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FREQUENTLY ASKED QUESTIONS ON VISCERAL LEISHMANIASIS (KALA-AZAR)

World Health Organization
Regional Office for South-East Asia

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FAQs

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Q 1: What is visceral leishmaniasis?

Visceral leishmaniasis (VL), also known as kala-azar is a life-threatening disease caused by the *Leishmania donovani* parasite. A parasite lives in another living creature, and gets all its nutrients at the expense of its host.

The signs and symptoms of infection with this parasite include anaemia (deficiency in the number or quality of red blood cells), fever, enlarged liver, enlarged spleen and significant weight loss. This disease is often fatal if left untreated. The disease is spread through female sandflies.

Leishmaniasis infections can occur in three different forms. Visceral leishmaniasis (VL) is the most serious form of the disease and causes death in the majority of its victims.

Q 2: Where is VL prevalent?

VL occurs in more than 70 countries of the world, with a total of 200 million people at risk. However, more than 90% of VL cases occur in just seven countries: Bangladesh, India, Nepal, South Sudan, Sudan, Ethiopia and Brazil.

Within the South-East Asia Region, Bangladesh, India and Nepal harbour an estimated 67% of the global VL disease burden. In India, most cases occur in the state of Bihar, but other states such as Jharkhand, Uttar Pradesh and West Bengal also report cases. Recently, VL has also been reported from Bhutan and Thailand. The VL cases are usually concentrated in clear geographical areas – in certain districts or villages. However, population movement means that these boundaries are not always clearly defined.

Q 3: Why is this disease important?

An estimated 200 000 to 400 000 new cases of VL occur every year. The death toll from the disease is estimated at around 20 000 to 40 000, which is surpassed only by malaria among the parasitic diseases. VL affects the most vulnerable – poor communities in remote, rural areas – and the disease is seen in clusters within households.

It is endemic mostly in countries that are least developed, or in the poorest regions of middle-income nations. VL is diverse and complex, and known to prolong the cycle of poverty as people cannot work and cannot afford treatment.

Q 4: Is VL a new disease?

No, the parasite was identified at the beginning of the twentieth century.

VL almost completely disappeared from the Indian subcontinent following the large-scale anti-malarial DDT spraying campaign in the 1950s. But the disease quickly re-emerged when these campaigns were terminated and the sandfly population increased again.

Q 5: How does a person gets VL?

Humans are infected via the bite of sandflies which carry the *Leishmania* parasite inside them. Only female flies can transmit the disease. A single bite from a sandfly can inject enough parasites into the bloodstream to infect a human.

Q 6: What are the signs and symptoms of VL?

Patients of VL suffer from fever, which can increase gradually or suddenly. The fever is persistent and irregular, often with two daily peaks, and alternating periods of no fever or low-grade fever. Other symptoms include fatigue, weakness, loss of appetite, significant weight loss, and enlarged lymph nodes/ glands, liver and spleen. As the disease advances, the spleen size increases, which may cause abdominal distension and pain.

Post-kala-azar dermal lesion (hyper-pigmentation of skin) may occur after apparent cure of the systemic disease, although this is now very uncommon.

The clinical features of VL are not specific and can be easily mistaken for any other common illness that comes with fever.

Q 7: Does infection or getting bitten by the sandflies always lead to illness?

No. Infection with *Leishmania* does not always lead to clinical illness, and there are infected people without any symptoms at all. For each sick person, there can be between 3–8 people who do not appear ill. Evidence indicates that asymptomatic and subclinical infections are common and apparently induce lasting immunity. The risk factors for developing illness include malnutrition, or if the person has any other disease that reduces immunity, such as HIV/AIDS.

Q 8: How long after being infected does the disease develop?

The period between sandfly bite and appearance of symptoms is between 2–6 months, and the range is between 10 days to sometimes even years.

Q 9: What are the known or presumed reservoirs *(the living creatures that host a parasite)*?

Reservoirs of the disease include humans, wild oxen and jackals and domestic dogs.

However, humans are the only known reservoir in Bangladesh, India and Nepal.

Q 10: What are the complications of VL? Can patients die?

VL can eventually lead to death unless treated. VL symptoms often persist for several weeks to months, and weaken the patient so other infections such as pneumonia, diarrhoea or tuberculosis can occur and mask the original symptoms. Patients can die either due to these coinfections, massive bleeding or severe anaemia.

After treatment, 5–10% of patients can also develop post-kala-azar dermal leishmaniasis (PKDL), a skin lesion. It usually appears between 1–3 years after the patient was initially cured.

Q 11: Where do the sandflies that transmit the disease live?

The sandflies that transmit the disease normally breed in forest areas, caves, cracks in the mud walls, or in the burrows of small rodents. That is why in some villages, where houses are in close proximity to cattle or cattle-sheds, there is a high probability of having sandflies around.

Q 12: What are important features of sandfly bites?

People might not realize that sandflies are present because:

- they do not make any noise
- they are small – only about one third the size of mosquitoes, or even smaller
- their bites are painless and might not be noticed.

Sandflies usually are most active during twilight, evening, and from dusk to dawn. But although they are less active during the day, they may bite if they are disturbed (for example, if a person brushes up against the trunk of a tree or other site where they are resting).

Q 13: Do these flies only bite humans?

Not always. In areas with different kinds of *Leishmania* such as *L. infantum*, dogs are the main reservoir. The disease is then known as zoonotic VL as it involves animals, and can be found in areas such as China, the Mediterranean basin, the Middle East and South America. In East Africa and South–East Asia, visceral leishmania are harboured only in humans. This is called anthroponotic VL, and the disease is eradicable in these areas.

Q 14: Can the diagnosis of VL be confirmed?

Yes. There are laboratory tests that can confirm VL diagnosis.

- Serological diagnosis – traditionally based on immunofluorescent antibody reaction (IFA) and enzyme-linked immunosorbent assay (ELISA), which are expensive. But cheaper freeze-dried antigen and dipsticks tests are also available.
- The most commonly used tests detect antibodies, which are markers that the body produces after being infected by VL. There are different types of antibody test, including:
  - the rapid immunochromatographic method called rK39. The rK39 rapid test has many advantages as it is easy to perform, quick (results in 10–20 minutes) and cheap (around US$ 1 per test). It can be used in remote places and does not require any special equipment or training. They are currently the best diagnostic tool available.
  - the direct agglutination test (DAT).

- The *polymerase chain reaction* (PCR) technique is the most sensitive test, but it remains expensive.
- The "gold standard" proof of VL is seeing the parasite through microscopic examination. But the procedures to get the samples require considerable technical expertise and are potentially dangerous, and so cannot be performed everywhere.

Q 15: What is the treatment of VL? Is it curable?

Yes, VL is curable with proper treatment. However, initially there were few medical options to treat VL and even those were not always easily available. VL is difficult to treat mainly because most of the drugs have to be given through intravenous injection, requiring hospitalization and close monitