mortality is decreasing, but still high, and was estimated at 789 per 100.000 live births in 2015(16). This is higher than the WHO African Region average of 542 per 100.000 live births(14). Sexual violence, both by armed groups and non-combatants/intimate partners is prevalent(17).

Although technically the country is not experiencing a famine at the moment, food insecurity and malnutrition are still widespread, with 4.9 million people severely food insecure last year(18). South Sudan experienced a cholera outbreak from 2016 to early 2018(19).

South Sudan - Health system

The civil wars left South Sudan with a largely dysfunctional health system. At least 76 non-governmental organizations (NGOs) and six UN agencies were active in the country in the early phase after the CPA, in a fragmented way with multiple "vertical" disease-specific programs. Apart from a few government hospitals in the larger towns, the absolute majority of health care services were provided by NGOs(20). In an assessment from 2007 only 30 percent of the population had access to health services(9).

Since NGOs were already providing the largest part of health services and the government did not have the capacity to deliver primary health care services, a model of contracting out was adopted in 2006. Three international NGOs were contracted as Lead Agencies for the delivery of services through a Basic Package of Health Services (BPHS)(20,21).

Currently, the organisational structure of the health system is based on four administrative levels: central, state, county and community level(22).

The health system faces challenges in all components, including governance, human resources, financing, information systems and service delivery. One of the biggest problems in the health system is insufficient numbers of health workers. Decades of civil war resulted in very low levels of education and few training opportunities. Primary health worker numbers are insufficient to meet BPHS standards, with severe shortages of mid-level cadres. Health services relied heavily on community health workers (CHWs). However, CHW training stopped in 2012(23). A ratio of 0.19 health worker for 1000 population was reported in 2011, which is very low in comparison to the WHO recommended minimum of 2.3 per 1000 population(24). Provision of health services often relies on task-shifting and service delivery by unqualified (NGO-trained) health workers.

Another factor hindering the delivery of health care services is the on-going conflict in several areas. Looting and destroying of healthcare facilities by both government and opposition forces is reported. Road security is impairing both access and service delivery. Other challenges include availability of essential medicines and poor quality of health services(23,25). Access to maternal health services is limited, and unevenly distributed between urban and rural areas. Skilled birth attendance was low at 21.5% in South Sudan, and 12.6% in Jonglei state in 2010(26).

Although the current health programme was designed to support the transition to a government-led system, resurgent conflict and political tensions have negatively

impacted all health system components, and the system still relies heavily on international NGO's, faith based organisations and external funding(23).
Moreover, on-going medical emergencies are happening throughout the country. As the healthcare system has limited capacity to respond to these crises, humanitarian/relief activities are on-going throughout the country(27).

Visceral Leishmaniasis – Introduction and transmission

Leismaniasis is a parasitic disease transmitted by sand-flies. Different species of the *Leishmania* parasite cause different forms of disease, ranging from self-curing cutaneous lesions to life-threatening visceral disease (also called Kala azar). VL in South Sudan is caused by the subspecies *Leishmania donovani*, transmitted by *Phlebotomus orientalis* (sand-fly) associated with *Acacia seyal* and *Balanites aegyptiaca* vegetation.
Transmission of *Leishmania donovani* is thought to be mainly from human to human in East Africa, as opposed to other parts of the world where animals are an important reservoir(28,29).

Presentation and diagnosis

The time between infection and start of clinical signs and symptoms is typically 2-8 months, and onset of the disease is usually gradual. VL affects the lymphatic and reticuloendothelial system, and many of these cells are heavily parasitized. Affected organs include the spleen, liver, mucosa of the small intestine and respiratory tract, bone marrow, lymph nodes and the other lymphoid tissues. Fever, malaise, weight loss and anorexia are common symptoms. Clinical signs are splenomegaly, hepatomegaly, wasting and lymphadenopathy. Laboratory features include pancytopenia and hypergammaglobulinaemia; liver function may be normal or altered. Complications occur from anaemia, bleeding, malnutrition and intercurrent infections. Without treatment, the disease can progress rapidly in weeks or months and is typically fatal(29–31).
Due to overlap of signs and symptoms with other diseases, it is difficult to make a clinical diagnosis; prior-probability of the clinical case definition is 30-60%(32,33). An additional challenge in diagnosing VL in pregnancy may be the examination of the spleen in advanced pregnancy. Diagnosis should be confirmed by laboratory test in all patients. Two serological tests—the direct agglutination test (DAT) and the rK39 antigen-based immunochromatographic test— can be used in field settings. Control programs in Asia and east Africa recommend treatment for suspect (primary) VL cases from endemic areas with a positive rapid diagnostic test (RDT) result(30). As the rk39 has a sensitivity of 85-90% in East African VL, a back-up diagnostic algorithm should be followed, including DAT and parasitological testing, in case rk39 is negative(29,34).
The serological tests cannot differentiate between active disease and positive serology from a past (subclinical) infection. In suspected VL relapse cases parasitological diagnosis by microscopy of a lymph node- or splenic aspirate is needed. Lymph node – and spleen aspirates can also be used to follow up treatment response(29).

Treatment and prognosis

VL is characterized by suppression of the cell mediated immune response. Containment of the disease following a successful treatment is associated with a strong cell mediated response. However, some Leishmania parasites can persist in the host cells after treatment and fulminant re-activation of the infection is possible when immunity is compromised, sometimes years later. Immunocompromised patients require higher doses of medication and longer treatment, and are at increased risk of relapse and death(30,35).
Different treatment regimens are in place in different regions in the world, due to variations in drug sensitivity and drug resistance profiles(30).
A 17-day course with combination therapy of the pentavalent antimonial Sodiumstibogluconate (SSG) and aminoglycoside Paromomycin (PM) is the current first line treatment in East Africa. Injections are given intramuscular, on an ambulatory basis if the patients' condition permits(36,37).

However, SSG is poorly tolerated in certain patient groups, with toxicity such as pancreatic, hepato- and nephrotoxicity, cardiotoxicity, gastro-intestinal disorders and, in pregnant women, spontaneous abortion. Specific patient groups (elderly, HIV co-infected, pregnant women) and patients with a high risk of dying should be treated with liposomal amphoceterin B (AmBisome) as it is much better tolerated in these patients. However, AmBisome requires cold chain, intravenous administration and hospitalization for 12 days and is approximately 8-9 times more expensive (using the WHO negotiated price) than the combination of SSG/PM(38,39).
The fourth available drug is miltefosine, a drug that was originally developed as an oral anticancer drug but was shown to have antileishmanial activity. Miltefosine is not recommended to pregnant women as it can lead to malformations of the fetus(29). Initial cure rates with SSG/PM for 17 days are 93-97%(29,37). Efficacy of liposomal amphoceterin B is 90% in observational field data in East Africa(40). Relapse rates after SSG/PM combination therapy are reported 2-6%(41,42). Overall mortality was 2.8% in a study with 6.633 patients from Lankien, South Sudan during an outbreak in 2013-2015. This is comparable to a case fatality rate of 3% in 28.328 patients treated in different centres in South Sudan between 2009 and 2012(38,43).

Chapter 2
Problem statement

The following section describes the magnitude of the disease burden of VL in South Sudan and introduces the topic of VL in pregnancy. Existing literature and knowledge gaps are discussed.

Epidemiology of VL

Endemicity of VL is shown in figure 1. A significant drop in worldwide reported cases has been observed in recent years. VL was responsible for the highest disease burden among the NTDs, according to data from the Global Burden of Disease Study 2013. Ninety percent of cases were reported from six countries, namely Bangladesh, Brazil, Ethiopia, India, South Sudan and Sudan(44,45).
However, reported cases from India and Bangladesh have dropped significantly between 2006 and 2016, while VL prevalence did not change significantly for other countries. South Sudan now has the biggest VL burden after India(46).

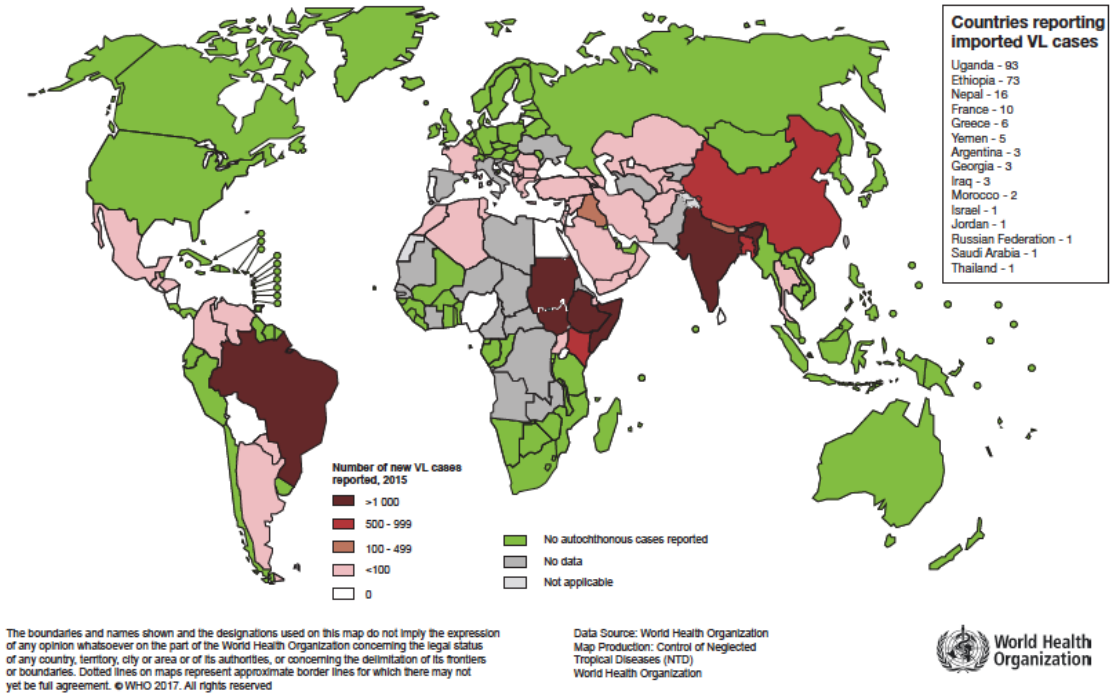

Figure 1 - Endemicity of visceral leishmaniasis worldwide in 2015 (47)

VL is endemic in four states in South Sudan; Upper Nile, Unity, Jonglei and Eastern Equatoria (names of the states as used before October 2015). The distribution of VL cases in South Sudan is shown in figure 2. Outbreaks tend to occur regularly and unexpectedly, part of this is related to introduction of the disease to previously non-endemic areas through migration of people(48,49).
The disease was first reported from southern Sudan in 1904, and the first epidemic in 1940. An epidemic in the 1980s (starting in 1984 but unrecognized until 1988) devastated the western part of Upper Nile state, ultimately causing ≈100.000 deaths in a population of 280,000 over a 10-year period(50,51). Annual reported cases have fluctuated between 2000 and 12000 over the past 10 years, but many cases remain undiagnosed and unreported, due to limited access to health services. The majority of cases in South Sudan is reported from Lankien and Old Fangak(52). Trends in reported VL cases in South Sudan are shown in figure 3(48).

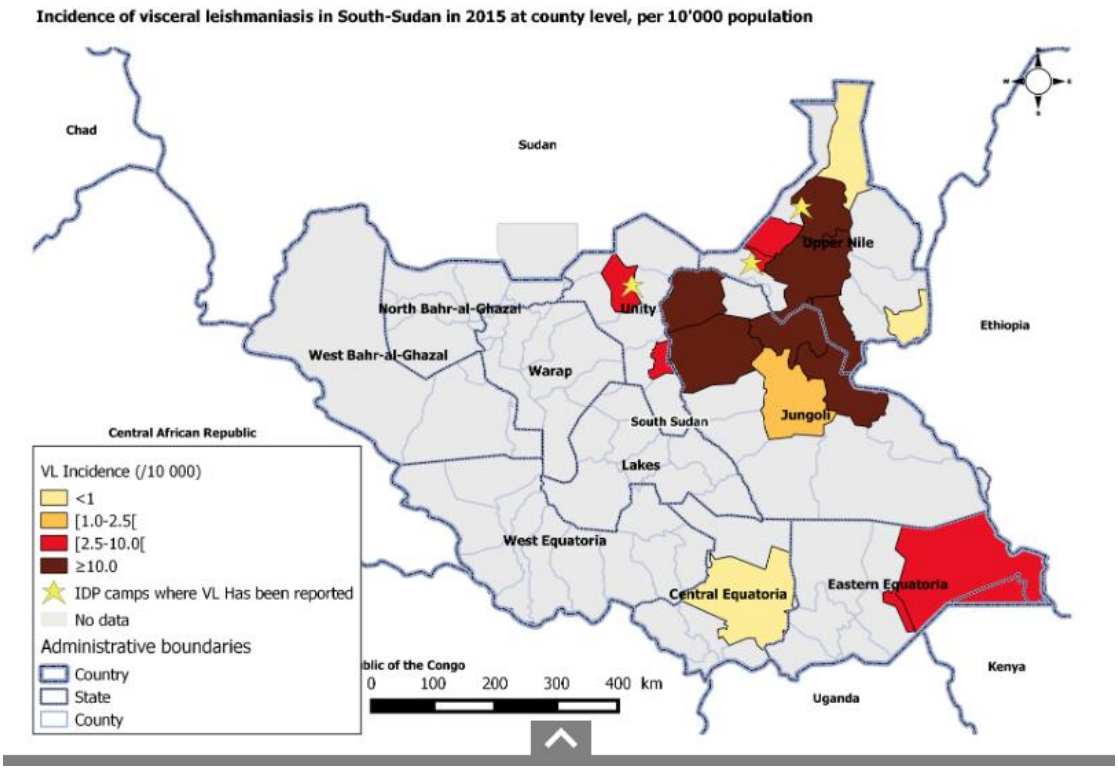

Figure 2 - Distribution of VL cases in South Sudan 2015 (48)

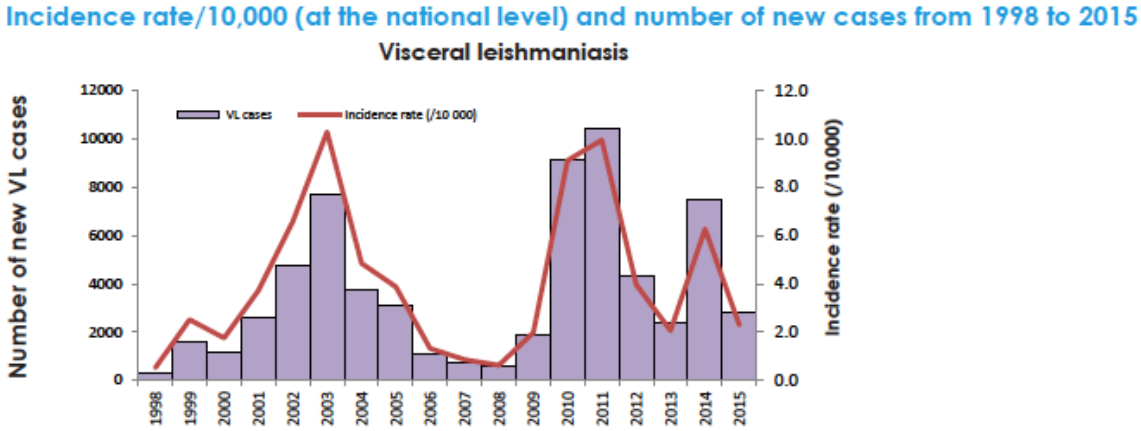

Figure 3 - Trend in reported visceral leishmaniasis cases in South Sudan (48)

Visceral leishmaniasis in pregnancy

Pregnant women constitute a particular patient group. It is known that the maternal immunological system is modulated during pregnancy. Pregnancy is described as a pro-inflammatory and anti-inflammatory condition, depending upon the stage of gestation(53). Current evidence of how the immune system interacts with leishmania infection in pregnancy is explored in a review from 2017. Based on animal studies, T cell balances and different resulting cytokine patterns are suggested to explain different scenarios of the maternal response to VL infection. In this paradigm, a Th1-predominant inflammatory response is associated with pregnancy loss but control of the infection, and a Th2-predominant response with a tolerant immune state to foreign antigens, manifesting as preservation of pregnancy but poor control of the infection. Th17 activity is found hostile to pregnancy but also associated with poor control of VL infection, and regulatory T cell activity is associated with maintenance of pregnancy and VL control. Studies in humans about the maternal immune response to VL and concurrent pregnancy are very limited.

Congenital transmission of VL via the transplacental route has been described in humans, but, apart from one case report from 1992, studies regarding placental invasion of parasites are only available from animal studies(54).

Several clinical studies and case series about visceral leishmaniasis in pregnancy are available. Two reviews from 2004 describe 21 and 22 cases respectively, partly the same cases. Vertical transmission and adverse pregnancy outcomes were reported, but mainly in untreated women(55,56). A study from Sudan in 2006 compared SSG treatment to AmBisome treatment in 39 pregnant women and found AmBisome safe and effective. Abortions occurred only in the SSG group (in 57%) and all patients except one defaulter were cured(57).

A recent publication from Sudan reported 18% case fatality rate among 45 pregnant patients treated with SSG in 2014-2015. Of the surviving patients, 77% had full-term deliveries of a live neonate, 15% experienced preterm delivery, 2% (1 patient) experienced spontaneous abortion and 2% (1 patient) had a stillbirth. Causes of death were reported to be hepatic failure (63%), bleeding manifestation (25%) and severe anaemia/hearth failure (13%)(58).

There is limited evidence available about clinical and epidemiological aspects of VL in pregnancy. No studies were found looking at susceptibility to develop VL in pregnancy compared to the general population, and differences in clinical presentation and outcomes between primigravida and subsequent pregnancies. Much more research has been done about another parasitic disease in pregnancy – malaria. From malaria it is known that it affects pregnant women more than the general population, and presents with more severe disease(59). Prevalence is higher in the first and second trimester of pregnancy(60). Malaria in pregnancy is associated with maternal anaemia, pregnancy loss, low birth weight and premature deliveries(60). Those aspects are not yet fully understood for VL in pregnancy.

Justification

There is limited evidence available about clinical aspects of VL in pregnancy and treatment outcomes, although adverse perinatal outcomes and in one study high maternal mortality have been described.
Better understanding of clinical aspects of VL in pregnancy, complications during treatment, and treatment and pregnancy outcomes is needed in order to identify factors that can be addressed to improve medical care for this patient group.
Moreover, understanding of determinants of VL in pregnancy and the current health system response is needed to make the recommendations fit the context.

This study focusses on VL in pregnancy, in the context of a treatment facility run by MSF in Lankien, South Sudan.
The facility provides primary health care services, comprehensive maternity care and treatment for tropical diseases including VL, and responded to VL outbreaks in 1997-1998, 2002-2004, 2009-2011 and 2013-2015. Patients treated in Lankien accounted for 50% of VL patients treated in South Sudan in 2017. Data from this facility therefore provide a valuable source of information to improve knowledge and understanding of clinical aspects and treatment outcomes of VL in pregnancy, in this low-resource setting.

Objectives

General objective

To describe determinants, health system response, and characteristics and maternal and perinatal outcomes of patients with VL in pregnancy; in order to formulate recommendations for improving care for patients with VL in pregnancy in the context of Lankien, South Sudan, and East Africa in general.

Specific objectives

1. To describe determinants for VL and access to care in South Sudan.
2. To describe the health system response to VL in South Sudan and in Lankien.
3. To describe patient characteristics, complications and treatment outcomes for patients with VL in pregnancy and to compare these to non-pregnant VL patients. To describe pregnancy outcomes for patients treated with VL in pregnancy.

Research questions

1. What are determinants for VL and access to care in this context?
2. How is the health system response to VL organised; in South Sudan and in Lankien specifically?
3. What are patient characteristics and treatment outcomes for VL in pregnancy?
   3a. What are characteristics of pregnant patients with VL treated in Lankien.
   3b. What are disease related complications of VL in pregnancy, and how does this differ from non-pregnant VL patients?
   3c. What are treatment outcomes for VL in pregnancy and how does this differ from non-pregnant VL patients?
   3d. What are risk factors for adverse outcomes?
   3e. What are obstetric and perinatal outcomes for pregnant women with VL in our treatment setting? And how does this differ from non-VL deliveries in this facility.

Methods

General approach and analytical framework
Two different methods were used to address the research questions.
A literature review was conducted, focussing on determinants of VL, access to care, and the health system response in South Sudan and Lankien specifically. Elements of the Dahlgren and Whitehead model of determinants of health are used to structure this section(61). The literature review addresses research question one and two.
A retrospective analysis using secondary data from a VL cohort from Lankien treatment facility in the period 2014-2018 was conducted, focussing on clinical aspects of VL in pregnancy and treatment outcomes. The data was collected under the scope of a study conducted by MSF, therefore clearance from KIT Reseach Ethics Committee was not needed. This study addresses research question three.

The conceptual model of Peabody et al., shown in figure 4, is used as a framework for the following chapters. It was published in 1999 in a book about policy and health in the context of Asia(62). The model was chosen because it aligns with the research questions and the model is an established model in the field of (quality of) healthcare in developing countries(63).
Only the elements inside the circle will be covered. Demographic and socio-economic factors and access to health relate to the first research question. The second research question relates to the structure and process of the VL response in South Sudan and Lankien.
A large focus will be placed on the third research question regarding health (treatment) outcomes of VL in pregnancy.

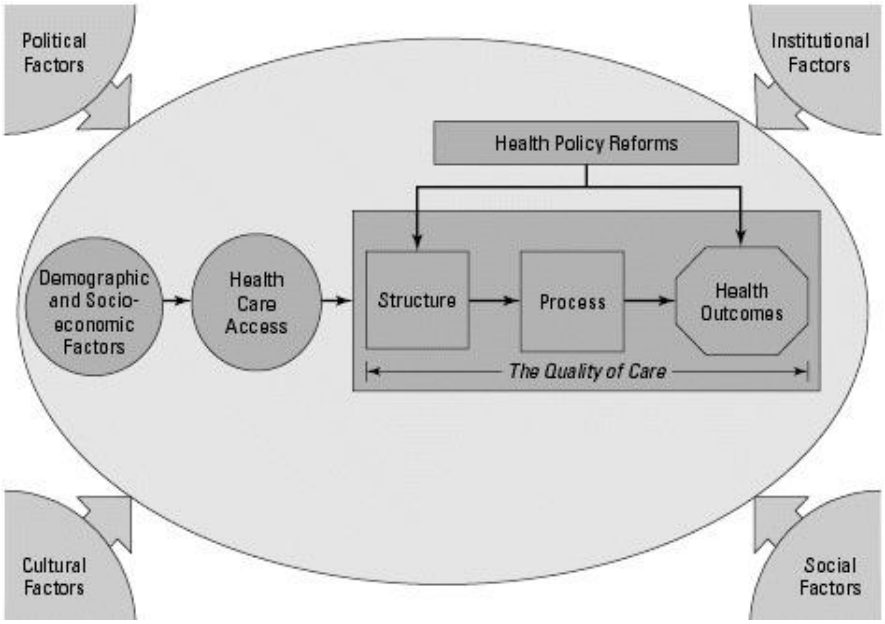

Figure 4 - A simplified model of factors affecting health outcomes (62)

Methods 1 – Literature review

A literature research was conducted using the following databases and search engines: Pubmed, Google Scholar.
The following key words were used in the search (in various combinations): visceral leishmaniasis, kala azar, South Sudan, WHO, determinants, access, healthcare, health system, health services, policy.
Inclusion was restricted to articles in English language. No restriction to year of publication was applied. Grey literature documents and reports were included.
Titles and abstracts obtained from the database searches were screened to identify and include relevant articles. Snowballing was used to identify other relevant reports and articles based on previous search results.
In addition to this literature search, MSF treatment guidelines were used to describe the process of care for VL patients in the treatment facility in Lankien.

Methods 2 – Retrospective analysis using data from a VL cohort

Ethics statement
This research fulfilled the exemption criteria set by the Médecins Sans Frontières Ethical Review Board for a posteriori analyses of routinely collected clinical data, and thus did not require additional clearance from MSF ERB. It was conducted with permission from the Medical Director of the MSF Operational Centre Amsterdam. All data were anonymised before analysis.

Study design and data source
MSF runs a project in Lankien providing treatment for VL patients. Clinical and operational data related to this project are routinely recorded as part program monitoring. This thesis describes and analyses the data of a subset of participants of the larger VL cohort. These are VL patients who also were pregnant at the time of diagnosis and/or treatment and a comparison group.
Patients discharged between October 2014 and April 2018, but excluding the period August 2016 until February 2018, were included in the analysis. No medical records from the period August 2016 until February 2018 were available for review, because they were destroyed by mistake.
Data sources included the database with routinely collected data and patient medical records to complete missing data missing from the database. Patients with VL in pregnancy were included in the analysis. From the VL cohort, a random selection of 283 non-pregnant women in reproductive age was formed to serve as comparison group. Patient characteristics, complications during treatment and treatment outcomes were compared between patients with VL in pregnancy and the comparison group.
Data about birth weight and gestation at time of delivery of (non-VL) institutional deliveries in Lankien health centre were obtained from the Delivery register, for the same period October 2014 – August 2016 and March/April 2018. Data about Haemoglobin (Hb) values in normal pregnancy were obtained from the laboratory record of the antenatal care (ANC) outpatient department. Data were collected from pregnant women who visited the ANC clinic in the month of August 2018.

A detailed description of the diagnostic criteria, severity score and treatment regimen that were followed in this VL cohort, can be found in Annex 1.

Inclusion and exclusion criteria
Records with no information on pregnancy status were excluded. Women of reproductive age (between 15 and 45 years), with either a negative urine pregnancy test or a note on the admission card indicating that the patient was not pregnant, were included as 'not pregnant'.

Data collection
Data was transferred into a purpose-made database created using Epidata software (version 4.4.2.0). Key dates, demographic, anthropometric, diagnostic and clinical characteristics of patients, treatment regime, complications during treatment and outcome were recorded.

Analysis
Results are presented for the following groups:

- VL in pregnancy
  - Group 1: Pregnant women diagnosed with VL (all trimesters).
  - Group 2: Women diagnosed with VL within 1-2 weeks postpartum or after spontaneous abortion, who were already symptomatic during pregnancy.
- Comparison group
  - Group 3: Comparison group of non-pregnant women with VL in the same age group (15-45 years).

Outcome
Patients were discharged as 'cured,' 'defaulted' or 'death'. A defaulter was defined as a patient who did not complete treatment, and had an unknown outcome. There is no systematic follow up of patients after discharge, because they return to areas remote from the treatment centre.
Patients with discharged as either 'parasitological cure' or 'clinical cure'. Parasitological cure means that a test-of-cure (ToC) by aspirate microscopy was performed to confirm cure at the end of treatment. According to the protocol, this is indicated for patients with an increased risk of treatment failure or relapse (i.e. patients with a prior episode of VL, or patients with inadequate or doubtful clinical response and pregnant patients up to the first 6 months postpartum).
For some patients, treatment was extended after the initial standard dose. This is presented as 'need for extended treatment'. The decision to extend treatment could either be 'based on positive ToC' or 'based on no clinical cure' according to the responsible physician.
Adverse outcomes were defined as 'adverse pregnancy outcome 1' (first trimester abortion, immature delivery, stillbirth), 'adverse pregnancy outcome 2' (same as adverse pregnancy outcome 1, but including premature delivery), 'need for extended treatment based on positive ToC', and 'death'.

Statistical analysis
Categorical variables are presented using absolute numbers and percentages. Continuous variables are summarised using means for (for normally distributed data), medians (for non-normally distributed data) and ranges. Where appropriate, differences in proportions are measured using Fisher's exact test and Pearson $\chi 2$ test and the results expressed as odds ratios and 95% confidence intervals. Differences in continuous variables are assessed using linear regression where the assumptions are met and non-parametric tests for non-normally distributed data. Logistic regression was used to identify independent variables associated with adverse outcomes. Data analysis was conducted using SPSS Statistics (version 25).

Chapter 3
Study findings

The study findings are presented in this chapter. The results of the literature review, addressing research question one and two, are presented first, followed by the results of the retrospective analysis using data from a cohort of VL patients, addressing question three.

Literature review - Results data collection

The review 16 articles and reports were included to answer research questions one and two in the following section.

Literature review - Results

Research question 1; What are determinants for VL and access to care in this context?

Age, sex and constitutional factors
Although health-care facilities in some regions report more male than female cases, no community-based studies are available to determine the sex ratio regarding risk to developing VL. Possible explanations include more frequent exposure of males than females, or under-reporting of females to health facilities due to differences in health seeking behaviour(29). In endemic areas of East Africa, the highest incidence is in children and young adults. The median age in various sites in Africa and Asia is 13-23 years. In endemic areas a large proportion of the adults may have acquired immunity, whereas naïve adults who enter an endemic area are at risk for the disease(29).
Poor nutritional status (specifically protein-energy malnutrition, vitamin A deficiency and zinc deficiency) increases the risk that an infection will progress to clinical disease(29). Although technically the country is not experiencing a famine at the moment, food insecurity and malnutrition have been a major concern during the last years, with 4.9 million people severely food insecure in 2017(18).
HIV infected individuals are a specific patient category, as VL cannot be permanently cured in these patients, and they become eventually unresponsive to all medicines, carrying a high parasite load. Their presence in high numbers may increase the infective reservoir(29).
HIV prevalence in South Sudan is estimated at 2.6%(3) However, this 2.6% is the estimation for the country average. HIV prevalence is higher in the urban centres and along the borders with Uganda and DRC, and lower in the rural VL endemic areas of Jonglei State. Routine HIV testing among VL patients in Lankien shows a HIV co-infection rate of <1%.
There is evidence that certain tribes in Sudan are genetically more susceptible to develop clinical disease after exposure than others(64).
We could suspect a higher susceptibility to develop VL in pregnancy, due to the altered function of the immune system in pregnancy. A higher susceptibility during pregnancy (and postpartum period) has been proven for other infections such as HIV and malaria(59,60,65). However, this has not yet been proven for VL.

Individual lifestyle factors
The habit of sleeping outside (under Acacia trees) during the dry season, which is common in South Sudan, increases the risk of contact with infected vectors and is therefore associated with an increased risk for VL, while the use of fine mesh insecticide-treated bed nets is protective for VL(29,66).

Social and community networks
Living close to another VL patient was a strong risk factor for VL in an Indian survey. Explanations include genetics (in families) affecting the susceptibility to develop the disease after infection, and limited range of the sand fly dispersal(67), apart from sharing the same living conditions and practices.

Living and working conditions
Agriculture and food production: Food security in South Sudan has been severely affected by the combination of conflict, economic crisis and lack of adequate levels of agricultural production in recent years(18). As described above, malnutrition leads to increased susceptibility to develop VL after infection with the parasite.
Working conditions: In Ethiopia disease spread is associated with seasonal labour movements, with labour migrants moving between endemic and non-endemic areas(29). The risk of developing VL due to movements associated with cattle herding in South Sudan are described below under socio-economic and cultural factors.
Water and sanitation: Poor sanitary conditions (lack of waste management, open sewerage) may increase sand fly breeding sites(29). As mentioned in the introduction, access to improved sanitation is 7% in South Sudan.
Health care services: VL and post kala-azar dermal leishmaniasis (PKDL) patients constitute a reservoir, which may enhance transmission to others if no treatment is sought or health services are unavailable(29). PKDL is an immunologic reaction after (successful) VL treatment, presenting with a rash, with a high parasite density in the skin lesions. Incidence is not known but considered significant. It is underreported due to passive case detection and patients often not seeking care, especially in mild cases(68). In a study from a VL outbreak in South Sudan in 2009-2012, 4.6-10.4% of VL patients who sought treatment were PKDL patients. In a prospective study from South Sudan in 2000, 57% of patients treated for VL developed PKDL, although the current treatment regimen is different from the regimen used in this study(43,69). Asymptomatic individuals infected with VL may also act as a reservoir for transmission(67).
Housing: The common type of house constructed of mud and grassy material provides little protection against attracting the vector(29).

General socio-economic, cultural and environmental conditions
Climate and environment: The ecological settings for transmission in East Africa are savannah regions with *Acacia-Balanitis* vegetation and forest areas with termite mounds(29). In the focus of the Western Upper Nile region sand fly vector *Phlebotomus orientalis* is the vector. The sand fly lives in forests of *Acacia seyal* and *Balanites aegyptiaca.* Eastern Equatoria has desert-like sandy soil with giant termite mounds. *Phlebomotus martini* is the vector in this setting. Transmission of VL occurs throughout the year, with a seasonal peak in the dry season (from February to May). A peak of clinical cases is observed after the rainy season several months later(70), although variations are observed from year to year.
Politics: Epidemics are fuelled by civil unrest. This is through the link with mass displacement of people (hiding in acacia forests during episodes of acute conflict), naïve populations moving to endemic areas, lack of diagnosis and treatment, food insecurity and malnutrition, and possibly the reservoir of parasites in untreated PKDL patients(15).
General socio-economic and cultural factors: Poverty increases the risk for leishmaniasis infection in several ways, due to factors including poor housing, crowding (fuelling the transmission cycle), poor nutrition and other immune-suppressive infections (e.g. TB)(29).
The most important factor for endemic transmission in South Sudan is the pastoralist population moving back and forth between cattle camps near the water during the transmissions season and the relatively dry areas near their 'permanent' homes.

Traditionally people walk in the cool of the night through the forests, exactly the time and place that sand-flies which transmit VL are biting(50).
No specific determinants for VL in pregnancy were found in the literature.

Access to care
Exact numbers of VL patients are not known, but it official figures are likely to underestimate the total amount of cases grossly(46).
The availability of health services in general is a concern in South Sudan. Factors limiting access to health care in general have been mentioned in Chapter 1; including poor infrastructure, lack of human resources for health, lack of essential medicines and poor quality of care.
The conflict in South Sudan plays a crucial role in population movements and influences access to care, with (geographical) access to care being hampered in times of increased civil unrest(15).
A survey several years back found 41% of health facilities in Jonglei state non-functional. Availability of VL treatment sites is described in the next section.
A recent study explored patients' perception of access to VL treatment in southern Gadarif, Sudan. Although treatment is free, affordability was an important factor to delay seeking care, as patients have to pay for the indirect costs, pushing families into poverty. Negative perceptions on quality of care and unavailability of staff and medicines were reported(71). A study among migrant workers in Ethiopia also revealed poor access to diagnosis and, consequently, significantly delayed access to treatment. Significant barriers to diagnosis and care were insufficient finances for care-seeking, prioritization of income-generating activities, unavailability of diagnostic test kits in primary health centers, and lack of VL awareness(72). No such studies about patients' perception of access to treatment (and acceptability) have been carried out in South Sudan recently.

Research question 2; How is the health system response to VL organised, in South Sudan and in Lankien specifically?

Visceral Leishmaniasis – Health system response
The current strategy to address VL in South Sudan is passive case finding, diagnosis and treatment, as described in the National Masterplan for Neglected Tropical Diseases (2016-2020). Implementing partners are Ministry of Health (MoH), WHO, Interchurch Medical Assistance (IMA) and KalaCORE(73).
The KalaCORE consortium, funded with aid from the UK government, has been formed from four organisations: Drugs for Neglected Diseases Initiative (DNDi); Mott MacDonald; the London School of Hygiene and Tropical Medicine (LSHTM) and MSF. The initial timeframe of the KalaCORE program was four years (2014-2018). Efforts from the KalaCORE program in East Africa over the past few years have focussed on improving access to diagnosis and treatment, and capacity building for an effective response to VL outbreaks, as opposed to South Asia where the aim is progress towards elimination(73,74),
KalaCORE is supporting around 30 VL treatment sites in South Sudan. The treatment sites are located in areas with higher VL prevalence. IMA supplies the treatment sites with tests, drug and training(74,75). Only 4 out of 30 facilities providing VL treatment are run by MoH. AmBisome treatment is available in MSF treatment facilities and in 8 of the VL treatment sites supported by IMA. Surveillance is a challenge, as few of the treatment sites report on time(75). Patients treated in MSF facilities accounted for 50% of the national reported caseload in 2017, with almost all of these cases reported from Lankien. An evaluation about the effect of the KalaCORE program is carried out at the moment.

MSF treatment facility in Lankien

MSF guidelines for VL provide background information, case definition, diagnostic algorithms and treatment algorithms for different patient groups. See Annex 1 for the MSF Kala Azar diagnosis and treatment protocol for South Sudan. The national guideline for treatment of VL is based on this protocol(76).

According to the MSF protocol, uncomplicated primary VL can be diagnosed with RDT and treated with SSG/PM in primary health care centres (PHCC), but patients with suspected relapse VL, severe VL and other patient groups requiring AmBisome treatment (including pregnant women) are referred to a primary health care unit (PHCU).

Pregnant patients with VL are admitted in the maternity ward with basic emergency obstetric and new-born care (BEmONC) plus the possibility for blood transfusion available.

Health workers working in the treatment facility in Lankien include nurse-assistants (or paramedics), community health workers, nurses, clinical officers and medical doctors.

All treatment is free of charge and meals are provided for patients and one caretaker per patient. More details about the treatment can be found in the protocol (Annex 1).

Retrospective analysis using data from a VL cohort – Results data collection

Results cohort analysis - Patient inclusion and exclusion
The total amount of female VL patients in the cohort in the study period aged 15-45 years was 639. Eighty-seven pregnant patients with VL were included in group 1 for analysis, including one patient aged 14 years. Seven pregnant patients were excluded because records could not be found. Twenty-six patients were included in group 2 (VL diagnosed 1-2 weeks postpartum). Several patients who were initially selected for the comparison group, turned out to be pregnant or postpartum after record review, and were included in group 1 and 2.
From the group of non-pregnant patients, 283 patients were randomly selected to form the comparison group (group 3). Out of this selection, 223 patients were included in group 3. Others were excluded because files could not be found (15), pregnancy status was unclear/not recorded in the file (12). Seven patients were excluded because after record review it turned out they were lactating women without indication of how long ago they had delivered.

Retrospective analysis using data from a VL cohort – Results

Research question 3; What are patient characteristics and treatment outcomes for VL in pregnancy?

1a. What are characteristics of patients presenting with VL in pregnancy?

Patient characteristics on admission are presented in table 1.
Patients in this cohort originated from three counties in South Sudan; Nyirol, Uror and Akobo. Around 90% of patients presented within one month of self-reported onset of symptoms.
There was no significant difference between age, county of origin, proportion of patients who presented within one month of symptoms, and proportion of patients admitted during or after the 2014/15 epidemic between patients with VL in pregnancy and the comparison group. (This was considered relevant because case-fatality rate may differ during and outside an epidemic and over the course of an epidemic.)
The proportion of patients admitted with primary VL and relapse VL was similar across the groups.
Pregnant patients had less (recorded) splenomegaly, a higher BMI, a lower Hb and lower severity score compared to the comparison group.
Patients diagnosed with VL postpartum (group 2) had a lower Hb and higher severity scores compared to the comparison group (group 3), and a lower Hb compared to pregnant patients (group 1).

A substantial number of records did not have information about co-infection with malaria or HIV. Malaria co-infection was diagnosed in 2.2% in the comparison group and 2.0% in group 1 and 2 combined (missing data respectively 39% and 12%). Missing data regarding HIV co-infection was 12.5%, but the available HIV results were negative for all patients.
Not all missing data implicate that patients were not tested for HIV, as sometimes the test-result is written on the outpatient-card that patients take home after discharge and not copied in the inpatient medical record. Diagnosed TB co-infection on admission was low, with only 1 case in the comparison group and 1 case among pregnant women.

Table 1 Patient characteristics on admission

	VL in pregnancy N=113		Comparison group N=223
	Group 1 Pregnant N= 87	Group 2 Postpartum N =26	Group 3 Non-pregnant N= 223
Age in years	Median 24, range 14-40, IQR 20-29		Median 22, range 15-45, IQR 16-31
Origin			
• Nyirol	101 (89.4%)		198 (88.8%)
• Uror	8 (7.1%)		18 (8.1%)
• Akobo	4 (3.5%)		7 (3.1%)
Date of admission			
• During 2014/15 epidemic	65 (57.5%)		111 (49.8%)
• After 2014/15 epidemic	48 (42.5%)		112 (50.2%)
Duration of symptoms			
• Up to 4 weeks	76 (91.6%)	24 (96.0%)	195 (89.9%)
• > 4 weeks	7 (8.4%)	1 (4.0%)	22 (10.1%)
Missing data	4	1	6
Splenomegaly			
• No splenomegaly	34 (39.1%)*	8 (30.8%)	63 (28.3%)
• 1-4 cm	34 (39.1)	6 (23.1%)	90 (40.4%)
• 5-7cm	13 (14.9%)	8 (30.8%)	44 (19.7%)
• >7cm	6 (6.9%)	4 (15.4%)	26 (11.7%)
Nutritional status			
• BMI	Median 17.6*, range 12.7– 23, IQR 16.1 – 18.9	Median 16.5, range 13.3-19.3, IQR 15.4 – 17.5	Median 16, range 10.9 – 28 IQR 14.7 – 17.0
• W/H Z score			
0 or <-1	3	1	13
<-2 = 1	1	1	4
<-3 = 0	0	0	3
<-4 = 0	0	0	1
Hb on admission in g/dL	Median 9.0*, range 5.1-14.6, IQR 7.7-10.3	Median 7.8*, range 4.1-12.0, IQR 6.9-8.7	Median 10.0, range 4.6-15.6, IQR 8.4-11.3
Severity score			
• 0	35 (40.2%)*	2 (7.7%)*	68 (30.5%)
• 1-4	49 (56.3%)	19 (73.1%)	134 (60.1%)
• ≥5	3 (3.4%)	5 (19.2%)	21 (9.4%)
Primary VL	99 (87.6%)		196 (87.9%)
Relapse VL	14 (12.4%)		27 (12.1%)
Treatment regimen			
• AmBisome	85 (97.7%)*	19 (73.1%)*	27 (12.1%)
• SSG/PM	2 (2.3%)	7 (26.9%)	196 (87.9%)

* P-value <0.05 (pregnant patients compared to non-pregnant patients and postpartum patients compared to non-pregnant patients)

Among the patients in the first trimester, four patients had symptoms for more than one month. These patients could possibly have been symptomatic before they became pregnant. The remaining patients, the vast majority, were pregnant before they became symptomatic with VL.

Of the patients with VL in pregnancy (group 1 and 2 combined), 26.8% was in the first trimester of pregnancy at the time of diagnosis and start of treatment, 35.1% in the second trimester and 38.1% in the third trimester. Parity of pregnant VL patients (group 1) was distributed as follows; nullipara 17.2%, para 1 24.1%, para 2 17.2%, para 3 17.2%, para 4 17.2%, para 5 3.4%, ≥para 6 3.4%.

Hb for patients with VL in pregnancy was significantly lower compared to other pregnant women coming for ANC visit (median 11.8g/dL).

1b. What are disease related complications of VL in pregnancy, and how does this differ from non-pregnant VL patients?

Table 2 Complications during VL treatment

	Group 1 Pregnant N=87	Group 2 Postpartum N=26	Group 3 Non-pregnant N=223
Blood transfusion Missing data	7 (9.7%)* 15	4 (17.4%)* 3	3 (1.4%) 7
Jaundice (on admission or during treatment) Missing data	7 (9.5%) 13	1 (4.0%) 1	6 (4.2%) 81
Antibiotic treatment for suspected infectious complications - Total (iv. or oral) - Intravenous Missing data	 49 (66.2%)* 34 (45.9%) 13	 22 (88%)* 16 (64%) 1	 40 (29.9%) 10 (7.5%) 89

* p value < 0.05 (pregnant patients compared to non-pregnant patients and postpartum patients compared to non-pregnant patients)

Recorded complications during treatment are presented in table 2.
Blood transfusions were more frequently needed for pregnant patients compared to non-pregnant patients (OR 7.64, 95% CI 1.92-30.4) and for postpartum patients compared to non-pregnant patients (OR 14.9, 95% CI 3.11-71.7). Patients who received blood transfusion had a median lowest Hb value of 5.1 g/dL, ranging from 3.5 to 7.3 g/dL.
Jaundice occurred in 9.5% of pregnant patients, although this was not significantly different from non-pregnant patients.
Antibiotics for suspected infectious complications were more frequently prescribed for pregnant patients compared to non-pregnant patients (OR 4.60, 95% CI 2.40-8.45) and for postpartum patients compared to non-pregnant patients (OR 17.2, 95% CI 4.88-60.8.
Antibiotics were prescribed for the following (suspected) infectious complications (all patients combined): respiratory tract infection (37), ear infection (7), suspected urinary tract infection (7), eye infection (3), skin infection (3), abscess (2), malaria (2).
Other reported complications include elevated creatinine (12), hypoglycaemia (7), confusion (3).
Common complains across all groups were gastric cramping and epigastric pain. Although this could be part of VL symptoms or a side effect of SSG, often tinidazole or metronidazole was prescribed to cover gastro-intestinal parasitic infection (these prescriptions are not included in 'antibiotics for infectious complications').

Two pregnant patients were accidently started on SSG/PM treatment because the clinician was unaware of their pregnancy. Both patients had an adverse pregnancy outcome (first trimester abortion and immature delivery respectively).

PM toxicity (signs of hearing loss) leading to discontinuation of PM occurred in 1 pregnant patient and in 10 (5.1%) non-pregnant patients in the comparison group. In 6 additional cases hearing problems were noted but PM was not discontinued by the clinicians.
Change of treatment regimen from SSG to AmBisome (due to SSG toxicity, jaundice or deteriorating condition with severity score ≥ 5) occurred in 7 (3.6%) of non-pregnant patients and none of the patients with VL postpartum.

1c. What are treatment outcomes for VL in pregnancy and how does this differ from non-pregnant VL patients?

Treatment outcomes were not significantly different between the groups. Cure rates were high and mortality was low. One death occurred among the pregnant VL patients. She was 7 months pregnant and was admitted for VL treatment after a diagnostic delay and died after the first dose of AmBisome. One patient died after being diagnosed with VL postpartum. She had delivered a premature baby in the hospital three days earlier. Dilatation and curettage (D&C) was performed for suspected infected RPOC. She died on the fifth day of treatment; suspected cause of death was sepsis.

Extension of treatment after the standard dose (SSG/PM for 17 days or six doses of AmBisome (30mg/kg)) was common. This was either based on a positive ToC result (no parasitological cure) or because of 'no clinical cure' according to the clinician (patients still symptomatic after completing treatment). Treatment was more often extended for pregnant and postpartum patients compared to non-pregnant patients. Also, the proportion of patients with extension of treatment based on a positive ToC was significantly higher in pregnant patients compared to non-pregnant patients (OR 2.72, 95% CI 1.11-6.69, and higher for postpartum patients compared to non-pregnant patients (OR 9.40, 95% CI 3.31-26.7).
The total number of doses AmBisome was not significantly different between patients in the different groups. The median dose of AmBisome was 30mg/kg, ranging from 25mg/kg to 66mg/kg (IQR 29.0 – 38.5).
The presented total dose of AmBisome treatment excludes patients who died or defaulted.

Table 3 Treatment outcomes

	Group 1 Pregnant N= 87	Group 2 Postpartum N =26	Group 3 Non-pregnant N= 223
Treatment outcome			
- Cured	84 (96.6%)	25 (96.2%)	218 (97.8%)
- Defaulted	2 (2.3%)	0	3 (1.3%)
- Died	1 (1.1%)	1 (3.8%)	2 (0.9%)
Among those cured:			
Treatment extended			
Total	31 (35.6%)*	12 (46.1%)*	22 (9.8%)
- Based on positive ToC	10 (11.4%)*	8 (30.7%)*	11 (4.9%)
- Based on no clinical cure	20 (22.9%)*	3 (11.5%)	9 (4.0%)
- Reason not documented	1	1	2
Total dose AmBisome			
No. of doses **			
- 6	50 (64.9%)	8 (44.4%)	12 (48.0%)
- 7-8	18 (23.4%)	4 (22.3%)	10 (40.0%)
- 9-10	7 (9.1%)	1 (5.6%)	3 (12.0%)
- 11-12	2 (2.6%)	4 (22.2%)	0
- >12	0	1 (5.6%)	0
Missing data	5	0	1
Discharge			
- Clinical cure	34 (40.5%)*	7 (28.0%)*	166 (76.1%)
- Parasitological cure	50 (59.5%)	18 (72.0%)	52 (23.9%)
Missing data	3	1	5

* p value < 0.05 (pregnant patients compared to non-pregnant patients and postpartum patients compared to non-pregnant patients)
** For patients who were started on AmBisome as initial treatment regimen, and excluding defaulters and deaths.

For 4 patients with VL postpartum in group 2 (16% of postpartum patients on AmBisome regimen) the treatment regimen was changed to SSG/PM after six doses of AmBisome due to unsatisfactory response to treatment. The same happened for one non-pregnant patient.
Discharge Hb was significantly lower for pregnant and postpartum patients (median 8.5 and 8.0g/dL respectively) compared to non-pregnant patients (median 10.7g/dL).
A substantial number of pregnant/postpartum patients was discharged without parasitological confirmation of cure, although according to the protocol, this is indicated in these patient groups.

1d. What are risk factors for adverse outcomes (adverse pregnancy outcomes and need for extended treatment)

The following variables were compared between VL patients with and without adverse (pregnancy) outcomes; age, BMI on admission, Hb on admission, severity score, weakness score, prior VL, presence of oedema, presence of jaundice, spleen size, self-reported duration of symptoms (up to 1 month or $\geq$ 1 month), trimester, parity (primigravidae or subsequent pregnancies). These factors are known risk factors for adverse outcomes from other studies. Analysis was not done for (ultimate adverse) outcome 'death' as there were only two deaths in the pregnant/postpartum group and two in the group of non-pregnant women.
For patients who were pregnant on admission (group1), BMI was significantly lower among patients who had an adverse pregnancy outcome (adverse pregnancy outcome 1) (median BMI 17.4 for patients without adverse pregnancy outcome and median 16.1 for patients with adverse pregnancy outcome). However, these adverse pregnancy outcomes consist mainly of abortions, as immature deliveries and stillbirths were rare, and occurred therefore mainly in the first trimester when BMI can be expected to be lower than in the subsequent trimesters.
Adverse pregnancy outcome 2 occurred more among primigravidae compared with subsequent pregnancies (OR 4.33, 95% CI 1.03 – 18.2) and more in the first and the third trimester than in the second trimester. No other factors were identified associated with adverse pregnancy outcomes for women who were admitted with VL in pregnancy.

For patients with VL in pregnancy and VL postpartum (group 1 and 2) combined the following variables were significantly different for patients who needed extended treatment based on positive ToC: prior episode of VL, presence of oedema, duration of symptoms > 1 month.
Logistic regression was performed to ascertain the effects these variables on the likelihood that treatment was extended based on positive ToC. The only factor that remained significant was duration of symptoms > 1 month before time of diagnosis with VL (10 times more likely to have extended treatment).

For non-pregnant women in the comparison group (group 3), the following variables were significantly different for patients who needed extended treatment based on positive ToC compared to other patients; age, severity score, weakness score, prior VL, spleen size on admission. In a logistic regression model however, none of factors were significant as independent variables to predict need for extended treatment.

In a logistic regression model (binary logistic regression) with all patients combined (group 1,2,3) 'treatment regimen' was the only independent variable to predict the need for extended treatment. Patients treated with SSG/PM were less likely to have extended treatment based on positive ToC than patients on AmBisome treatment. Severity score on admission, Hb on admission, age, pregnancy status, primary/relapse VL and duration of symptoms were no independent predictors, although prior episode of VL (p 0.054) and duration of symptoms > 1 month before time of diagnosis (p 0.072) were almost significant.

1e. What are obstetric and perinatal outcomes for pregnant women with VL in our treatment setting? And how does this differ from non-VL deliveries in this facility.

Table 4 Obstetric and perinatal outcomes

	Group 1 Pregnant N=87	Group 2 Postpartum N=26
Data about pregnancy outcome available Missing data	81 6	24 2
Still pregnant at time of discharge Delivered during treatment	64 (79%) 17* (21%)	
Adverse pregnancy outcome 1 Adverse pregnancy outcome 2	8 (9.9%) 16 (19.8%)	6 (25.0%) 13 (54.2%)
Diagnosed with VL during 1st trimester - Pregnant on discharge - Abortion Diagnosed with VL during 2nd trimester - Pregnant on discharge - Immature delivery Diagnosed with VL during 3rd trimester: - Pregnant on discharge - Premature delivery - Term delivery Unknown gestation Live birth, unknown gestation Stillbirth	 17 (77.3%) 5 (22.7%) 31 (93.9%) 2 (6.1%) 9 (47.4%) 9 (47.4%) 1 (5.3%) 13 1	 N/A 4 N/A 1 N/A 7 4 8 1
PPH	6/17 (35%)	5/24 (20.8%)**
Retained products of conception requiring MVA/D&C	5/17 (29%)	6/24 (25%)

* Including one patient who delivered 4 days after completing treatment
** No reliable data from home deliveries

Seventy-nine percent (79%) of pregnant women were still pregnant at time of discharge and 21% delivered during the treatment (including one patient who came back for premature delivery 4 days after discharge from VL treatment).
Abortion and premature delivery were common, and occurred both before VL diagnosis and during treatment. Adverse pregnancy outcome in the second trimester was rare. Twenty-nine patients delivered in the third trimester (during treatment or before starting treatment). Data about birth weight are available for only 13 patients, with a median weight of 1.9kg, range 1.2 – 2.6kg.
Median birth weight of deliveries in Lankien health facility from healthy pregnant women in the same period is 3.0kg (n=698). Immature or premature deliveries make up 21.9% of all deliveries in the health facility. However, this is not representative for the prevalence of premature deliveries in the community, as the percentage of institutional deliveries is low and health facilities tend to receive complicated cases, thereby giving a biased view of what happens in the population.
Retained products of conception (RPOC) for VL patients were reported after first trimester abortion in six cases, after immature delivery in one case and after third trimester delivery in 4 cases.
Postpartum haemorrhage (PPH) was reported in 1.1% of normal (non-VL) deliveries and retained or incomplete delivery of placenta in 2.3%.

Chapter 4
Discussion

Determinants

VL is endemic in certain parts in South Sudan. The ecological settings for transmissions are the savannah regions with Acacia-Balanitis vegetation and forest areas with termite mounds and presence of the sand fly vector.
An important factor for endemic transmission in South Sudan is the pastoralist population moving back and forth between cattle camps and their 'permanent' homes, thereby walking at night. Sleeping outside houses in the dry season is another important risk factor for transmission.
VL control strategies should take these factors into account.
Epidemics in South Sudan are historically related to periods with civil unrest. Population movements from endemic to non-endemic areas and vice versa, malnutrition, poor housing, seeking shelter in the forests, and non-availability of health care services are factors identified from epidemics in the past. Peace and stability are vital for better VL control efforts and containment of future epidemics.

Health system response and access to care

The health system response to VL in South Sudan was described.
VL response is a joint effort by MoH, the KalaCORE consortium; and main implementing partners of VL treatment services are IMA and MSF. The MoH is strongly dependant on these implementing partners for service provision. An evaluation of the impact of the efforts from the KalaCORE efforts is being carried out at the moment.
The focus of the VL response in South Sudan is currently on improving access to care and improving outbreak preparedness. On the Indian subcontinent, where the focus has been on elimination efforts, a significant decline in reported cases was observed in recent years. In the current political environment with civil unrest, and with the current (health care and physical) infrastructure, such efforts are not feasible in South Sudan. Since South Sudan is the country with the second highest disease burden (after India) of VL, hopefully progress can be made towards elimination efforts in the future.

Access to care is challenging for several reasons in many places in South Sudan. Eighty-nine percent (89%) of patients in this cohort originated from Nyirol county, where the treatment facility is located. Although especially during the rainy season even short distances can be a difficult journey, a high proportion of patients (around 90%) presented within one month of self-reported onset of symptoms, which is used as an indicator of access to treatment in some other studies. No community-based surveys or other data showing the proportion of patients that does not reach a health facility are available, therefore no reliable conclusions about access to care can be drawn from this study.
Affordability is mentioned as a barrier to care in Ethiopia, mainly related to indirect costs. VL treatment is free in South Sudan, but such data about indirect costs are not available. Similarly, no studies about perception of service provision have been conducted.
Patients with VL in pregnancy constitute a particular patient group, because they need treatment with AmBisome, which requires cold chain and skilled health workers for intravenous administration. This is available in MSF treatment facility in Lankien but only in 6 of the treatment sites managed by IMA. Also, in MSF treatment facilities where uncomplicated primary VL cases can be treated in PHCU's, pregnant women have to be referred to the PHCC for AmBisome treatment and BeMONC facilities. In summary, access to VL treatment is challenging is South Sudan, and access to appropriate treatment for pregnant women even more.

Patient characteristics and treatment and perinatal outcomes for VL in pregnancy

Patient characteristics

The different patient groups were comparable in some aspects, but not all.
Age, county of origin, duration of symptoms and the proportion of primary and relapse VL were similar. The proportion of patients diagnosed with VL without splenomegaly was higher among pregnant women. It is likely that for some of these patients (especially in the third trimester) splenomegaly was difficult to assess and has been recorded as 'no splenomegaly' by mistake. Also in the other groups the reliability of physical exam for splenomegaly can be questioned, as this was often performed by community health workers dealing with high patient loads. BMI was higher among pregnant women, but this is likely to be due to the pregnancy and not representing a better nutritional status of pregnant women. No narrow range of BMI cut-off points exist that can be used for a specific trimester in this population. Mid upper arm circumference (MUAC) could be considered as a superior substitute for BMI to assess nutritional status. Association between MUAC and VL treatment outcome has not been studied for pregnant women, but MUAC is advised for nutritional programs in humanitarian settings as it has been shown a reliable indicator of risk of low birth weight(77).
An important difference between the three groups was the treatment regimen. Almost all pregnant women were with AmBisome, irrespective of the severity score and presence of jaundice, according to protocol. Non-pregnant women were treated with AmBisome only in case of severity score ≥5 or presence of jaundice. Most non-pregnant women were treated with SSG/PM. This needs to be considered when comparing the treatment outcomes of the different groups. The choice of treatment regimen in the postpartum group was ambiguous. The preferred treatment for patients diagnosed with VL postpartum is discussed below under treatment outcomes.
Few patients in this cohort were diagnosed with TB co-infection. TB-incidence in South Sudan was estimated 146/100.000 in 2017(78). However, a higher TB incidence can be expected in VL patients.(79) Because of the immuno-suppression in VL the prevalence of extra-pulmonary tuberculosis (EP-TB) could be relatively high. Because (EP-)TB is challenging to diagnose in field settings, TB treatment is often started empirically for patients who do not respond well to VL treatment. Tuberculosis infection is estimated 5.7-29.7% in VL-HIV co-infected patients, but no HIV infected patients were included in this cohort. This is different from settings in Ethiopia for example where 15-20% of VL patients are co-infected with HIV. The true prevalence of TB in VL(-HIV) infection and the clinical impact remain unclear(80).
Also, few malaria co-infections were reported. Malaria is endemic in South Sudan, with 159 infections per 1000 people at risk in 2016.(81) A possible explanation could be that some people were treated for malaria before being tested for VL. This information was not available as patients take their out-patient medical records home. There was a malaria outbreak in Lankien in the end of 2016, but data from these months were not available (see results section). Rates of malaria-VL coinfection in other studies vary from 3.8-60.8% depending on the treatment setting(82).

Disease related complications

Hb on admission was significantly lower for pregnant women compared to non-pregnant women and lower for postpartum women compared to pregnant women. The latter can be explained by blood loss during delivery, or a possibly a more severe stage of VL causing both anaemia and inducing delivery. Blood transfusions were more often needed in pregnant and postpartum patients compared to non-pregnant patients. Blood transfusions were given in case of severe anaemia (median Hb 5.7g/dL, range 3.3 – 7.3). The possibility of blood transfusion in this setting was dependant on the availability of compatible donors, often relatives of the patients.
Jaundice (either on admission or occurring during treatment) was reported in 8% of pregnant women. Jaundice is a sign of severe VL and hepatic failure was listed first

among causes of death in a study from Sudan about VL in pregnancy. Second and third causes of death were bleeding manifestation and severe anaemia/heart failure(58).
In this Sudanse cohort, the pregnant women were treated with SSG (source: personal communication). None of the jaundiced patients in the cohort we described died. The lower mortality in our cohort may be partly explained by the availability of AmBisome and live-saving blood transfusions.
Antibiotics were more often prescribed in pregnant and postpartum women compared to non-pregnant patients. It is possible that because the pregnant and postpartum patients were treated as inpatients, they were observed more closely (than most non-pregnant women, treated as outpatients) and ongoing fever may have caused the clinicians to prescribe antibiotics. There may have been over-diagnosis of respiratory tract infections in patients who had a cough as part of VL symptoms. On the other hand, VL is an immuno-suppressive condition and secondary infections are a known complication. Empiric antibiotic therapy can be a reasonable choice for certain patients in this resource constrained setting. However, it should be noted that the number of missing data regarding antibiotic use in the comparison group was quite high, so no strong conclusions can be drawn from these numbers.

Treatment outcomes
Mortality among pregnant and postpartum women was 2/133=1.8%.
The mortality in the group of non-pregnant patients may be slightly underestimated in this analysis. Two deaths were excluded because their medical records could not be found, and two were excluded because they were lactating women without an indication of how long ago they had delivered. Mortality rate in all non-pregnant female patients this age group in the study period was 2.8% (source: database with routinely collected data), which is comparable to previous reports(38,43).
In the pregnant and postpartum group treatment was more often extended compared to non-pregnant patients. This was either due to positive ToC's or 'no clinical cure' according to the clinician. However, compared to non-pregnant patients on AmBisome treatment, there was no significant difference in total dose of AmBisome. In a multivariate model, 'treatment regimen' was the only independent predictor for need to extend the treatment based in a positive ToC, with a higher change for AmBisome regimen compared to SSG/PM regimen.
Discharge Hb was lower in the group in the pregnancy and postpartum group compared to the non-pregnant patients. This is not surprising as Hb on admission was also lower in this group. Many pregnant and postpartum patients were discharged anaemic, despite routine treatment with ferrous sulphate and folic acid for all patients. This is a risk especially for pregnant women who may deliver at home after discharge from VL treatment.
According to the treatment protocol, patients diagnosed with non-severe VL postpartum may be treated with SSG/PM. However, some patients diagnosed shortly postpartum with non-severe VL were treated with AmBisome following the treatment regimen for pregnant women. Treatment with SSG/PM may be preferable for these patients as there is less often a need to extend treatment, treatment can be continued on an outpatient basis if the condition of the mother (and baby) permits, and it is cheaper. Patients with severe VL postpartum should naturally be treated with AmBisome.
A significant proportion of patients with VL in pregnancy were discharged without parasitological confirmation of cure. This is indicated because patients with VL in pregnancy are known to have altered function of the immune system and are thought to be at higher risk for disease relapse. As long as no prospective studies provide more insight in the risks of relapse for different groups of VL patients, it is important for clinicians to adhere to the protocol. Especially because patients often return to villages far from the treatment center after discharge from treatment.
On the other hand, for some patients, treatment was extended before awaiting the ToC results. Adherence to the protocol is important, because AmBisome has a long tissue half-life and an early decision to extend treatment may be unnecessary overtreatment.

Obstetric and perinatal outcomes

VL affected both primipara and multipara and occurred in all trimesters.

Twenty-one percent (21%) of pregnant patients delivered during or directly after finishing treatment. Most adverse pregnancy outcomes involved miscarriages in the first trimester or premature deliveries in the third trimester. It is interesting that few miscarriages/immature deliveries were recorded in the second trimester. The relation between adverse pregnancy outcomes and different immunological states of the pregnant women in different trimesters remains a point for future research.

More adverse pregnancy outcomes (adverse pregnancy outcome 2, including premature deliveries) were found among primigravidae. A similar outcome is known for malaria infection during pregnancy, with placental malaria with its adverse outcomes being more common among primigravidae, although the mechanism may be different. Placental malaria is thought to be caused by a variant of the parasite that selectively binds chondroitin sulfate A in the placenta, and primigravidae may lack immunity against this variant(59). Such information about placental invasion and the relation with different variants of the Leishmaniasis parasite is not known for VL in pregnancy.

When interpreting the perinatal outcomes, it should be noted that exact gestation of pregnancy was often not known, but estimated based on history of last menstruation and assessment of the abdomen on admission and/or assessment of the baby postpartum. No documentation from early ANC visits or ultrasound reports were available. A differentiation between intra-uterine growth restriction or low birth weight due to prematurity is therefore difficult.

Data about home deliveries after discharge from VL treatment were not available. Neither were data available from delivery in the health facility after discharge from VL, because these records could not be linked to the VL patient records. Because no follow-up data are available, it is possible that the actual number of adverse pregnancy outcomes is higher than the presented figures. Moreover, no follow-up data are available for neonatal outcomes. Preterm birth is the most important determinant of adverse infant outcomes in terms of survival and quality of life globally, and adverse outcomes are significant especially in low resource settings(83,84).

Part of the data about birth weight and gestation at time of delivery is missing, therefore no conclusions can be drawn from these numbers, but the available data show low birth weight deliveries, which is in line with the high number of premature deliveries.

Data about blood loss during delivery were not available from patients admitted postpartum after home delivery. PPH was reported in a high percentage of in-hospital deliveries, but did not lead to any maternal mortality, probably thanks to the presence of skilled health personnel, and availability of uterotonic drugs and blood transfusion.

Manual vacuum aspiration (MVA) or D&C treatment for RPOC were reported in 29-39% of cases. The reported incidence of RPOC in non-VL patients varies widely(85). Retained placenta is known to occur more frequently in women with preterm vaginal delivery than in women with term vaginal delivery (9.1% vs 1.1)(86). Routine evaluation for RPOC after all cases of miscarriage or pregnancy termination is likely to result in false positive diagnoses and unnecessary interventions since RPOC do not always lead to morbidity. On the other hand, evaluation is indicated for women with bleeding that is heavy or prolonged, and those with fever, uterine tenderness, or significant abdominopelvic pain. If RPOC are thought to be causing the symptoms, treatment with surgical evacuation or medication is warranted(87).

In VL patients it may be difficult to distinguish between fever due to VL and infected RPOC. In already anaemic patients prone for infectious complications and bleeding the threshold for clinicians to perform MVA/D&C may have been lower than in non-VL patients. A high rate of RPOC in VL patients has not been reported elsewhere.

Although it is most likely that a significant of adverse pregnancy outcomes can be contributed to VL infection, no community-based studies are available to compare pregnancy outcomes of patients with VL in pregnancy to pregnancy outcomes of healthy women. Compared to non-VL deliveries in the same treatment facility, prematurity was more common among VL patients and birthweight was lower.

Limitations, strengths and generalisability (retrospective cohort analysis)

Limitations
Limitations of the study include some missing data, especially for pregnancy and neonatal outcomes from women admitted shortly after home delivery. This is due to the retrospective study design.
Final pregnancy outcomes after discharge from VL treatment and neonatal outcomes until discharge and beyond are not known because follow-up data are not available. The same accounts for follow-up from VL perspective.
No community-based data are available to compare pregnancy outcomes between VL patients and the population. A comparison can be made with non-VL patients who delivered in the same facility, but these represent only a proportion of all deliveries.

Strengths
We described a large cohort of patients with VL in pregnancy and the early postpartum period. Previous publications about VL in pregnancy are limited in number and available studies have smaller patient cohorts.
Availability of patient records in general was good and data about patient characteristics on admission and treatment outcomes were complete in most cases.
Due to many years of experience with VL patients in this setting and well-established protocols, patient care was uniform/according to protocols in most aspects.

Generalisability
The following has to be considered regarding the generalizability of these findings to another setting. Different Leishmaniasis subspecies present with different clinical pictures and drug susceptibility, and this study was conducted in the East African setting. This study involved a patient cohort with low HIV prevalence and low rates of TB- or malaria-coinfection. The treatment setting can be described as a low resource setting, but with established experience in diagnosing and treating VL and essential drugs and facilities (cold chain, AmBisome, facilities for blood transfusion, obstetric care) available.

Future research
The following topics were identified for future research.
In adult patients, poor nutritional status is a known risk factor for death in VL patients. BMI may not be a useful indicator for nutritional status in pregnancy; MUAC is suggested as a superior substitute. The association between MUAC/nutritional status in pregnant women and VL treatment outcomes should be studied further.
In this cohort, only postpartum patients were only included 1-2 weeks after delivery and if they were already symptomatic before delivery. It would be interesting to also study women admitted in the following weeks or months postpartum and during the lactation period, to assess the response to treatment and the occurrence of relapses after treatment in pregnancy.
Follow-up of pregnancy outcomes after discharge and neonatal outcomes (survival, morbidity, and the occurrence of congenital VL) after delivery are important to understand the total the burden of VL in pregnancy. However, longitudinal follow-up is very challenging in this setting where people return to their villages after completing treatment, poor infrastructure, especially during the rainy season, and insecurity.
Much about the immunological response and pregnancy outcomes per trimester remains unknown. It would also be interesting to study placenta's of VL patients after delivery for the presence of placental invasion with parasites, including those who experience premature deliveries during treatment or after apparently successful treatment.
An overview of new drug developments is outside the scope of this thesis, but new drugs that are inexpensive, less toxic, administered orally, short acting, and do not require hospitalization, would surely improve the treatment of VL patients and patients with VL in pregnancy in particular.

Conclusion

VL is one of the NTDs and a disease associated with poverty. South Sudan has the second highest disease burden of VL in the world. Transmission is endemic in certain regions, and an important factor for transmission is the pastoralist population moving back and forth between cattle camps and their 'permanent' homes, thereby walking at night. Also sleeping outside in the dry season is an important risk factor, as the sand-flies transmitting the disease bite at night. Larger outbreaks are related to civil unrest, displacement and malnutrition. Access to health care is a concern in South Sudan, and reported cases are likely to underestimate the total burden of VL.
The health system response, supported by KalaCORE consortium, focusses on control, as elimination efforts are not feasible under the current circumstances. The South Sudanese health system is heavily dependent on NGOs for service delivery, and this will probably remain the case in the near future. An evaluation from the KalaCORE program is pending.
Treatment with AmBisome is indicated for patients with VL in pregnancy, which poses an extra challenge for access to care for pregnant patients, because not all VL treatment sites offer AmBisome treatment.
MSF has many years of experience treating VL in South Sudan, and 50% of reported cases in South Sudan were treated in Lankien in 2017.
A retrospective analysis using a cohort of VL patients was conducted to study characteristics and maternal and pregnancy outcomes of VL in pregnancy. Main findings include more severe anaemia on admission compared to non-pregnant women, and increased need for blood transfusion compared to non-pregnant women with VL (OR 9.3; 95%CI 2.5-34.2). Suspected infectious complications requiring antibiotic treatment were common, and antibiotics were prescribed more often (OR 6.0; 95%CI 3.4-10.6) compared to the comparison group. Extension of treatment after standard six doses of AmBisome (30mg/kg) was common for both pregnant and non-pregnant patients. This emphasises the importance of careful evaluation of cure after completing the standard treatment.
PPH and RPOC were reported frequently, but no maternal mortality due to PPH occurred in the hospital setting. Home delivery after VL treatment is a potential risk however, since many patients were discharged anaemic.
Adverse pregnancy outcomes (including miscarriage, immature delivery, premature delivery and stillbirth) were observed in 19.8% of patients admitted with VL in pregnancy and in 54.2% of patients diagnosed with VL in the first 1-2 weeks postpartum. Pregnancy outcomes after discharge from VL treatment and follow-up of neonates born to mothers with VL remain topics for future research.
Cure rates were high (96.5%) and mortality was low (1.8%) in this cohort of patients with VL in pregnancy. The availability of AmBisome treatment for pregnant women with VL, the availability of blood transfusion and the availability of BEmONC facilities have probably contributed to low mortality. It is important that these services are sustained in Lankien and these factors should be recognised in case of future planning of MSF VL treatment sites elsewhere. Good maternal cure rates in this cohort provide an optimistic example for treating VL in pregnancy in low resource settings.
Improvements for care at the MSF facility include better adherence to the protocol regarding evaluation of cure; avoiding sending pregnant women home without parasitological confirmation of cure and avoiding unnecessary overtreatment by extending treatment with extra doses of AmBisome without performing ToC.
The national guideline for treatment of VL in South Sudan states that AmBisome should be available at referral treatment sites. Continuing effort is needed to make this treatment more widely available. Ideally, pregnant women with VL should be treated in facilities with also blood transfusion and BEmONC services available, although this may not be a realistic goal in the short term.
Ultimately peace and stability in South Sudan would be beneficial to facilitate the health system response to VL.

Recommendations

- Ensure availability of AmBisome treatment for women with VL in pregnancy
- Ensure BEmONC facilities and possibility of blood transfusion to manage common complications of VL in pregnancy
- Improve adherence to the treatment protocol regarding evaluation of cure before discharge and before extending treatment
- Pregnancy outcomes after discharge from VL treatment and follow-up of neonates born to mothers with VL are suggested as topics for future research
- MUAC could be considered as a substitute for BMI as indicator of nutritional status for pregnant women with VL, but the association with treatment outcomes remains a topic for future research

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Annex 1 – MSF Kala azar treatment protocol

Kala Azar
Diagnosis and Treatment Protocol

For use by senior medical staff in South Sudan projects

MSF Holland
February 2016

Abbreviations used:
ART = Anti-Retroviral Therapy
BMI = Body Mass Index
d = day
DAT = Direct Agglutination Test
Hb = Haemoglobin
HIV = Human Immunodeficiency Virus
IT = Individual Test
KA = Kala Azar, same as VL = Visceral Leishmaniasis
kcal = kilocalorie
MSF = Médecins Sans Frontières [french] = Doctors Without Borders
PHCU = Primary Healthcare Unit
PHCC = Primary Healthcare Center
PICT = Provider Initiated Counselling and Testing (for HIV)
PKA = Primary Kala Azar
PKDL = Post-Kala Azar Dermal Leishmaniasis
PKMDL = Post-Kala Azar Mucosal-Dermal Leishmaniasis, same as PKDL Grade 3
PM = Paromomycin
RDT = Rapid Diagnostic Test
SSG = Sodium Stibogluconate (also known as Pentostam®)
TB = Tuberculosis
TOC = Test of Cure

1. INTRODUCTION TO KALA AZAR

Kala Azar, also called *Visceral Leishmaniasis* or VL, is a disease spread by sand flies *(Phlebotomus orientalis)*. These small insects live in the Red Acacia trees found in South Sudan. The sand fly ingests the Kala Azar parasites during biting a Kala Azar infected person. The Kala Azar parasite *(Leishmania donovani)* that lives inside the sand fly enters the body when a healthy person is bitten by an infected sand fly.
The parasite affects specific cells (macrophages) of the immune system - the body's defence army against diseases. These cells are mainly found in the spleen, the lymph nodes, and the bone marrow (where the blood is made, inside the long bones). This is the reason for a person with Kala Azar to present with a big spleen (splenomegaly), anaemia and often enlarged lymph nodes.

Kala Azar patients have very few red blood cells. This is called anaemia and makes the patient feel very tired and weak.
Kala Azar patients also have very few cells necessary for the clotting of blood (platelets), so they bleed easily and sometimes a lot.
Kala Azar patients also have very few white blood cells, meaning that the immune system (body's "defence army") is weak. The body cannot fight infections well.
Kala Azar patients get severely ill, and infections such as pneumonia and diarrhoeal diseases are very common among these patients. They can easily die from these infections.
Kala Azar patients lose a lot of weight, and most of them are malnourished on

admission.

Strongly enlarged picture of a sand fly – the life size is only 2 – 4 mm (smaller than a grain of rice)!

2. CLINICAL FEATURES (SIGNS & SYMPTOMS) OF KALA AZAR

2.1. History

It is very important that you start your consultation with taking the history. Let the patient tell their complaints, and then ask them specifically about the symptoms in the list below. Specific questions will help the patients to remember, in case they forgot some of the symptoms.

Symptoms	% of patients suffering from it
Fever (mainly in the afternoon)	**95**
Uncomfortable spleen	**85**
Wasting (weight loss)	**80**
Loss of appetite	**70**
Cough	**75**
Epistaxis (nose bleeding)	**50**
Diarrhoea	**40**
Vomiting	**15**
Oedema (swelling of the feet)	**5**
Jaundice (yellowish discoloration of the eyes)	**5**

You must also ask:

- **How long has the patient been sick? (Kala Azar patients are sick longer than 2 weeks but rarely longer than 6 months).**
- **Has the patient been treated for Kala Azar before? If yes: How long ago was he/she treated? What treatment was given? Which route was used (IM/IV/PO)? How long did the treatment take?**
  This will determine the (suspected) type of KA and thus the diagnostic test to use (and, if they test positive for Kala Azar, to choose the best treatment).

2.2. Clinical examination

- **Does the patient look sick?**
- **Look for signs of anaemia in the eyes, tongue and hands (very pale or white).**
- **Look for jaundice in the eyes (yellow colour).**
- **Examine the groin, neck and armpits for enlarged lymph nodes.**
- **Count and record the respiratory rate and auscultate the lungs, to find out if the patient has pneumonia.**
- **Check and record the degree of dehydration.**
- **Get the patient to lie down and check for the size of the spleen: measure the spleen size using a tape measure along the mid-clavicular line (the line starting from the middle of the collarbone [clavicula] downwards) from the bottom of the ribs along the direction of growth; record the size of the spleen in cm.**
- **Examine for an enlarged liver: measure the liver size the same way you measured the spleen size; record the size of the liver in cm.**

- **Check and record the temperature.**
- **Press the front of the shins with your thumb in one place for three full seconds and release, to find out if there is fluid in the tissue (oedema).**
- **Check whether the patient has Malaria (RDT [Paracheck] or blood film).**

This table shows what proportions of patients have the following signs:

Signs	% of patients presenting with it
Splenomegaly	**95**
Lymphadenopathy	**75**
Anaemia *(pale conjunctives)*	**75**
Hepatomegaly	**60**
Jaundice	**5**
Oedema	**5**

Patients with Kala Azar have been sick for more than 2 weeks.
They could be referred from other clinics, MSF OPD/IPD or be self referral cases.

You must always ask patients whether they have recently been tested positive for Malaria and completed a full course of treatment with an antimalarial. If not, do a rapid test for Malaria (SD Bioline) on all suspected Kala Azar patients. If the test result is positive, treat the patient with Artesunate/Amodiaquine (see protocol or Annex 2 for dosage). If the patient has received Malaria treatment in the past three weeks, ask the lab for blood film microscopy for Malaria parasites, because the RDT will remain positive for several weeks after end of treatment.

3. TYPES OF KALA AZAR

3.1. Primary Kala Azar (PKA)

Primary KA is defined as when patients have Kala Azar for the first time.

3.2. Relapse Kala Azar

Relapse is defined as when patients come with Kala Azar after previous successful treatment for KA. Most relapses occur within 6 months of initial discharge; these are called *first relapses*. A patient who had a first relapse, was re-treated and got cured again, can get a *second relapse*. Patients who relapsed already once have a higher chance of a second relapse, and a higher chance of failing to respond to treatment – because of host factors (HIV, TB etc) and because of parasite drug resistance.

- **First Relapse: patients who present with KA after previous treatment for KA once.**
- **Second Relapse: patients who present with KA after treatment for a first relapse.**
- **Third Relapse: patients who present with KA for the third time after treatment for a second relapse.**

3.3. Treatment after interruption

For a patient who already received partial treatment and comes back after defaulting, or if the treatment is re-started after it was interrupted by the doctor or the nurse due to development of side effects, it is called "Treatment after interruption".

3.4. PKDL and PKMDL

PKDL and PKMDL stand for "Post-Kala Azar Dermal Leishmaniasis" and "Post-Kala Azar Mucosal-Dermal Leishmaniasis". These pathologies are immunological complications of successful treatment of Kala Azar, and usually develop shortly after treatment for Kala Azar, but sometimes appear already during treatment. They occur if not all the parasites have been killed, but instead they leave the internal organs to move to the skin.
PKDL starts with lumps (papules) on the face and can spread to the chest, back and arms. When it affects the nose, mouth and eyes and causes sores, it is called PKMDL.

In most cases PKDL is mild and does not need treatment. It doesn't look nice but otherwise it will not harm the person; it disappears by itself after some time. A person with PKDL should take extra care to sleep under a mosquito net (like all patients with *Leishmania* infections) to prevent spreading the Kala Azar parasites to the sand flies and thus to other people.

Grading:

- **Grade 1 PKDL – the rash is only on the face**

- **Grade 2 PKDL – the rash is also on the chest and other parts of the body**
- **Grade 3 PKDL or PKMDL – the rash is dense and covering most parts of the body, and may be crusting or scaling; there may be sores in the nose and/or mouth, or the eyes are affected (PKMDL)**

Only severe Grade 2 PKDL (disfiguring nodules in the face) and Grade 3 PKDL/PKMDL require treatment, especially if the eyes are affected (risk of blindness).

4. DIAGNOSIS OF KALA AZAR

4.1. Case definition

To diagnose Primary Kala Azar or Relapse Kala Azar, a patient must first meet the criteria of the case definition for suspected Kala Azar.
You should only **test patients who fit the *case definition*:**

History of fever for more than 2 weeks

and

Splenomegaly
or
Lymphadenopathy
or
Wasting (W/H <-2 Z-score or <16 BMI)

4.2. Diagnostic tests

4.2.1. IT Leish rapid test (rK39)

This is a rapid dipstick test that is very specific. This means that if the patient meets the clinical case definition, and the test is positive, the patient does have KA, although it might miss some cases (false negative results).
See Annex 1 on how to perform the test.
The test stays positive for a long time even after the patient is cured; therefore, do NOT use the test if a patient has had KA before. Patients fitting the case definition with a high suspicion of KA and a negative IT Leish test should get a DAT (see below).

4.2.2. DAT (Direct Agglutination Test)

DAT is used to diagnose Primary Kala Azar in KA suspect cases, and is more sensitive than the IT Leish. This test is done in a laboratory, but the sample can be taken anywhere (see Annex 1). The DAT test stays positive for a long period of time even after the patient is cured; so do NOT use the test if a patient has had KA

before. If the DAT test does not give a clear result ("borderline"), refer the patient for a spleen or lymph node aspirate.

4.2.3. Aspirates

Microscopic examination of tissue smear obtained by either lymph node or spleen aspiration is the only way to diagnose relapses. Spleen aspirate is the most reliable and sensitive, but it must be done by a doctor or well trained senior medical person, as the procedure bears a certain risk of bleeding. *Avoid* spleen aspirate in patients with: bleeding tendency (e.g. frequent nose bleeding) or a history of bleeding, low haemoglobin (<5), jaundice, spleen size below 2-3 cm, young children and pregnant women.
Lymph node aspirates can be done safely by trained staff, but are less sensitive than spleen aspirates (many false-negative tests).

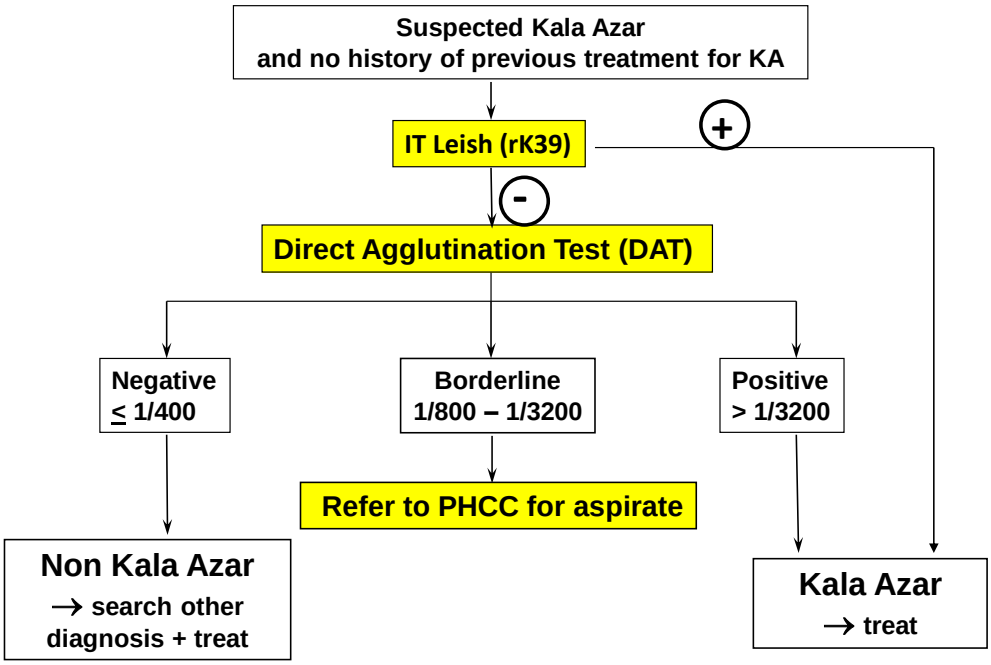
4.2.4. Clinical diagnosis – PKDL/PKMDL

Diagnosis of PKDL/PKDML is based on clinical presentation and history. Check appearance and distribution of lesions.

4.3. Choice of diagnostic method

4.3.1. PHCU Protocol

Diagnostic algorithm for Primary KA on PHCU level

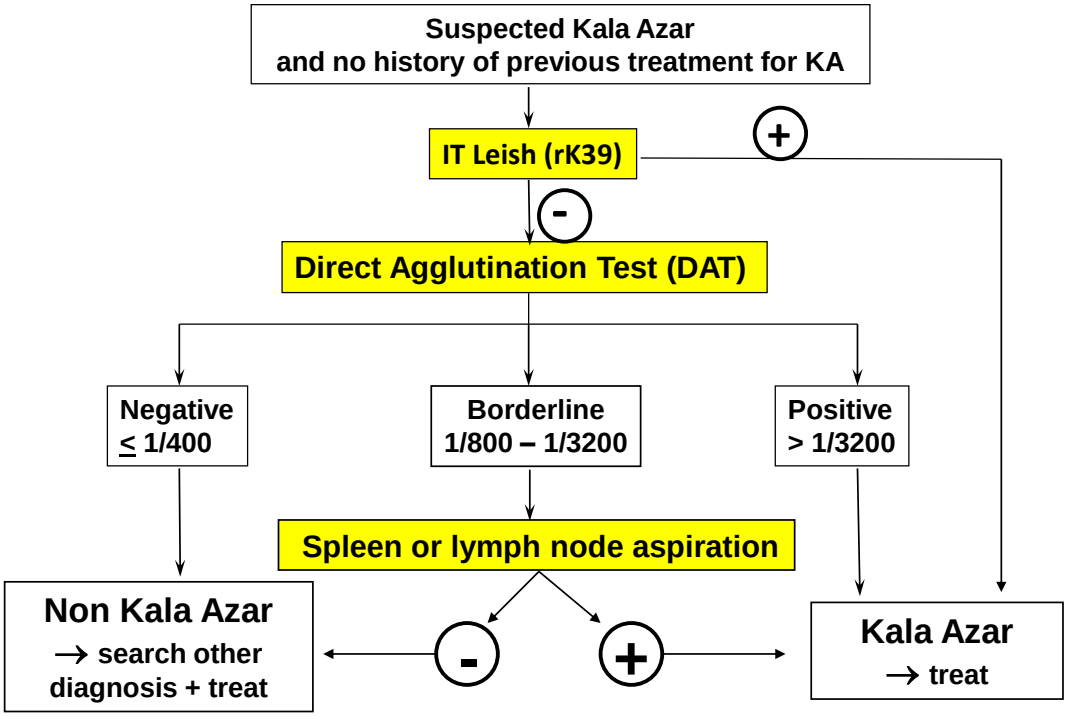


Severely sick patients eligible for AmBisome treatment (see chapter 15.) should be referred to PHCC for treatment.

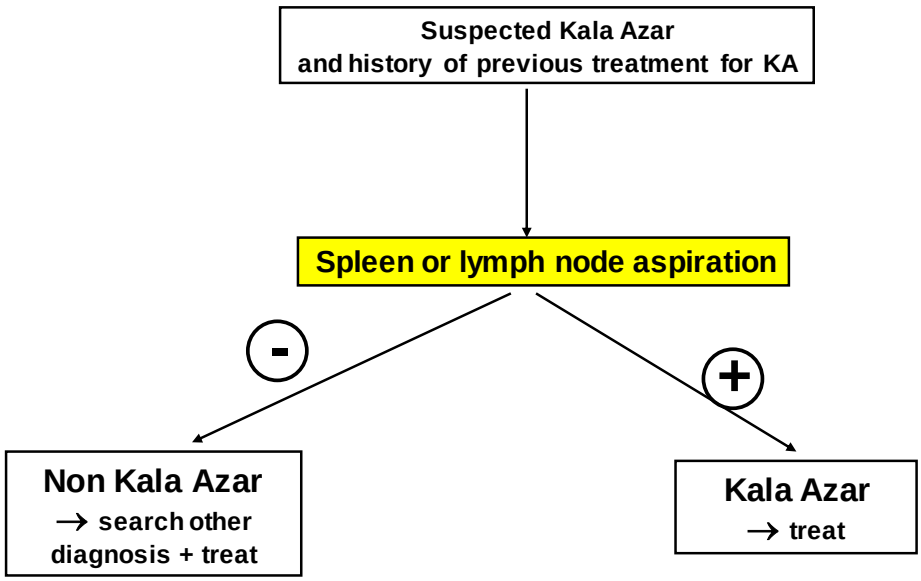
Suspected relapse patients (clinical suspected KA with history of previous treatment for KA) should be referred to PHCC for aspirate diagnosis.

4.3.2. PHCC Protocol

Diagnostic algorithm for Primary KA on PHCC level



Diagnostic algorithm for Relapse KA



4.3.3. Clinical suspicion and negative tests

In some clinically suspect patients the rK39, DAT and lymphnode aspirate are negative, and only after several attempts the lymphnode aspirate turns positive, resulting in significant treatment delay. (Splenic aspirates are more sensitive). In such cases a quantitative DAT test can give earlier confirmation of disease. An increasing DAT titre between two DAT tests 5-7 days apart is adequate confirmation, even of the titres are still below the positive threshold of 1:6,400.

5. DIFFERENTIAL DIAGNOSIS FOR PATIENTS WITH NEGATIVE DAT, IT LEISH OR ASPIRATE TEST

In South Sudan there are several other diseases that may clinically look like Kala Azar (prolonged fever, splenomegaly):

5.1. Malaria

Although acute Malaria makes people sick for just a few days, there are also chronic forms of Malaria. Children who suffered from Malaria many times may have a big spleen, but it usually feels firmer. They can be malnourished under this condition too. But once you have treated the Malaria properly, they should improve quickly.
Treat with Artesunate/Amodiaquine (see Annex 2).

5.2. Typhoid fever

- **High fever**
- **Bradycardia (slow heart rate)**
- **Duration less than 1 month**
- **Impaired mental status (confusion)**
- **Constipation or diarrhoea**
- **Acute abdomen**

See PHCC protocol.

5.3. Typhus

- **Fever – variable length**
- **Hepatosplenomegaly**
- **Bleeding tendency**
- **Treatment: Doxycycline 200 mg PO single dose**

5.4. Brucellosis

Patients have a long history of fever, little or moderate splenomegaly and an enlarged liver. Usually there is also joint or bone pain. If you suspect Brucellosis, refer to PHCC.

5.5. Schistosomiasis (Bilharzia)

The patients may present with a very large liver and spleen, which they have often had for a very long time. Most patients are not so unwell, usually with no fevers, although sometimes they might have a liver damage which causes ascites (fluid in the abdomen).
Stool or urine analysis will show eggs of *Schistosoma*.
Treatment: Praziquantel.
NB: Inform the patient that treatment will not reduce spleen and liver size immediately; it will just stop the disease getting worse.

5.6. Splenic abscess

This is unusual; it makes the patient very sick. Patients have high fever and a very tender spleen. They may tell you that someone in the village has cut or injected them. Pus will be seen on a spleen aspirate.
Treatment: Metronidazole and Ciprofloxacin.

5.7. Extrapulmonary Tuberculosis

Patients present with malnutrition and a history of fevers for up to several months. They will not have an enlarged spleen, but they may have very large lymph nodes (depending on the type of TB).
Refer to a TB treatment center.

5.8. Tropical splenomegaly

This is an immunological reaction to Malaria. The patients may have had a very large spleen (often combined with an enlarged liver) for years. There is no fever. For management, only thing to do is exclude acute Malaria.

5.9. AIDS/HIV

The HI virus damages the immune system, so that the body of an infected person cannot properly fight against diseases. Patients often get diarrhoea, which may lead to malnutrition/wasting and dehydration like in a Kala Azar patient. They may also have cough, oral thrush (white coating on the tongue), Herpes zoster rash (Shingles) or scars, as well as other infections.
Make sure to treat all the other diseases potentially associated with HIV infection. If possible, refer to a facility offering ART.

5.10. Leukaemia (Chronic Myeloid Leukaemia)

These patients have fever, a big spleen and episodes of bleeding. They are also susceptible to other infections. Blood testing shows a high white blood cell count. Refer to hospital.

6. HIV AND KALA AZAR – PROVIDER INITIATED COUNSELLING AND TESTING

Provider Initiated Counselling and Testing (PICT) for HIV should be performed on all confirmed KA patients (according to standard procedures), because the result will determine their KA treatment - *there is a high risk for SSG toxicity-related mortality in HIV co-infected patients!* – and ART should be started as soon as possible to improve immunity and reduce the risk of relapse.

All confirmed HIV/KA co-infected patients must get an aspirate to determine the baseline parasite load, to be able to check later on the efficacy of treatment through a test-of-cure (TOC).

If a patient is too ill to receive PICT on admission, he/she should automatically be entered into the regimen for severe KA (see 15.).
Counselling and Testing should be discussed with the patient as soon as the condition allows.

7. ADMISSION TO THE KALA AZAR PROGRAMME – ADMISSION CHECKLIST

7.1. Explanations to the patient

Explain the disease, the program, the specific treatment and its expected duration (including the possibility of prolongation), the special nutritional needs, possible side effects and the decision on the end of treatment (clinical, TOC). Make sure the patients understand that it is very important to come every day for their injections!
Take your time to answer any questions that might arise; this will create trust and increase adherence to the treatment.
Keep in mind that the South Sudanese know Kala Azar and its traditional treatment (SSG).
The later developments (AmBisome and Miltefosine) are not well known yet, therefore a good explanation is crucial for adherence.

7.2. Non food items

Give a cup, a bar of soap, a blanket and a mosquito net to each patient on admission.

7.3. Routine drugs

Give Vitamin A (Retinol) and Folic acid routinely; see Annex 2 for dosage. Vaccinate all patients between 6 months and 16 years of age against Measles on the day of admission if they do not have documented proof of vaccination. Because children with KA are immunosuppressed, vaccine efficacy is expected to be lower. Therefore it is recommended that children receive a second measles dose on discharge, even if this is less than one month after the vaccination on admission.

7.4. Filling in the patient card

The patient card always needs to be filled in diligently - all the information is very important for follow up, treatment decisions and program improvement.

The patient card must contain:

- Patient number **(serial number) according to the KA register: ensures that only a KA patient gets treated for KA. Important for follow up in case of PKDL or relapse.**
- Name **of** KA treatment center**: to estimate the distance to the place of residence.**
- Name **of the** patient**.**
- Date of admission **to the program.**
- Referred from**: self-referral, other health structures, or outreach team.**
- Sex **of the patient: women of reproductive age must start contraception when put Miltefosine (see 10.).**
- Age **in months or years: part of severity scoring (see 15.).**
- Place of residence **for the past 6 months: county, payam and village. Important for mapping of cases and tracing of defaulters.**
- Previous KA treatment: **if yes – *try to find out as many details as possible*. Where, what test was used, which drug was given for how long? Previous treatment history is essential to classify patients as relapse, treatment after interruption or PK(M)DL.**
- Duration of illness **in months before admission.**
- Indicator of weakness**: collapse/severely weak/other. Part of severity scoring (see 15.).**
- Weight **in kg: to calculate drug dosage and evaluate response to treatment.**
- Height **in cm (children) or m (adults).**

- Nutritional status **on admission: Part of severity scoring (see 15.).**
  Z-score **for children and adolescents less than 19 years:**
  The Z-score expresses the weight of a child or an adolescent in relation to his/her height, and thus the nutritional status.
  The *Z-score table* shows the deviation from the median weight for a given height:
  <-2 Z-score means moderate malnutrition, <-3 Z-score means severe malnutrition.
  *Body Mass Index **(BMI)*** **for adults above the age of 18:**
  BMI expresses the weight of an adult in relation to his/her height, and thus the nutritional status.
  Calculation of BMI:
  Weight in kg divided by height in metres divided by height in metres again = BMI Example: patient weight 58 kg and height 1.67 m -> 58 ÷ 1.67 ÷1.67 = 20.8 BMI
  BMI <16 means severe malnutrition.

- Size of spleen **and liver on admission in cm: to evaluate response to treatment.**

- Lymphadenopathy**: yes/no.**

- Haemoglobin (Hb) **in g/dl: part of severity scoring (see 15.).**

- Pregnancy**: yes/no. Different treatment regimen for pregnant women.**

- Jaundice**: yes/no. Different treatment regimen for jaundiced patients.**

- Oedema**: -/+/++/+++.**

- **Overall** severity score**: see 15. To determine treatment regimen.**

- TB co-infection**: yes/no.**

- VCT code**: encoded HIV serostatus. Different treatment regimen for HIV co-infected patients.**

- **Date and result of** IT Leish **(OptiLeish) test.**

- **Date and result of** DAT **test in well titre, if done.**

- **Date and result of microscopy of spleen or lymph node** aspirate **in grading, if done.**

- **Final** diagnosis**: Primary KA (PKA), Relapse KA, or PKDL/PKDML.**

- Date **of** start **of treatment**, treatment regimen **and** dosage**.**

- Routine drugs **and other treatments, if any.**

- Vital signs**: temperature, pulse rate, blood pressure (in adults), respiratory rate.**

- **Comprehensive** medical history**: ask specifically for vomiting, diarrhoea, bleeding and cough.**

8. TREATMENT REGIMEN

8.1. PHCU

8.1.1. Primary Kala Azar

Paromomycin for 17 days and SSG for 17 days (PM17/SSG17).

8.1.2. PKDL/PKMDL

Paromomycin for 17 days and SSG for up to 30 days (PM17/SSG30).
Refer to PHCC if there is no improvement after 30 days of SSG.

8.1.3. Severe Kala Azar, Relapse & Severe PKMDL

Refer suspected relapses and severe cases of PKA and PKMDL to PHCC.

8.2. PHCC/Hospital

8.2.1. Primary Kala Azar

Provider Initiated Counselling and Testing - PICT (also if tested negative before)

- **HIV negative (tested) patients, or patients who refuse HIV testing:**

Assess severity – see 15.
If severity score is <5:
Paromomycin for 17 days and SSG for 17 days (PM17/SSG17).

TOC is not needed if clinically cured; if the condition has improved and symptoms have disappeared, a patient can be discharged (see chapter 13.1).

If the patient has not clinically responded well to treatment (e.g. still has fever, is still feeling ill, no appetite, or no reduction of spleen size), do a TOC between on day 21; if negative, discharge from KA program and refer for further medical investigation.
If TOC is positive, continue with SSG until getting a negative TOC, up to a maximum of 60 days (SSG60). The TOC is repeated weekly; once you have a negative TOC, stop treatment. If symptoms are still persisting, refer for further medical investigation.
If TOC after 60 days of SSG treatment is still positive: *contact KA Adviser to decide on a new treatment regimen*.
NB: Dates of the planned Tests of Cure should be written on the patient card!

- **Severe cases: see 15.3.**

- **HIV positive patients: see 8.4.1.**

8.2.2. First Relapse Kala Azar

Provider Initiated Counselling and Testing - PICT (also if tested negative before)

- **HIV negative (tested) patients or patients who refuse HIV testing:**

Assess severity – see 15.
If severity score is <5:
Paromomycin for 17 days and SSG for at least 30, up to a maximum of 60 days (PM17/SSG30–60).

TOC is done on day 23 and 30. If both tests are negative and the patient is well: discharge. If one of the TOCs is positive, continue treatment and repeat TOC weekly until two consecutive tests are negative.
If TOC remains positive after completion of 60 days of SSG, and/or the patient remains unwell, *contact KA adviser* and start with AmBisome 5 mg/kg/dose twice weekly (e.g. Tuesday and Friday) for at least 2 weeks and up to a maximum of 8 weeks. Repeat TOC weekly; continue treatment until two consecutive TOCs are negative.
If TOC remains positive after 8 weeks of AmBisome, *contact KA adviser again*.
NB: Dates of the planned Tests of Cure should be written on the patient's card!

- **HIV positive patients: see 8.4.2.**

8.2.3. Second and Third Relapse Kala Azar

Contact KA adviser. Choice of drug combination and length of treatment for multiple relapse patients will depend on previous treatments and response.

In relapsed patients, try as much as possible to exclude HIV and TB; in the presence of these
diseases, cure of KA may be impossible. TB may not be clinically obvious, but is a common cause of frequent relapses or inability to cure – you may need to treat TB empirically.
HIV positive patients must start ART.
See algorithm in Annex 3.

8.2.4. PKDL/PKMDL

Patients should also be assessed for severity (like KA patients) and tested for HIV, to decide whether they should avoid SSG treatment. However, such cases are rare; if you find one, contact KA adviser for advice.
Otherwise, treat with PM17/SSG30; if needed, SSG treatment can be extended up to
60 days.
Stop treatment when there is clear improvement of the PKDL rash; there is no

need to continue until the skin rash has completely healed. No TOC necessary.
If the patient shows no improvement, *contact KA adviser*.

8.2.5. Pregnant and lactating women

Pregnant women with KA have an increased risk of spontaneous abortion, still birth, and premature birth as compared to non-KA pregnant women. Pregnant women with KA are also more at risk of death because of severe anaemia and decreased immunity. During and after delivery the anaemia and higher bleeding tendency (low platelet count) may result in fatal haemorrhagic complications. Blood transfusions may be indicated more frequently.

During pregnancy and lactation, immunity is decreased, which may reduce treatment response and inhibit an effective cell-mediated immunity after treatment. However, clinical assessment of cure in pregnant women is hampered because the spleen cannot be palpated, and because weight loss is difficult to measure. Therefore, a test of cure is indicated during pregnancy and the first 6 months of lactation. It has to be taken into account that during the second and third trimester of pregnancy a spleen aspirate is not possible, and one has to rely on (less sensitive) lymph node aspiration for TOC.

Because of the harmful effects of most KA drugs in pregnancy, routine pregnancy testing should be done before treatment initiation. If no test is available, check if you can find out whether the woman might be pregnant: physical examination, first day of last menstruation.

AmBisome is the drug of choice in pregnancy as it is the safest option. SSG has proven to be toxic, resulting in high incidence of spontaneous abortion as well as premature delivery. Paromomycin can cause ototoxicity in the foetus. Miltefosine is potentially teratogenic and should never be used during pregnancy.

Vertical mother-to-child transmission resulting in congenital KA in the infant has been reported. Therefore, following up infants born from mothers diagnosed with KA might increase diagnosis and prevent avoidable deaths in infants.

There is vertical transmission of antibodies from the mother to the infant. Therefore an infant of a mother who had KA during pregnancy will be serologically positive (IT Leish, DAT), even if it does not have KA itself. However, an infant who is symptomatic of KA, has a positive serology, and a mother who had KA during pregnancy, is very likely to have KA, and should be started on treatment.

8.2.6. Jaundiced patients

Patients who have jaundice (yellow eyes) should always be referred directly to a senior medical person; these patients are very sick, and have a high risk of dying. The senior medic will confirm the jaundice, and testing will be done to prove whether they really have KA.
If the Kala Azar test turns out positive, the patient is treated with full course AmBisome.

8.3. Treatment of Kala Azar in HIV positive patients

8.3.1. Primary Kala Azar in HIV positive patients

Baseline parasite load will be determined by aspirate before start of treatment.

Treatment: AmBisome 5 mg/kg/dose x 6 doses over 12 days + Miltefosine x 28 days.
In projects which offer Anti-Retroviral Therapy, the patient should start ART. Women in childbearing age must start effective contraception (preferably Depo Provera) due to the contra-indication of Miltefosine during pregnancy. Because Miltefosine remains in the body for a long time after treatment, contraception should be given during treatment and for three months after.

TOC is done on day 28; if negative, the patient can be discharged.
If it shows no or no *significant* parasite reduction (≤1 grade), start the patient on PM17/SSG17-30. TOC 2 will then be done on day 45 (after 17 days PM/SSG); if negative: discharge; if positive: continue with SSG up to 30 days and repeat TOC on day 58 (SSG30); if negative: discharge; if positive: *contact KA adviser*.
If TOC on day 28 shows *significant* parasite reduction (≥2 grades), the patient will have another full course AmBisome 5 mg/kg/dose x 6 doses over 12 days + Miltefosine x 28 days. TOC 2 will be done on day 56 (after the second course); if negative: discharge; if positive: start with PM17/SSG17-30. TOC 3 will then be done on day 73 (after 17 days PM/SSG); if negative: discharge; if positive: do TOC 4 on day 86 (SSG30); if negative: discharge; if positive: *contact KA adviser*.

NB: Put extra emphasis on hydration to reduce the risk of SSG toxicity - the patient should drink plenty of water, and must be monitored for signs of dehydration.

8.3.2. First Relapse Kala Azar in HIV positive patients

Baseline parasite load must be determined by aspirate before start of treatment.

Treatment: AmBisome 5 mg/kg/dose x 6 doses over 12 days + Miltefosine x 28 days; start ART.
ONLY in case of complete clinical and parasitological unresponsiveness to AmBisome+Miltefosine combination therapy during Primary Kala Azar treatment, relapse treatment will be initiated with PM17/SSG30-60.

TOC 1 will be performed on day 28 and TOC 2 on day 35; if both negative: discharge.
If TOC positive and no or no *significant* parasite reduction (≤1 grade): PM17/SSG30-60; perform TOC weekly after day 23 of SSG; if 2 consecutive TOCs are negative: discharge; if TOC on day 60 of SSG is still positive: *contact KA adviser*.
If TOC positive, but *significant* parasite reduction (≥2 grades): AmBisome 5 mg/kg/dose x 6 doses over 12 days + Miltefosine x 28 days; perform TOC on day 28 and day 35 of the second course of AmBisome/Miltefosine. If both negative: discharge. If positive: start PM17/SSG30-60; from day 23 of SSG start performing TOCs weekly - if negative for two consecutive weeks: discharge; if positive on day 60 of SSG: *contact KA adviser*.

8.4. Summary table: Treatment of Leishmaniasis

Situation	*Treatment regimen*	*TOC*
Primary KA	PM17/SSG17	Do only if patient still appears clinically sick on day 21
Primary KA, slow responder (TOC positive after PM17/SSG17)	Continue treatment with SSG up to 60 days *Consider TB*	First TOC is positive on day 21. Continue SSG and repeat TOC weekly until test is negative; if still positive after 60 days SSG: *contact KA adviser*
Primary KA, HIV positive	AmBisome 5 mg/kg/dose x 6 doses over 12 days plus Miltefosine x 28 days Start ART *(if possible)*	Baseline parasite load. TOC on day 28. If negative, discharge; if positive: see algorithm
First Relapse	PM17/SSG30-60 *Consider TB*	TOC on day 23 and 30. If both test are negative, discharge; if positive, continue once per week until two consecutive tests are negative; if positive after 60 days SSG: see algorithm
First Relapse, HIV positive	AmBisome 5 mg/kg/dose x 6 doses over 12 days plus Miltefosine x 28 days Start ART. *Consider TB*	Baseline parasite load. TOC on day 28. If negative, discharge; if positive: see algorithm
2nd, 3rd Relapse etc	***Choice and length of combination therapy depending on previous treatment experiences: contact MedCo.*** *Consider TB treatment*	*2 consecutive negative TOCs, one week apart, are required before discharge: contact KA adviser*
SSG toxicity	AmBisome 5 mg/kg/dose x 6 doses over 12 days or Continue PM/SSG after break	Do only TOC if patient still appears clinically sick on day 21
Pregnancy, and until 6 months post-partum	AmBisome 5 mg/kg/dose x 6 doses over 12 days	Do routine ToC on day 21, and if positive, repeat on day 28?
Jaundice	AmBisome 5 mg/kg/dose x 6 doses over 12 days *Check urine for Bilirubin*	Do only if patient still appears clinically sick on day 21
Severe KA (Primary + Relapse)	AmBisome 5 mg/kg/dose x 6 doses over 12 days	Do only if patient still appears clinically sick on day 21
PKDL/PKMDL	**PM17/SSG30-60**	**Not needed.** **If no improvement:** ***contact KA adviser***

8.5. Daily routine

For all **patients** every day**...**

- ✓ **Take the TEMPERATURE**
- ✓ **ASK THE PATIENT how he/she feels *(not the caretaker, if possible!)***
- ✓ **LOOK FOR SIGNS OF DRUG SIDE EFFECTS (including hearing problems when treated with PM) and INTERCURRENT ILLNESS**
- ✓ **LOOK FOR SIGNS OF DEHYDRATION and encourage fluid intake**

8.5.1. Clinical assessment

Ask the patient how he/she feels and note it on the card. It is very important to document every day so that there is a treatment record; thus you can see whether the patient is improving, and how fast.

8.5.2. Ferrous fumarate 185 mg (=60 mg elemental iron) + Folic acid 0.4 mg tabs

Give Ferrous fumarate 185 mg + Folic acid 0.4 mg daily to all KA patients *except to severely malnourished children* (MUAC <125mm, W/H <-3 Z-score and/or bilateral oedema) as for them, the iron can be dangerous!
Otherwise give:

- **½ tablet (30 mg elemental iron) to children less than 15 kg**
- **1 tablet (60 mg elemental iron) to patients of 15 - 35 kg**
- **2-3 tablets (120-180 elemental iron) to patients above 35 kg**

8.5.3. Folic acid 5 mg tablets

Give 2 tablets of Folic acid 5 mg daily to all KA patients, adults and children.

8.5.4. High-energy food

***Besides the regular food from the WFP-ration,* patients should get additional 1000 kcal/day in form of specialized food such as PlumpyNut, F100 milk or BP 5 biscuits. Depending on what is available, the same should be given to all patients during**

treatment. Observed nutrition is the ideal, i.e. one of the sachets of PPN can be given while the patient is waiting for consultation, so the consultant has a better idea of appetite.

Amount of kilocalories per food item:

Item	***BP 5***	***PlumpyNut***	***F100***
Quantity	**1 bar**	**1 sachet**	**500 ml (=1 cup)**
Kcal	**250**	**500**	**500**

Tell the patient and the relative that it is very important that the *patient* gets this as it is *medicine* for him/her, and will help to make his/her body strong to fight Kala Azar.

Malnourished adults should receive additional 2000 kcal/day; children must be admitted to a Therapeutic Feeding Program (TFP).

8.6. Weekly activities

8.6.1. Chart review

Do a chart review once a week on a fixed day to see the patient's progress (size of spleen, weight gain etc) and to check for possible mistakes in calculations of drug dosages, BMI etc.
Also make sure that the daily documentation is complete and correct, and done with diligence.

8.6.2. Weight

Weigh the patient every week and recalculate the dosage of the Kala Azar medication; *it is very important that the patient gets the correct dose.*
Weight gain is also a sign of treatment progress.

8.6.3. Weekly food distribution

Usually, this comes from WFP; each patient receives a ration which also includes an amount for the caretaker.

8.6.4. Distribution of soap

Each patient receives one piece of soap per week.

9. PATIENT EDUCATION

- ✓ **Health Education prevents people from becoming sick or helps them to get healthy again quickly.**
- ✓ **It is just as important as treating the disease!**
- ✓ **Teach the patient how to avoid getting Kala Azar so they can protect themselves and their family members.**
- ✓ **Teach the patients how to prevent intercurrent illnesses while they are receiving KA treatment.**

9.1. Bed nets

Each patient is given a bed net on admission; they can take it home on discharge. Make sure that they are using it correctly, and continue to do so after the treatment has finished. This will prevent the spread of the parasites to sand flies while they are sick, and it will help them not to get Kala Azar (and Malaria as well) in the future.

9.2. Water

Ensure that clean water is always available in the clinic compound for the patients to use at any time; clean water will significantly reduce the risk of diarrhoea.
***Patients must drink plenty of water* – more than usual - during treatment for KA, as drug side effects and toxicity are worse in dehydration, resulting in an increased risk of death. Advise adults to drink at least 6 large cups of water a day; advise children to drink at least 3 - 4 large cups of water a day.**
Make sure that the daily oral medication is taken with clean water as well.

9.3. Latrines

Advise people to use latrines, and teach them how to use them properly, including hand washing. This will prevent diarrhoea-causing germs from being passed from one patient to another.

9.4. Personal hygiene

Soap is given during the weekly distribution and should be used by patients and caretakers. It will help stop skin infections and transmission of various infections transmitted by contact such as common colds, diarrhoeal diseases, etc.
Teach patients and caretakers to keep themselves and their children clean.
Explain to the mothers that dirty faces attract flies, and flies cause diseases, including diarrhoea and conjunctivitis.

9.5. Coughing

Anybody that has a cough should cover the mouth with his/her hand and spit out the sputum in a safe place – ideally, a container (e.g. empty drug containers) should be used. That helps to stop cough-causing germs from infecting other persons.

10. DRUGS USED TO TREAT KALA AZAR

10.1. Sodium Stibogluconate (SSG)

10.1.1. General information

SSG comes in 30ml vials containing 100 mg/ml and is given IM.
Store in a cool place and protect from sunlight.
The contents should not be used more than 1 month after removing the first dose – write the date of opening on the vial.

10.1.2. Dosage

See Annex 2.

10.1.3. Side effects/contraindications

SSG can help cure patients with Kala Azar, but it can also sometimes cause harm to patients if side effects occur. *It is contraindicated in pregnant women.*
Patients should be daily asked for presence of side effects (vomiting, abdominal pain, diarrhoea).
Possible side effects include:

- *Vomiting*

This is common and can be very severe, leading to dehydration and even death. Make sure you ASK EVERY PATIENT EVERY DAY whether they have been vomiting. If necessary, give Metoclopramide (see Annex 2 for dosage). It is very important to monitor patients that are vomiting very closely for signs and symptoms of SSG toxicity. ALWAYS advise your patients to drink a lot of water during treatment.

- *Cramping*

Abdominal cramps are common in Kala Azar patients. Sometimes it is caused by SSG. Check that it is not due to worms or diarrhoea.

- *Painful injection site*

Check for injection abscess. If there is an injection abscess inject in another site and treat the abscess according to protocol.

- *Joint pain*

Give Paracetamol to ease the pain.

- *Heart problems*

SSG can make the heart have an unusual beat. It may suddenly stop, causing the patient to die. This is extremely rare but is a greater risk if the patient is dehydrated. ALWAYS encourage the patient to DRINK PLENTY OF WATER.

- *Neurological problems*

This means problems with the nerves. Some patients can get a tremor (shaking) in their limbs, or are unstable when they stand up. Explain to the patient that this is due to the treatment and will stop when they finish their treatment.

- *Kidney impairment*

Ask the patient if they passed urine in the last 8 hours and check for the quantity and colour (dark yellow urine is concentrated and the patient should be encouraged to drink more).

10.1.4. SSG toxicity

SSG toxicity means that the patient becomes severely ill due to SSG. It is rare, but it can cause death!
Signs and symptoms of SSG toxicity:

- **The patient becomes confused or develops tremor or convulsions while on SSG treatment**
- **Severe vomiting that does not improve with Metoclopramide**
- **Severe abdominal pain - when the abdomen is examined there is generalized peritonitis suggesting pancreatitis**

What to do if you suspect SSG toxicity

- **If possible call the doctor or senior nurse**
- **Stop SSG (and PM) for 2-5 days**
- **Re-hydrate the patient so they pass urine at least 5 times per day**
- **Give Metoclopramide for vomiting**
- **If the symptoms improve, reintroduce SSG/PM at usual dose:**
    - **If the SSG/PM treatment is interrupted for less than 5 days, continue the treatment until day 17 (the patient will receive the full 17 doses)**
    - **If SSG/PM is interrupted for more than 5 days, restart SSG/PM from day 0 and give full course (17 days of SSG/PM) in the PHCU**
- **In PHCC, if the vomiting/toxicity signs continue for more than 5 days without SSG/PM, start AmBisome**

10.2. Paromomycin (PM)

10.2.1. General information

Paromomycin (PM) comes in 2ml ampoules containing 500 mg/ml Paromomycin sulphate (equivalent to 375 mg/ml Paromomycin base) and is given IM.

10.2.2. Dosage

See Annex 2.

10.2.3. Contraindications

***PM is contraindicated in pregnant women*. It can cause ear and kidney damage to the baby.**

PM is also contraindicated in patients with hearing problems

10.2.4. Side effects

Deafness & ringing in the ears:
Before initiating treatment a hearing test should be done (e.g. with the whispering test, at 50 cm distance from the back, and/or a tuning-fork), and paromomycin should be withheld in patients with impaired hearing.

Stop paromomycin in case of complaints of hearing loss & ringing in the ears during treatment. This should be checked daily during treatment, and a hearing test should be performed in case of suspicion.
If the planned schedule was PM17/SSG17 (PKA), extend SSG treatment to 30 days. If the planned schedule was PM17/SSG30 (relapse), extend SSG treatment to at least 40 days.

10.3. AmBisome

10.3.1. General information

AmBisome (also known as *liposomal Amphotericin B)* comes in 50 mg powder vials. *It needs cold chain during transportation, and cool storage (<25^{o}C).* It is dissolved with 12ml water for injection; the concentration is then 4 mg/ml. The filter (supplied together with the AmBisome) should always be used before administration. It is given as an infusion over 2-4 hours in Dextrose 5%.

10.3.2. Full course AmBisome *(Hospital/PHCC only)*

a. What is full course AmBisome?

**"Full course" means that AmBisome 5mg/kg/dose is given every second day until 6 doses
are completed.**

b. Who gets full course AmBisome?

- Patients intolerant of SSG
- Severe KA (score ≥ 5**)**
- **Pregnant women**, irrespective of severity of KA
- **Patients ≥ 45 years of age**, irrespective of severity of KA
- **HIV co-infected patients:** in combination with Miltefosine daily for 28 days.

- Primary non-responders: **Patients who are unresponsive to first line treatment.**
  This is defined as no decrease in the grade of parasite load after adequate treatment; for those patients who were not aspirated on admission, we use 4+ in TOC as definition for primary unresponsiveness.
- Jaundiced patients
- Children <2 years, **in case proper daily patient monitoring in the OPD cannot be guaranteed**

In severely ill KA patients initiation of treatment is urgent in order to reduce parasitaemia and further deterioration. Therefore AmBisome treatment should be started immediately after admission, even is this in the afternoon or evening.

10.3.3. Dosage

See Annex 2.

10.3.4. Side effects

There are few serious side effects associated with AmBisome.

However. before starting the first dose a small test dose should be given to rule out the risk of AmBisome allergy (which can give anaphylactic reactions). A test infusion of 1 mg is administered for about 10 minutes, after which the patient is observed carefully during half an hour. If no severe allergic reaction has occurred the infusion can be continued.

Some patients complain of lower back ache if the infusion is running too fast – in this case adjust the infusion to run more slowly.

Do not give together with diuretics (e.g. Furosemide), because that may cause severe hypokalaemia.

10.4 Miltefosine

10.4.1 General information

Miltefosine comes in 10 mg or 50 mg capsules. It should be taken with meals to reduce the side effects. Doses of 100 mg (2x 50 mg) can best be divided over two separate meals.

10.4.2 Dosage

See Annex 2.
Miltefosine will, in principle, only be used if a patient with KA is also HIV positive.

However, in occasional cases Miltefosine can also be used ex-protocol in patients who did not respond to AmBisome treatment, but in whom SSG is contra-indicated (e.g. elderly).

In children the linear dosing (per kg body weight) is inadequate for effective cure, and dosing should be based on body surface (allometric dosing). In these cases contact the KA adviser.

10.4.3 Contraindications

Miltefosine is contraindicated in pregnancy and during lactation. **It is potentially harmful for the fetus. Women in childbearing age who are not pregnant must use an effective contraceptive (Depo Provera). Because Miltefosine can cause vomiting, oral contraceptives are not recommended. Because Miltefosine remains in the body for a long time after treatment, contraception should cover the treatment period plus 3 months after.**

Miltefosine is contraindicated in case of pre-existing severe damage of the liver (jaundice) or impaired kidney function.

10.4.4 Side effects

Miltefosine is well tolerated most of the time, but frequently causes transient nausea with mild to moderate vomiting and diarrhoea may occur, which will disappear after some days.
Rarer side effects include anorexia and abdominal pain.

11. INJECTIONS

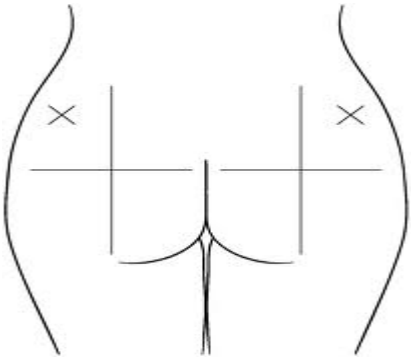
11.1. Preparations

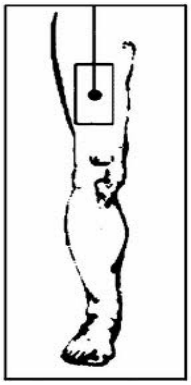
- **Collect and prepare all the materials you need.**
- **Always make sure you use a new, sterile needle and syringe for every injection.**
- **Make sure you keep everything very clean.**
- **Draw up the correct amount of medication for the patient; check again with the card after you have drawn it up to make sure that you didn't make a mistake.**
- **Inject the patient in a different area every day. You can use the buttocks and the thigh to give the injection.**
- **If the patient complains of pain and swelling at an old injection site, check for an injection abscess**.

11.2. Practical execution

- **Put on gloves.**
- **Choose the correct site for giving the injection.** ***Use the upper outer buttock or the thigh to give the injection.*** **Give the injection ALWAYS in the thigh for babies.**
- **Clean the site with iodine.**
- **Give the injection.**
- **Use clean cotton wool or gauze to wipe the site after injecting.**
- **Put the needle in the sharps box straight away after the injection** ***(do not recap!)*****.**
- **Use a separate needle for every injection.**
- **NEVER give SSG and Paromomycin at the same injection site.**
- **For volumes of 10 ml or more, split the dose in two syringes and inject in two different sites.**

- **SSG injections that are given forcefully (<1 sec/ml) are unnecessarily painful, and can cause tissue damage and abscesses. Injections should be given slow (>2 sec/ml)**





12. INTERCURRENT ILLNESSES

! IT IS VERY IMPORTANT TO TREAT INTERCURRENT ILLNESSES.

IT IS THESE ILLNESSES WHICH CAN KILL THE PATIENT !

12.1. Diarrhoea

Patients will not die from the diarrhoea-causing germ, but they can die from dehydration.
It is very important to keep the patients well hydrated to prevent death.
Patients with diarrhoea must drink a lot!

Treatment

a. *Dehydration – see 12.3. below*

b. *Drug treatment:*
- **Diarrhoea > 1 day, diarrhoea with fever, bloody diarrhoea and severe diarrhoea:**
  Treatment: Ciprofloxacin or Tinidazole (see Annex 2 for dosage).
  If diarrhoea continues on day 3, continue Ciprofloxacin up to day 5, for a maximum of 10 days.
- **For children below 8 kg, use Metronidazole only (see Annex 2 for dosage).**

12.2. Vomiting

In a Kala Azar patient, vomiting can be due to different causes:
- **SSG toxicity**
- **Miltefosine side effects**
- **Diarrhoeal illness**
- **Excessive coughing**
- **Tinidazole or Metronidazole can also cause nausea/vomiting as a side effect**

As with diarrhoea, patients with vomiting are at risk of dehydration. Vomiting must be treated straight away as patients can die from dehydration.
The patient must replace the water that their body is losing through the vomiting.

Treatment

a. *Medical advice*

Advise patients with mild vomiting to eat several small meals rather than one big meal, and to drink small amounts frequently. Do not let children drink a lot at once, as they will vomit again.

b. Dehydration - see 12.3. below

c. Drugs

If the patient is vomiting only after coughing, do not give medicine. Encourage the patient to drink more. If the vomiting is not from coughing, give Metoclopramide tablets first. Advise the patient to wait 1 hour before taking other medicine or eating.

d. SSG toxicity

If the patient has continuous vomiting and no expat is on ground, stop SSG for 2-5 days and see 10.1.3. (SSG side effects).

12.3. Dehydration

Dehydration can develop due to vomiting, diarrhoea or bleeding and is very dangerous **in Kala Azar patients. You can prevent this from happening! Ask how many times they have vomited or had diarrhoea. Ask the patient how much they are drinking, and check urine output. Always encourage fluid intake!**

12.3.1. Diagnosis/grading

Mild **Dehydration – the patient is *thirsty* but otherwise all right.**

Moderate **Dehydration – the patient is thirsty with rapid pulse, deep breathing, dry mouth, dark and concentrated urine, slow skin pinch, mildly sunken eyes and a sunken fontanelle in babies.**

Severe **Dehydration – the patient may be drowsy or unconscious, a weak and rapid pulse (sometimes not palpable), cold and clammy hands, deep and rapid breathing, very slow skin pinch, severely sunken eyes, urine production absent and a very sunken fontanelle in babies.**

12.3.2. Treatment

a. Mild to moderate dehydration

- **Give ORS: Mix 1 sachet with 2 cups of clean water (1 litre). Explain this carefully to the patient.**
- **If the patient is a severely malnourished child (Z-core < -3) give half strength ORS (in PHCU) or Resomal (in PHCC). Make half strength ORS by mixing 1 sachet of ORS with 4 cups of water.**
- **50 ml per kg should be drunk in the first 4 hrs. Make sure the patient stays in the clinic so this can be monitored.**
- **For children, make sure the mother knows how to give the ORS with a spoon or cup in small amounts regularly. The mother should also continue breast-feeding.**

b. Severe dehydration

- **If patients are severely dehydrated, they probably need IV re-hydration.**
- **Ideally use Ringer's lactate (RL).**

- **Give 20 ml/kg body weight every hour until the patient starts to improve - when they become more awake or pass urine.**
- **Then give 10 ml/kg body weight every hour and closely monitor their condition. Once they can take ORS, change to oral fluids.**
- **CHECK THE PATIENT EVERY HALF HOUR TO SEE IF THEY ARE GETTING BETTER OR WORSE. IF YOU ARE CONCERNED CALL A SENIOR STAFF!**
- **If the patient is very severe and no one is trained to give IV fluids, naso-gastric (NG) tubes can also be used to give fluid to someone who cannot drink. Insert a naso-gastric tube (only if you are trained!) and check the correct position in the stomach.**

12.4. Cough

A Kala Azar patient may have a cough for several reasons.

12.4.1. Kala Azar cough

This is a dry cough that occurs because of the Kala Azar parasites. Check the patient's temperature, count the respiratory rate and listen to the chest to make sure it is not pneumonia. Increased water consumption has shown to improve KA cough.

12.4.2. Upper Respiratory Tract Infection (URTI)

This is an infection in the high chest or throat. The patient may have a sore throat and runny nose. A common cold does not need any treatment; just encourage the patient to drink more water.

12.4.3. Pneumonia

This is an infection of the lung and is very serious in a Kala Azar patient.

a. Signs & Symptoms

- **Sputum(greenish) or new bloody sputum**
- **High fever**
- **Fast breathing (high respiratory rate)**
- **Chest pain**
- **Check for crackles (crepitations) in the lungs by using stethoscope (auscultation)**

b. Treatment

- **Mild & moderate pneumonia: Amoxicillin PO**
- **Severe pneumonia: Ceftriaxone IV for 3-5 days until improvement, then switch to Amoxicillin PO**

12.4.4. Tuberculosis (TB)

If the patient still has chest problems after two different courses of antibiotics, check for TB. Ask the patient if there is a family history of TB and refer to TB program for further investigation. Also consider the possibility of extra-pulmonary TB.

12.4.5. Aspiration pneumonia

This occurs when someone has a convulsion and vomits, and some of the vomit goes into the lungs. Be careful when inserting naso-gastric tubes; wrong positioning (lungs instead of stomach) might cause an aspiration pneumonia. It is treated with Metronidazole and Amoxicillin (Ceftriaxone and Metronidazole in severe cases).

12.5. Bleeding

Kala Azar patients have low platelets so their blood does not clot normally and they bleed easily. They can die if they lose too much blood.

12.5.1. Bleeding of the gums

- **If the patient has gum bleeding there is probably an infection in the mouth as well.**
- **Give Amoxicillin and consider Multivitamin tablets.**
- **Also encourage the patient to rinse their mouth with warm water after eating (teeth brushing would be ideal).**

12.5.2. Bloody diarrhoea

- **Treat using the diarrhoea protocol.**

12.5.3. Bleeding after childbirth or abortion

- **If the bleeding is severe, the patient may need to be transferred to PHCC (preferably a PHCC with surgical capacity).**
- **Seek advice of experienced staff.**

- **If the bleeding is not severe, give ORS; Metronidazole and Amoxicillin in case there is an infection.**

12.5.4. Nose bleeding

If the patient has nose bleeding, ask the patient to sit with their head forward (reading position) and get them to pinch their nose at the bottom of the bony bit. It is important that the patient or their caretaker holds the nose for a long time. If the bleeding goes on for more than 30 minutes consider packing the nose.

How to pack a nose

- **It is uncomfortable for the patient when you are packing the nose.**
- **Explain to the patient that it is very important to stop the nose bleeding.**
- **Use a nasal tampon if available. Insert one of these into the bleeding nostril. It will automatically expand and stop the bleeding.**
- **If a nasal tampon is unavailable, use gauze soaked with 1 vial of Adrenaline and some Vaseline (petroleum jelly) in a kidney dish. If you do not have Adrenaline, just use Vaseline. The Vaseline helps the gauze to enter the nose smoothly.**
- **Make sure the gauze is not too wet, when using Vaseline wipe away the excess.**
- **Carefully put one end of the gauze into the nostril that is bleeding using a curved blunt forceps.**
- **The gauze should be put right to the back of the nose because that is where the blood is coming from.**
- **Tape the nose pack securely against the face.**
- **If the blood is coming from both nostrils, then pack both sides.**
- **To help putting the gauze right to the back of the nose, get the patient to sit with their head against a wall.**
- **Check that you do not push the gauze too far by looking inside the mouth. If you can see some bandage inside the mouth, you should remove it and start again.**
- **One day later the bandage can be removed; if the bleeding starts again, the nose needs to be packed again.**

12.6. Eye infection

a. Signs & Symptoms

Red, itchy eyes with pus discharge, especially in the morning after waking up.

b. Treatment

Teach the patient to wash their hands with soap and water before touching their eyes. Teach them to clean the eye with clean water three times a day. If the problem does not clear up, give some tetracycline eye ointment and advise the patient or caretaker to use it 4 times a day until 2 days after the infection has gone.

12.7. Ear infection

Otitis media is not a contraindication to continuation of PM. However, a careful exam and discussion should be performed if otitis media also seems to have diminished hearing as a symptom. Err on the side of caution if diminished hearing is present.

a. Signs & Symptoms

- **Fever and headache**
- **Pain in the ears**
- **Pus from the ears**
- **Deafness**
- **In children: irritability - crying all the time.**

b. Treatment

- **Wash ears with soap.**
- **Give 7 days of Amoxicillin and check if the symptoms have improved.**
- **If they have not improved, continue the Amoxicillin for another 5 days.**

12.8. Skin and wound infections

Any cut to the skin can become infected and may form a pocket of pus under the skin, called an abscess.

a. Signs & Symptoms

- Hot, red shiny skin
- Pus from wound
- Round lump that feels like it is full of fluid
- Fever
- Pain

b. Treatment

- **An abscess must be opened and drained.**
- **Small abscesses can be drained with a syringe or may need to be cut with a sterile blade. See a senior staff for help.**
- **Do dressings every day after the abscess is drained.**
- **Give Metronidazole and Cloxacillin.**
- **In skin infections where there is no abscess, the patients need a treatment with Cloxacillin. These wounds also need to be cleaned and a dressing applied daily. Give Paracetamol if the patient is complaining of pain. *(Do not give Ibuprofen or Aspirin as these drugs can increase the risk of bleeding in KA patients!)***

12.9. Malaria

a. Signs & Symptoms

- **High fever**
- **Joint and muscle pains**
- **Headache**
- **Fast breathing**
- **Convulsions/unconsciousness**

b. Treatment

- **Do a RDT (SD Bioline) or blood film to confirm Malaria.**
- **If positive: treat according to guidelines (AS/AQ PO, or Artesunate IV for severe cases).**
- **If the patient has a history of convulsions, you must observe him/her closely and consider Diazepam. Discuss with senior medical staff.**

REMEMBER: Severe (cerebral) Malaria looks just like Meningitis, so make sure you treat for Meningitis if the RDT is negative, or there is no response to antimalarial treatment. Use Ceftriaxone to treat Meningitis.

12.10. PKMDL Iritis

If the eyes are affected they need special treatment. Tell the patient to wash the eyes twice a day – give Normal Saline and gauze, otherwise advise to clean with boiled and cooled water. They may need Tetracycline eye ointment if the eyes are super-infected.
If the infection is severe, refer to a doctor or *contact MedCo*.

12.11. TB co-infection

In patients who have both KA and TB, it is very difficult to cure KA, if TB is not treated at the same time. Therefore both diseases must be treated simultaneously. *Keep in mind that TB can present extra-pulmonary as well.* Taking a proper history is essential.

12.12. HIV co-infection

When a person has both HIV and KA, it is very serious. HIV infection makes KA worse, and KA makes HIV worse. It is difficult to cure a patient of KA if he/she is infected with HIV, because they fail to generate an effective cellular immunity against KA, and therefore easily relapse. If available, start antiretroviral therapy (ART) in co-infected patients. This treatment will help to improve the immune system and reduce the risk of KA relapse and other opportunistic infections. Co-infected patients also receive a different KA treatment regimen.

12.13 Hypoglygaemia

Fatal hypoglycaemia occurs regularly in young children and pregnant women. While adrenal failure can contribute to hypogylcaemia, it is generally attributed to a liver problem (loss of liver glycogen). The main intervention should be by giving feed and/or IV glucose. The main feature of adrenal failure is circulatory collapse (shock) rather than low blood glucose. Steroids are recommended if the patient has signs of dehydration / circulatory collapse (cold peripheries, slow capillary refill, low BP, fall in BP on standing) or if the patient looks critically ill. Hydrocortisone IV 100mg 8 hrly for a large adult, or 2-4 mg dexamethasone IV 8 hourly. Use lower doses for smaller individuals. Steroid treatment can be discontinued once the patient improves, as it is not likely that the adrenal failure persists.

13. DISCHARGE PROCEDURE

At the end of the treatment you need to decide whether the patient is cured from Kala Azar or needs more treatment.

Advise patients to come back if symptoms return, or they develop a severe skin rash. **Patients should bring their discharge card when they**

13.1. Clinical cure/Test of Cure (TOC)

Clinical response evaluation:
Signs of response are absence of fever, reduction in spleen and liver size, restored appetite, and feeling well.
Important other elements which may not be present by the end of treatment, because they will take longer: weight gain and increase of Hb. Knowing the patient and their individual progress is key assessing clinical response.

TOC:
A spleen or lymph node aspirate, which is examined in the lab under the microscope for parasites. If possible, do a spleen aspirate instead of a lymph node aspirate, as this is much more sensitive.

Timing of ToC:
Because it takes time for the parasite load to become undetectable as a response to treatment, an aspirate may still be positive at the end of treatment (day 12 for AmBisome, or day 17 for SSG/PM), even in patients who respond well to

treatment. Patients with very high initial parasite load, and slow responders can have detectable parasitaemia for a longer period. In the great majority of patients the cellular immunity will deal with the remaining parasites, and eventually parasites are no longer detectable. This is general considered to be around 28 days after starting effective treatment. It is therefore recommended to do a ToC at day 28. However, if it is not possible to keep patients for such a long period, a ToC can be done at day 21. It does not make sense to do a test-of-cure before day 21, as a positive ToC at that time does not say anything about cure or failure.

AmBisome has a very long tissue half-life (~14 days), and is therefore still active long after the last dose is given. Therefore, many patients who are still symptomatic on day 12 may show good clinical response in the following days.

Patients requiring a ToC:

1. **Primary KA (HIV-neg):**
   - **If the patient improved well under treatment, he/she can be discharged without TOC.**
   - **Do a TOC only if the patient is still symptomatic at day 21. Even if the patient was not well on the last day of treatment (which is more likely for patients admitted with severe KA disease), if he/she shows good clinical recovery before day 21 the patient can be discharged without ToC.**

2. **Primary KA (HIV-pos):**
   - **Continue treatment until ToC is negative**

3. **Relapse KA:**
   - **Two consecutive TOCs have to be negative before discharge.**

4. **Pregnant women, and until 6 months post-partum:**
   - **Pregnancy (esp. late pregnancy and persisting into the post-partum period) is a major immunosuppressive or immuno-modifying condition, which may hamper the development of an effective cell-mediated immunity. ToC should be routine on day 21 in patients who are pregnant, or who are <6 months post-partum**

What to do with a negative TOC in a patient who is still symptomatic at the end of treatment:

If splenic aspirate:

- **patient can be discharged from KA treatment**

If lymph node aspirate:

- **in case of doubt, do a second LN aspirate (increased sensitivity), or**
- **observe patient for a week, and repeat LN aspirate one week later if still symptomatic.**

However, discharge from KA treatment does <u>not</u> mean that the patient should be sent home if he/she is not well or still symptomatic. In this case one should look for differential diagnosis.

*Table: **different patient categories, treatment regimens, and ToC protocols***

Patient group	Treatment regimen	ToC protocol
Primary KA, HIV-negative	**PM17/SSG17**	ToC only if still symptomatic after Rx on d.21, and if pos, repeat on d.28
Primary KA, HIV-positive	**AmBisome 30mg/kg (5mg/kg/d x 6) plus Miltefosine x 28 d**	**ToC on d.28; Continue treatment with AmBisome + miltefosine until ToC-neg**
Relapse KA, HIV-negative	**PM17/SSG30-60**	**Discharge after two neg ToC on d.23 and d.30**
Relapse KA, HIV-positive	**AmBisome 30mg/kg (5mg/kg/d x 6) plus Miltefosine x 28 d**	**ToC on d.28; Continue treatment with AmBisome + mltefosine until ToC-neg**
Pregnancy + lactating <6M	**AmBisome 30mg/kg (5mg/kg/d x 6)**	**ToC on d.21, and if positive, repeat on day 28**
Severe KA	**AmBisome 30mg/kg (5mg/kg/d x 6)**	**ToC only if still symptomatic after Rx; d.21**
SSG toxicity	**AmBisome 30mg/kg (5mg/kg/d x 6)**	**ToC only if still symptomatic after completing Rx; (≥d.21)**
PKDL	**PM17/SSG30-60**	**ToC not done**

13.2. Extended treatment in patients failing treatment

Patients failing SSG+PM treatment will continue with daily SSG injections with weekly ToC, until the ToC becomes negative, and up to a maximum of total 60 doses of SSG. If the patient still fails treatment after 60 doses, consult the KA adviser in Amsterdam.

Patients failing a full course of AmBisome treatment (6 doses) will continue with two doses of AmBisome per week with weekly ToC, until the ToC becomes negative, and up to a maximum of total 12 doses of AmBisome. If the patient still fails treatment after 12 doses, consult the KA adviser in Amsterdam

13.3. Examination and recording on the patient card

a. **Treatment end date**
b. **Outcome of treatment:**
    i. **Discharge with negative TOC**

ii. **Discharge with clinical cure**
iii. **Default**
iv. **Death**

c. **Discharge weight**
d. **Discharge BMI or Z-score**
e. **Discharge Hb**
f. **Discharge spleen and liver size**
g. **Test of Cure, if applicable - dates, number of TOCs and results**

13.4. Discharge drugs

- **Give 30 ferrous/folic tablets (one tab per day for 30 days); if a child weighs less than 10 kg, cut 15 ferrous/folic tablets in half (half tab per day for 30 days).**
  If the patient is pregnant, give 60 tablets (one tab twice a day for 30 days).
- **Repeat the Measles vaccination for patients below 16 years of age, if there was a minimum time of 4 weeks between admission and discharge.**

13.5. Discharge card

- **All discharged patients receive a discharge card, which they must bring to the health center if they develop again symptoms of KA or severe PKDL.**
- **Record on the card:**
  a. **Place of treatment**
  b. **Name and patient number**
  c. **Age**
  d. **Sex**
  e. **Place of residence (county/payam/village)**
  f. **Dates of admission and discharge**
  g. **Final diagnosis**
  h. **Type of test done for confirmation**
  i. **TB co-infection yes/no**
  j. **VCT code**
  k. **Treatment regimen**
  l. **Outcome:**
     - **Discharge with negative TOC**
     - **Discharge with clinical cure**
  m. **Spleen and liver size on discharge**
  n. **Lymphadenopathy on discharge**
  o. **Weight on discharge**
  p. **BMI or Z-score on discharge**
  q. **Hb on discharge**

14. DEFAULTING PROCEDURE

What to do if a patient defaults:

- **Trace the defaulted patient and try to get him/ her back in the program.**
- **Treatment after interruption:**
    - **If the treatment is interrupted for less than 5 days, resume treatment on the day he stopped.**
    - **If the treatment is interrupted between 5 and 15 days, resume treatment at the day it was stopped, and do a Test of Cure at the end of treatment.**
    - **If the treatment is interrupted for more than 15 days, do a spleen or lymph node aspirate when the patient returns. If the result is positive, restart the treatment at day 0, and do a Test of Cure at the end of treatment; if the aspirate result is negative, resume treatment at the day the treatment was interrupted, and do a Test of Cure at the end of treatment.**
- **If the patient defaults for more than 2 months, treat as a relapse case.**

15. SEVERE KALA AZAR

- **Patients with increased risk of death from Kala Azar can be identified by a scoring system; they must receive special treatment. The scoring system uses the patient's nutritional status, age, Hb and level of weakness to assess the risk of death.**
- **If a patient scores 5 or above according to the tables below, he/she is at more than 20% risk of death and is therefore eligible to special treatment.**
- **Seriously ill KA patients are often intolerant of SSG; whereas AmBisome is the least toxic and most rapidly acting KA drug. AmBisome has >2 weeks half-life in spleen, liver and bone marrow.**
- **If a severely ill patient is diagnosed with KA, the doctor or a senior KA nurse should be called in order to decide on the treatment regimen.**
- ***Missed patients:***
  If a patient within 1-3 days of starting PM17/SSG17 treatment is noticed to be severely ill, but was not categorized as severe KA on admission, he/she can be re-scored and, if necessary, changed to AmBisome treatment.

15.1. Scoring the patient

- **Check age of the patient**
- **Check BMI for patients from 19 years of age onwards, or Z-score for patients below**
  19 years
- **Check Haemoglobin level (Hb)***
- **Assess the patient's level of weakness**
- **Use the tables below to determine the score for each variable**
- **Add up scores**
- **Fill in the severity scoring table on the treatment card**

**** admission Hb may be overestimated because of dehydration; this will show as a drop in Hb during the first days after admission when the patient is re-hydrated. Therefore, Hb should be repeated on day 2-5 in order to be able to evaluate Hb response to treatment. This may also prompt a re-evaluation of the severity score.***

Severity scoring charts

Age group 19 years and above: Adults

BMI		Age		Hb	
Cut-off	***Score***	***Cut-off***	***Score***	***Cut-off***	***Score***
over 16	**0**	**below 30 yrs**	**0**	**over 8 g/dl**	**0**
14 - 16	**1**	**30 – 39 yrs**	**1**	**6 – 8 g/dl**	**1**

Age group below 19 years: Children & Adolescents

W/H Z-score		Age		Hb	
Cut-off	***Score***	***Cut-off***	***Score***	***Cut-off***	***Score***
-2 and above	**0**	**above 5 yrs**	**0**	**over 8 g/dl**	**0**
<-2	**1**	**2 – 5 yrs**	**1**	**6 – 8 g/dl**	**1**
<-3	**2**	**1 – 2 yrs**	**3**	**4 – 6 g/dl**	**2**
<-4	**3**	**below 1 yr**	**4**	**below 4 g/dl**	**4**
13 – 13.9	**2**	**40 – 44 yrs**	**3**	**4 – 6 g/dl**	**2**
12 – 12.9	**3**	**45 yrs and above**	**5**	**below 4 g/dl**	**4**
below 12	**4**				

Level of weakness

State of collapse = score 5

- **Definition of collapse in adults/older children: unable to sit up unaided AND cannot drink unaided**
- **Definition of collapse in babies: floppy when held in arms AND unable to feed unaided**

Severely weak = score 3

- **Definition of severe weakness in adults/older children: cannot walk 5 m without assistance**
- **Definition of severe weakness in babies: unable to sit upright unaided**

Other types of weakness = score 0

15.2. Treatment of Severe Kala Azar

- **Full course AmBisome: 5 mg/kg/dose x 6 doses over 12 days.**
- **Hydration.**
- **Nutrition: in case of severe malnutrition give therapeutic feeding according to nutrition protocols. Otherwise give food supplement of 1000 kcal (2 sachets of PlumpyNut/day).**
- **Antibiotics: treat any suspected infection aggressively with parenteral broad-spectrum antibiotic treatment.**

Give Ceftriaxone IV or IM: adults 1 g once daily; children 50 mg/kg once daily.

- **Diarrhoea: treat diarrhoea aggressively with the appropriate drugs for amoebiasis, giardiasis and bacterial causes.**
- **If the patient is in a state of collapse, give stress doses of corticosteroids:**
  Children: Hydrocortisone IV 5 mg/kg/injection (or Prednisolone PO 1 mg/kg STAT)
  Adults: Hydrocortisone IV 100-500 mg/injection (or Prednisolone PO 50 mg STAT)
  Hydrocortisone injections may be repeated up to 3x/day, if needed.
  Treatment should be stopped as soon as the patient improves.
- **Consider blood transfusion if Hb is less than 4g/dL or if there are signs of acute respiratory distress.**
- **TOC is only needed if the patient still appears clinically sick at day 21 after starting treatment.**

ANNEXES

Annex 1: Testing procedures

a. IT Leish test (rK39)

Introduction:

- The IT Leish test ("Kala Azar dipstick") is a rapid diagnostic test to detect antibodies of Kala Azar (rK39).
- The test is made with whole blood from a finger-prick.
- The result is obtained within 25 minutes to complete the full procedure:

Summary of the time needed

Procedure	*Time*
Labelling strip, recording name in the book, adding buffer in well 1 and 2	**2 minutes**
Wiping the finger and pricking	**1 minute**
Collecting blood into plastic pipette	**1 minute**
Strip with blood in well 1 (conjugated)	**10 minutes**
Strip with washing buffer in well 2	**10 minutes**
Interpreting and recording results	**1 minute**

Materials used:

- **Dipstick strip**
- **Well cover**
- **Ampoule of buffer**
- **Gloves**
- **Lancet**

- **Disinfecting swab**
- **Cotton wool swab**
- **Sharps container**
- **Plastic pipette**
- **Registration book**
- **Pen**
- **Timer**

Procedure:

- **Tear open the aluminium package and take out all the materials.**
- **Arrange the materials on a clean flat surface.**
- **Label the strip (patient's name or number and date).**
- **Record the details of the patient in the registration book.**
- **Add one drop of buffer to the first well (conjugate well).**
- **Add four drops of buffer to the second well (washing well).**
- **Allow to stand for one minute.**
- **Put on gloves.**
- **Clean the fingertip of the patient with the disinfecting swab.**
- **Leave it to dry.**
- **Prick the finger.**
- **Discard the lancet in the sharps container.**
- **Wipe the first drop away with dry cotton wool.**
- **Take the pipette.**
- **Squeeze the top of pipette and keep it squeezed.**
- **Place the open tip into the drop of blood.**
- **Release pressure and draw up blood up to the black line.**
- **Add the entire volume of blood by squeezing the pipette gently to the first well (conjugate well).**
- **Stir gently with upper end of the pipette.**
- **Discard the pipette into suitable waste container.**
- **Allow to stand for 1 minute.**
- **Pull out the dipstick holder with the label.**
- **Insert legs of the dipstick holder into the holes beside the conjugate well (first well).**
- **Allow to stand for 10 minutes.**
- **Transfer the dipstick to wash well (second well).**
- **Allow to stand for 10 minutes.**
- **Remove the dipstick from the wash well.**
- **Click it back into the clear plastic piece.**
- **Close the well with the well cover.**
- **Break them off.**
- **Break the two legs off from the clear plastic piece.**
- **Discard them into a suitable waste container.**
- **Read the reaction and interpret the results.**
- **Record the results in registration book.**
- **Keep the dipstick for future reference.**

Interpretation of results

Valid results

Result	*Bands/marks*	*Remarks*
Positive	Two **pink bands are clearly seen**	**(i) Reaction field should be cleared of blood** **(ii) Indicates presence of antibodies against L. donovani**
Negative	One **pink band is clearly seen**	**(i) Reaction field should be cleared of blood** **(ii) Indicates absence of antibodies against L. donovani**

Invalid results

Problem	*Reaction field*	*Possible cause*	*Remarks*
Dipstick not sufficiently cleared	**Reaction field remains red**	**(i) No washing buffer added into wash well** **(ii) Wrong washing buffer used** **(iii) Wind** **(iv) Direct sunlight**	**Repeat the test**
Control band not present	**No mark seen**	**(i) Strips exposed to extreme heat.** **(ii) Expired strips**	**1. Repeat to confirm** **2. Report to lab supervisor or MedCo if the result is the same**

Important notes:

- If the dipstick does not give a clear result, repeat the test.
- **Patients who have been treated for Kala Azar before CANNOT be tested** with the dipstick, as it will still give a positive result for many months or even years after treatment, even if a patient currently does not have Kala Azar. If a suspect patient was treated for Kala Azar before, send him/her to the PHCC for aspirate microscopy.
- Store the tests in a *cool and dry place*, below 30 degrees Centigrade.

b. DAT test

Introduction

A DAT (Direct Agglutination Test) is done on some drops of blood, which are taken from the fingertip onto a piece of filter paper.

NB: **Patients who have been treated for Kala Azar before CANNOT be tested with the DAT, as it will still give a positive result for many years, even if a patient currently does not have Kala Azar. If a suspect patient was treated for Kala Azar before, refer him/her for aspirate microscopy.**

Materials needed:

- **Filter paper – "*Whatman 3" - Other types of paper WILL NOT WORK!***
- **Gloves**
- **Lancet**
- **Disinfecting swab**
- **Cotton wool swab**
- **Sharps container**
- **Registration book**
- **Pen**

Procedure:

- **Label the paper properly with the patient name/number.**
- **Put on gloves.**
- **Clean the fingertip of the patient with the disinfecting swab.**
- **Leave it to dry.**
- **Prick the finger to produce a drop of blood.**
- **Discard the lancet in the sharps container.**
- **Collect the blood on the *Whatman 3* filter paper. The blood must produce a spot approximately 2 cm diameter on the paper. *Do not let the finger touch the paper.***
- **The drop must also soak through the paper to the other side - check this.**
- **Put the filter paper in the box (separate from the other papers) and let it dry.**
  NB: Do not leave it in the sun – the sun destroys parts of the blood and the test will not work well!
- **The blood sample will last for 2 weeks. If you don't have a lab, collect the samples for the next transport.**
- **Fill in the registration book.**

c. Lymph Node Aspirate

Introduction

A fluid sample is taken from a lymph node and examined under the microscope to see if parasites for Kala Azar are (still) present. The lymph nodes which are usually used for sampling are located in the groin area (inguinal LNs).
Always explain the procedure to the patient and family before beginning.

Materials needed:

- **Gloves**
- **Sharps container**
- **21G needle (green)**
- **5ml syringe**
- **Clean microscope glass slide**
- **Gauze swab**
- **Cotton wool swab**
- **Disinfectant (alcohol or iodine)**
- **Diamond pencil**
- **Methanol**
- **Registration book**
- **Pen**
- **Slide box (if transport to the lab is needed)**

Procedure:

- **Label the slide with the patient's lab number using a diamond pencil.**
- **Clean the slide with gauze or dry cotton wool.**
- **Rest the patient on the back with their legs stretched out. Another person can hold down the patient if he/she is restless or agitated. If the patient is a small child, the mother can hold the child on her legs.**
- **Put on gloves.**
- **Decide by palpation which inguinal lymph node is the largest one; this one will be used for the procedure.**
  Note: The LNs that you puncture for aspiration don't need to be greatly enlarged.
  In South Sudan, LNAs are typically done on inguinal LNs around 1cm in diameter.
- **Clean the skin over the LN with a cotton wool swab soaked in alcohol or Iodine and let it dry.**
- **Hold the lymph node firmly between thumb and index finger and carefully insert the 21G needle. The insertion can be horizontal or at a slight angle to avoid hitting blood vessels.**
- **Encourage lymph fluid to flow up the needle by twirling the needle whilst gently "milking" the lymph node. For about 1 minute, continue massaging the LN and twirling the needle while moving it a little in and out of the lymph node tissue. You should see some pinkish fluid reaching the hub after about 1 minute.**
- **Withdraw the needle rapidly with your index finger sealing its hub.**
- **Put a gauze swab on the puncture site and ask the patient to press it on.**

- **Attach the 5ml syringe, containing a little air, to the needle and squirt the aspirate onto the glass slide.**
- **Spread the sample material thinly along the slide (you can use the needle flat on the slide to do this).**
- **Discard the needle in the sharps container.**
- **Allow the slide to dry on the air.**
- **Fix the specimen with methanol.**
- **Fill in the registration book.**
- **Hand the slide to the microscopist or store it safely in the slide box for transport.**

d. Splenic Aspirate

Introduction
A tissue sample is taken from the spleen and examined under the microscope to see if parasites for Kala Azar are (still) present. The aspirate can only be taken from a significantly enlarged spleen.

A splenic aspiration should only be performed by a medical doctor or senior medical person who has been trained and is experienced in the procedure.

Contra-indications:
Splenic aspiration should not be done if any of the following contra-indications are present:

- **Spleen not or barely palpable (spleen size below 3 cm)**
- **Jaundice**
- **Signs of active bleeding (nose, skin, digestive tract, etc…). A minor nose bleeding is not a contraindication**
- **Severe anemia (Hb < 5.5); in settings where there is no possibility for blood transfusion a higher cut off can be used**
- **Pregnancy (amenorrhea) of ≥ 24 weeks**
- **Patient in very bad general condition**
- **Patient unable to remain still or not cooperative**

Ideally, there should be rapid access to blood transfusion in case of bleeding.

Materials needed:
- **Gloves**
- **Sharps container**
- **23G needle (blue)**
- **5ml syringe**
- **Clean microscope glass slide**
- **Gauze swab**
- **Cotton wool swab**
- **Disinfectant (alcohol or iodine)**
- **Diamond pencil**
- **Methanol**
- **Registration book**
- **Pen**
- **Slide box (if transport to the lab is needed)**

Procedure:
The two important prerequisites for the safety of the procedure are **rapidity**, so that the needle remains within the spleen for less than 1 second; and **precision**, so that the entry and exit axes of the aspirating needle are identical to avoid tearing the splenic capsule.

- Inform the patient about the procedure and get consent.
- Ask the patient to lie on his/her back.
- For young restless children, it is preferable to have two assistants; one to hold the hands across the chest with shirt raised and the other to hold the child's pelvis firmly.

- Palpate the extent of spleen under left costal margin.
- Clean the area of skin over the spleen with cotton wool soaked with poviodine or 70% alcohol.
- Allow the skin to dry.
- Wipe the glass slide with dry gauze
- Clearly label the slide:
    - Lab Number of patient
    - Test of cure, relapse or diagnosis
    - Aspirate source (LN or SP)
    - Date
- Take a sterile needle (23G, blue) and a 5 ml syringe.
- Attach the needle to the syringe and insert the needle under the skin.
- Create a vacuum in the syringe.
- Ask the patient to hold his/her breath
- **Insert, quickly and gently, the needle into the spleen (the syringe will suck the tissue from the spleen because there is pressure in the syringe). This process should take less than 10 seconds. Handling of the syringe during aspiration should be done with a single hand and axis of needle entry and exit must be the same**
- **Discharge the tissue onto a slide and make a smear immediately, to avoid clotting of the aspirate**
- **Place the needle in the sharp container marked "SHARPS"**
- **Pulse and blood pressure need to be monitored every half hour for 4 hours and then every hour for 6 hours. Patients should ideally have a few hours of bed rest. If not possible, instruct patients to strictly avoid any vigorous physical activity in order to minimize risk of trauma/bleeding.**

Annex 2: Drug dosages

a. Sodium Stibogluconate (SSG) 20 mg/kg/d

- **SSG comes in 30ml vials with 100 mg/ml and is given IM.**
- **The content of a vial should not be used more than 1 month after removing the first dose.**
- **Store in a cool place *(do not freeze)* and protect from sunlight.**
- ***In small children (<15 kg), the dosage is calculated in mg/m² body surface area.***

SSG dosages for children above 12 months and adults

Weight in kg	*Dose in ml*	*Weight in kg*	*Dose in ml*	*Weight in kg*	*Dose in ml*
		28	**5.6**	52	**10.4 (5.2x2)***
5	**2.0**	29	**5.8**	53	**10.6 (5.3x2)***
6	**2.5**	30	**6.0**	54	**10.8 (5.4x2)***
7	**2.5**	31	**6.2**	55	**11.0 (5.5x2)***
8	**3.0**	32	**6.4**	56	**11.2 (5.6x2)***
9	**3.0**	33	**6.6**	57	**11.4 (5.7x2)***
10	**3.0**	34	**6.8**	58	**11.6 (5.8x2)***
11	**3.0**	35	**7.0**	59	**11.8 (5.9x2)***
12	**3.0**	36	**7.2**	60	**12.0 (6.0x2)***
13	**3.0**	37	**7.4**	61	**12.2 (6.1x2)***
14	**3.0**	38	**7.6**	62	**12.4 (6.2x2)***
15	**3.0**	39	**7.8**	63	**12.6 (6.3x2)***
16	**3.2**	40	**8.0 (4.0x2)***	64	**12.8 (6.4x2)***
17	**3.4**	41	**8.2 (4.1x2)***	65	**13.0 (6.5x2)***
18	**3.6**	42	**8.4 (4.2x2)***	66	**13.2 (6.6x2)***
19	**3.8**	43	**8.6 (4.3x2)***	67	**13.4 (6.7x2)***
20	**4.0**	44	**8.8 (4.4x2)***	68	**13.6 (6.8x2)***
21	**4.2**	45	**9.0 (4.5x2)***	69	**13.8 (6.9x2)***
22	**4.4**	46	**9.2 (4.6x2)***	70	**14.0 (7.0x2)***
23	**4.6**	47	**9.4 (4.7x2)***	71	**14.2 (7.1x2)***
24	**4.8**	48	**9.6 (4.8x2)***	72	**14.4 (7.2x2)***
25	**5.0**	49	**9.8 (4.9x2)***	73	**14.6 (7.3x2)***
26	**5.2**	50	**10.0 (5.0x2)***	74	**14.8 (7.4x2)***
27	**5.4**	51	**10.2 (5.1x2)***	75	**15.0 (7.5x2)***

For doses of 10 ml or more, split the dose in two syringes and inject in two different sites.

Recommended treatment for children up to 12 months of age is AmBisome. However, in case of failure or in sites where AmBisome is not available, infants can be treated with PM/SSG. *To adjust for possible toxicity in very young children, dosages need to be corrected for age.*

SSG dosages for infants

	Infants <6 months	Infants 6–12 months	Children >12 months
Weight in kg	*Dose in ml*	*Dose in ml*	*Dose in ml*
<3	**0.5**	**0.75**	***contact MedCo***
3	**0.75**	**1.0**	
4	**1.0**	**1.5**	
5	**1.0**	**1.5**	**2.0**
6	**1.0**	**2.0**	**2.5**
7	**1.0**	**2.0**	**2.5**
8	**1.5**	**2.5**	**3.0**
9	**1.5**	**2.5**	**3.0**
10	**1.5**	**2.5**	**3.0**

b. Paromomycin sulphate 15 mg/kg/d *(equivalent to Paromomycin base 11mg/kg/d)*

- **Paromomycin comes in 2ml ampoules (containing 500 mg/ml Paromomycin sulphate, equivalent to 375 mg/ml Paromomycin base) and is given IM**.
- **Never give Paromomycin and SSG in the same injection site**.

Weight in kg	*Dose in ml*	*Weight in kg*	*Dose in ml*
1-2.9	**-**	**39-41.9**	**1.2**
3-5.9	**0.1**	**42-44.9**	**1.3**
6-8.9	**0.2**	**45-48.9**	**1.4**
9-11.9	**0.3**	**49-51.9**	**1.5**
12-14.9	**0.4**	**52-54.9**	**1.6**
15-18.9	**0.5**	**55-58.9**	**1.7**
19-21.9	**0.6**	**59-61.9**	**1.8**
22-24.9	**0.7**	**62-64.9**	**1.9**
25-28.9	**0.8**	**65-68.9**	**2.0**
29-31.9	**0.9**	**69-71.9**	**2.1**
32-34.9	**1.0**	**72-74.9**	**2.2**

35-38.9	**1.1**	**75 and above**	**2.3**

c. AmBisome 5 mg/kg/dose

- **Ambisome comes in vials of 50 mg dry powder and is given IV**.
- **It needs cold chain during transportation, and cool storage (<25°C).**

Weight in kg	*Dose* *in number of vials every second day for full course*	*Weight in kg*	*Dose* *in number of vials every second day for full course*
below 5	***contact MedCo***	**35.5 - 37.9**	**4-4-4-4-3-3**
5 – 10.4	**1-1-1-1-1-1**	**38 – 40.4**	**4-4-4-4-4-3**
10.5 – 12.9	**2-1-1-1-1-1**	**40.5 – 42.9**	**5-4-4-4-4-4**
13 – 15.4	**2-2-1-1-1-1**	**43 – 45.4**	**5-5-4-4-4-4**
15.5 – 17.9	**2-2-2-2-1-1**	**45.5 – 47.9**	**5-5-5-5-4-4**
18 – 20.4	**2-2-2-2-2-1**	**48 – 50.4**	**5-5-5-5-5-4**
20.5 – 22.9	**2-2-2-2-2-2**	**50.5 – 52.9**	**6-5-5-5-5-5**
23 – 25.4	**3-2-2-2-2-2**	**53 – 55.4**	**6-6-5-5-5-5**
25.5 – 27.9	**3-3-3-3-2-2**	**55.5 – 57.9**	**6-6-6-6-5-5**
28 – 30.4	**3-3-3-3-3-2**	**58 – 62.9**	**6-6-6-6-6-6**
30.5 – 32.9	**4-3-3-3-3-3**	**63 – 67.9**	**7-7-7-6-6-6**
33 – 35.4	**4-4-3-3-3-3**	**68 – 72.9**	**7-7-7-7-7-7**

How to give AmBisome

Always use complete AmBisome vials. *AmBisome must be stored in a fridge.* It can withstand a short time outside the fridge; *it must not be frozen*.

- **As AmBisome is given IV, an IV access (IV canula) is necessary.**
- **Dilute each vial of AmBisome with** 12 ml **of Water for injection; concentration of this solution is AmBisome 4 mg/ml.**

- **Shake well for at least 30 seconds to completely disperse AmBisome. Visually inspect the vial for particles and residual matter, and continue shaking until complete dispersion is obtained.**
- **Prepare a 500 ml drip of Dextrose 5% [G5]** ***(****Do not use Normal Saline!****)*****.**
- **Let some Dextrose run out of the drip according to the numbers of vials you give:**
  For 1 vial of AmBisome leave 100 ml in the drip, for 2 vials leave 200 ml, for 3 or more vials use all of the 500 ml.
- **Attach the AmBisome filter to the drip of Dextrose 5% using a 21G needle.**
- **Add the reconstituted AmBisome to the drip by passing it through the filter.** ***A new filter should be used for each vial of AmBisome added.***
- **Mix well.**
- **Connect the infusion to the IV canula; allow it to run over 3 hours.** ***Calculate drop rate per minute according to the type of IV giving set used.***
- **AmBisome is given** every second day **until 6 doses are completed.**

c. Miltefosine 2.5 mg/kg/d

- **Miltefosine comes in 10 mg or 50 mg capsules.**
- ***In children (<25 kg), the dosage is calculated in mg/m² body surface area.Contact the KA adviser in Amsterdam for correct dosing***

Weight in kg	*Dose in mg*
< 8	***contact MedCo***
8 -11	**40**
12 – 14	**50**
15 – 17	**60**
18 – 21	**70**
22 - 25	**80**
> 25	**100**

d. Amoxicillin 50 mg/kg/d

- **Amoxicillin comes in tablets of 250 mg.**

Age	***Child*** **below 2 months**	***Child*** **2 m – 11 m**	***Child*** **1 – 4 yrs**	***Child*** **5-14 yrs**	***Adult*** **15 years and above**
Weight	**below 4 kg**	**4 – 7.9 kg**	**8 – 14.9 kg**	**15 – 35 kg**	**over 35 kg**

Amount	**¼ x 2 x 7**	**½ x 2 x 7**	**1 x 2 x 7**	**2 x 2 x 7**	**3 x 2 x 7**

e. Vitamin A (Retinol) single dose

- **Retinol comes in 200,000 IU gel capsules.** ***(NB: Sometimes also 50,000 IU capsules are found.)***

Age	**< 6 months**	**6 m – 1 yr**	**> 1 year**
Amount	**1 drop**	**3 drops**	**1 cap**

f. Artesunate/Amodiaquine (AS/AQ)

- Artesunate/Amodiaquine comes as tablets in blister packs for a full 3 day treatment of uncomplicated Malaria, according to the weight of the patient.

Artesunate + Amodiaquine Baby (2–11 months): 25 mg AS + 67.5 mg AQ (3 tab)
Artesunate + Amodiaquine Toddler (1-5 years): 50 mg AS + 135 mg AQ (3 tab)
Artesunate + Amodiaquine Child (6-13 years): 100 mg AS + 270 mg AQ (3 tab)
Artesunate + Amodiaquine Adult (14 yrs + above): 100 mg AS + 270 mg AQ (6 tab)

Age	**Baby below 1 yr**	**Toddler 1– 5 yrs**	**Child 6 – 13 yrs**	**Adult 14 yrs and above**
Weight	**4 – 8 kg**	**9 – 17 kg**	**18 – 35 kg**	**over 35 kg**
Day 1	**1 tab Baby**	**1 tab Toddler**	**1 tab Child**	**2x1 tab Adult**
Day 2	**1 tab Baby**	**1 tab Toddler**	**1 tab Child**	**2x1 tab Adult**
Day 3	**1 tab Baby**	**1 tab Toddler**	**1 tab Child**	**2x1 tab Adult**

g. Ceftriaxone

- **Ceftriaxone comes in 250 mg and 1 g powder vials and is given IM.**

Children and adolescents **below 16 years: 50 mg/kg/d IM in 3 or 4 injections for 3-5days,**
followed by a full course of Amoxicillin for 7 days.
Adults **of 16 years and above: 1 g IM in 3 or 4 injections for 3 days,**
followed by a full course of Amoxicillin for 7 days.

h. Ciprofloxacin 30 mg/kg/d

- **Ciprofloxacin comes in 500 mg tablets, to be taken twice daily for 3 days.**

Weight	*Amount*
below 8 kg	***DO NOT GIVE***
8 – 11.9 kg	**¼ x 2 x 3**
12 – 19.9 kg	**½ x 2 x 3**
20 kg and above	**1 x 2 x 3**

NB: Try to avoid Ciprofloxacin in children below the age of 15!

i. Cloxacillin 50 mg/kg/d

- Cloxacillin comes in 250 mg capsules.

Weight	**8-14.9 kg**	**15-34.9 kg**	**35 kg and above**
Amount	**1 x 2 x 7**	**2 x 2 x 7**	**4 x 2 x 7**

j. Metronidazole

- **Metronidazole comes in 250 mg tablets.**

Age	***Child*** **< 1 yr**	***Child*** **1 – 4 yrs**	***Child*** **5 – 14 yrs**	***Adult*** **15 yrs and above**
Weight	**4 – 7.9 kg**	**8 – 14.9 kg**	**15 – 34.9 kg**	**35 kg and above**
Amount	**½ x 2 x 7**	**1 x 2 x 7**	**2 x 2 x 7**	**3 x 2 x 7**

k. Metoclopramide PO and IM

- **Oral Metoclopramide comes in 10 mg tablets, to be taken as long as necessary.**

Weight	**11 – 14.9 kg**	**15 - 34.9 kg**	**35 kg and above**
Amount	**¼ x 3**	**½ x 3**	**1 x 3**

- Injectable Metoclopramide comes in 2ml ampoules with 5 mg/ml, to be given IM as long as necessary.

Weight	**11 – 14.9 kg**	**15-19.9 kg**	**20-34.9 kg**	**35 kg and above**
Amount	**0.2 ml x 3**	**0.4 ml x 3**	**1 ml x 3**	**2 ml x 3**

l. ORS (Oral Rehydration Salts)

Weight	*Sachets per day*
9 -11.9 kg	**1**
12 - 24.9 kg	**1-2**
25 kg and above	**2-4**

- ORS comes as powder in sachets for preparation with 1 l of water.

m. Paracetamol (Acetaminophen) 60 mg/kg/d

- **Paracetamol comes in tablets of 100 or 500 mg.**

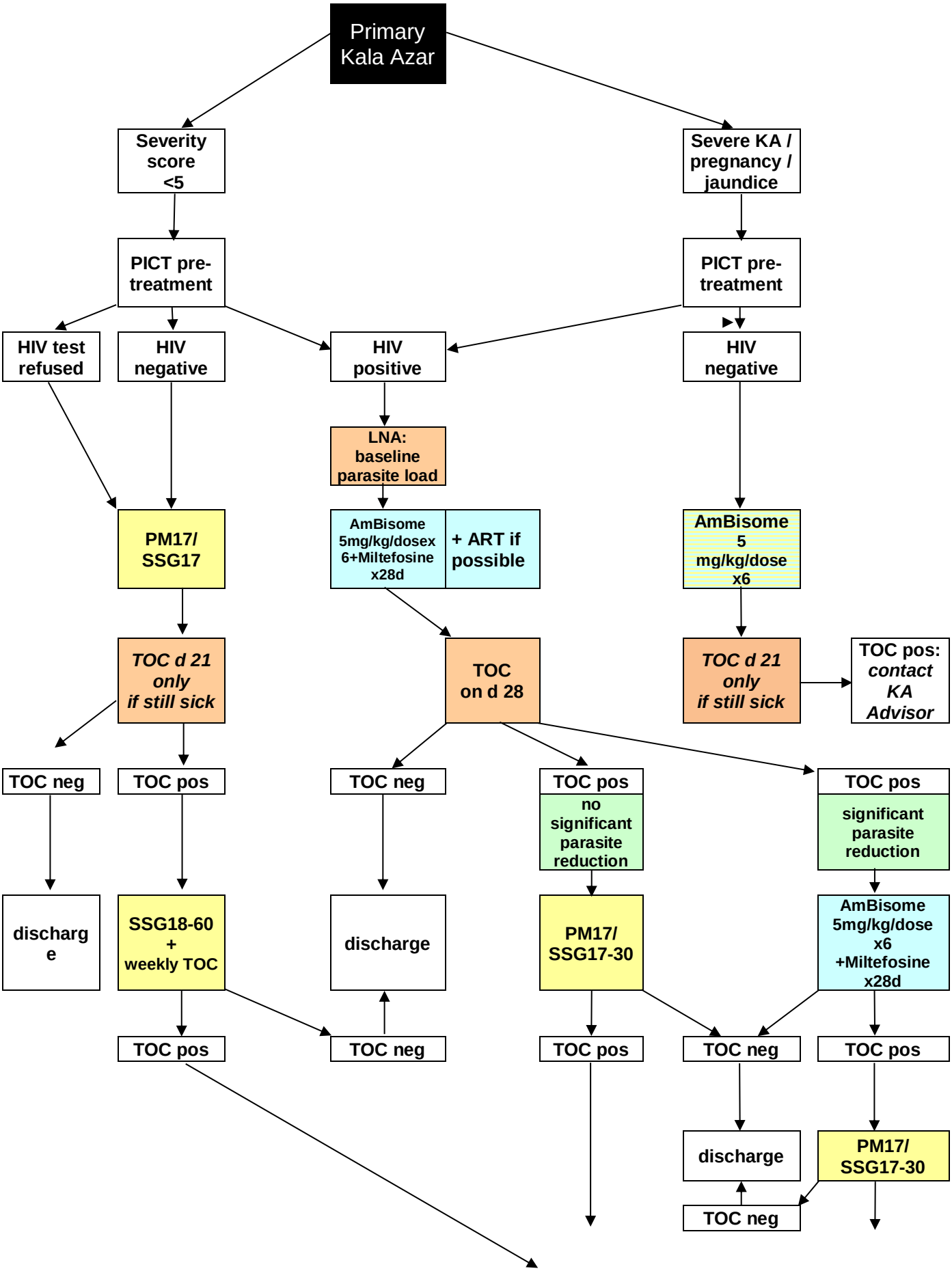
Age	***Child*** **<2 months**	***Child*** **2 – 11 m**	***Child*** **1 – 4 yrs**	***Child*** **5 – 14 yrs**	***Adult*** **15 yrs and above**
Weight	**up to 3.9 kg**	**4 – 7.9 kg**	**8 – 14.9 kg**	**15 – 35 kg**	**over 35 kg**
Amount of 100 mg *tabs*	**½ x 3 x 3**	**1 x 3 x 3**	**2 x 3 x 3**	**-**	**-**
Amount of 500 mg *tabs*	**-**	**-**	**½ x 3 x 3**	**1 x 3 x 3**	**2 x 3 x 3**

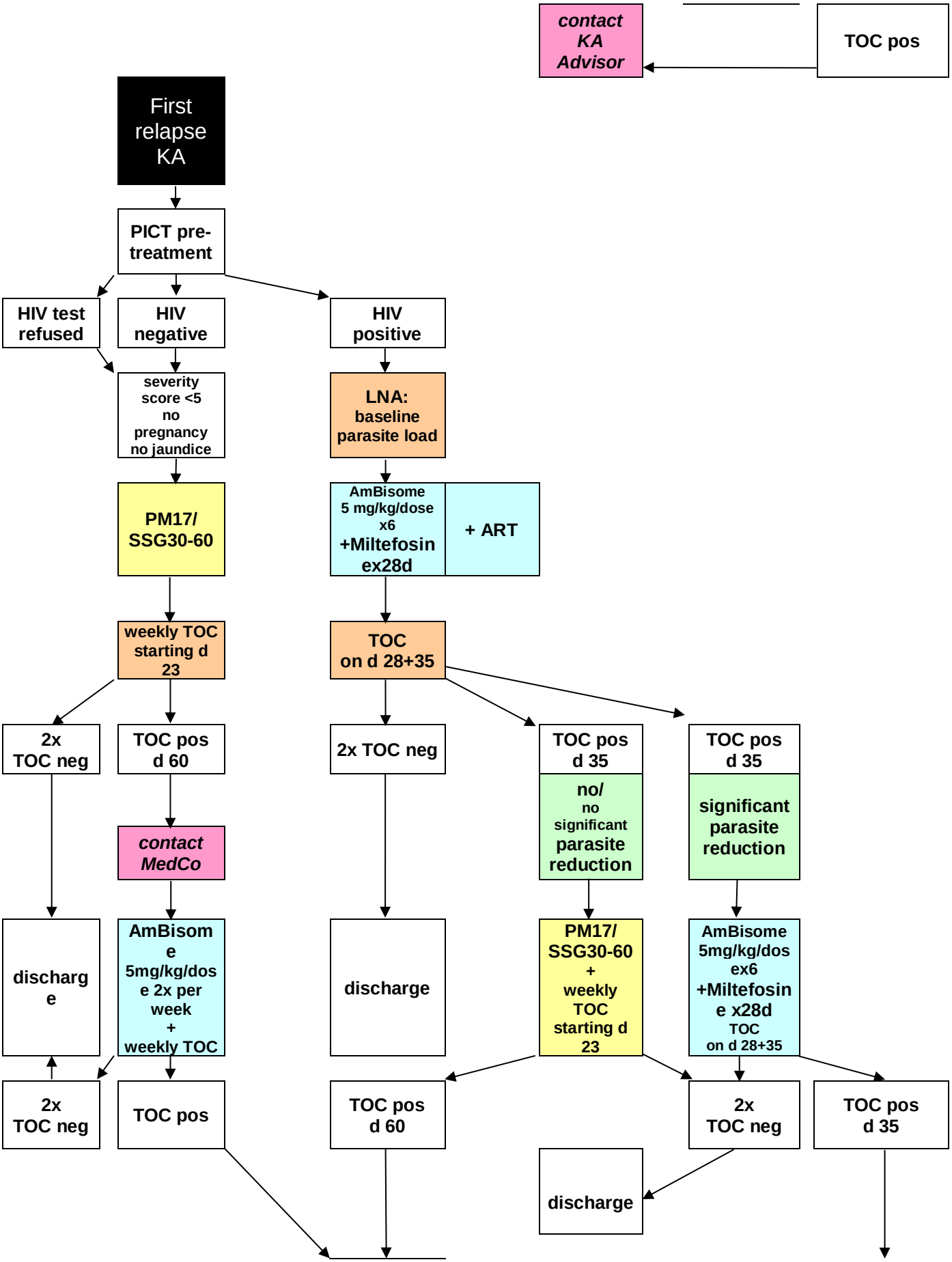
n. Tinidazole 50 mg/kg/d

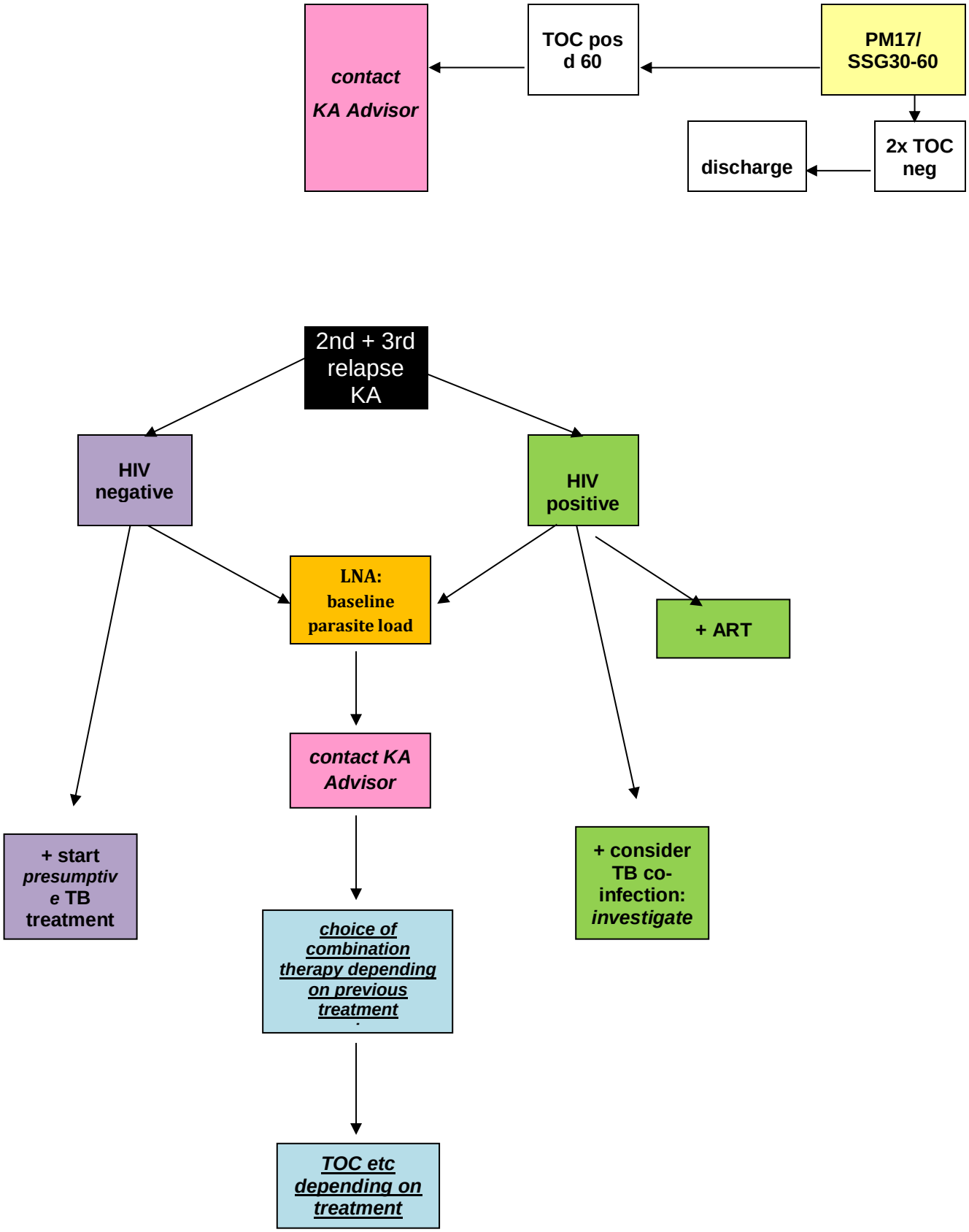
- **Tinidazole comes in 500 mg tablets.**

Weight	**below 8 kg**	**8 – 13.9 kg**	**14 – 23.9 kg**	**24 – 35 kg**	**over 35 kg**
Amount	***use Metronidazole***	**1 x 1 x 3**	**2 x 1 x 3**	**3 x 1 x 3**	**4 x 1 x 3**

Annex 3: Treatment algorithms




contact KA Advisor
TOC pos
First relapse KA
PICT pre-treatment
HIV test refused
HIV negative
HIV positive
severity score <5 no pregnancy no jaundice
LNA: baseline parasite load
PM17/ SSG30-60
AmBisome 5 mg/kg/dose x6 +Miltefosin ex28d
+ ART
weekly TOC starting d 23
TOC on d 28+35
2x TOC neg
TOC pos d 60
2x TOC neg
TOC pos d 35
no/ no significant parasite reduction
TOC pos d 35
significant parasite reduction
contact MedCo
discharg e
AmBisom e 5mg/kg/dos e 2x per week + weekly TOC
discharge
PM17/ SSG30-60 + weekly TOC starting d 23
AmBisome 5mg/kg/dos ex6 +Miltefosin e x28d TOC on d 28+35
2x TOC neg
TOC pos
TOC pos d 60
2x TOC neg
TOC pos d 35
discharge


contact
KA Advisor
TOC pos
d 60
PM17/
SSG30-60
discharge
2x TOC
neg
2nd + 3rd
relapse
KA
HIV
negative
HIV
positive
LNA:
baseline
parasite load
+ ART
contact KA
Advisor
+ start
presumptiv
e TB
treatment
+ consider
TB co-
infection:
investigate
choice of
combination
therapy depending
on previous
treatment
TOC etc
depending on
treatment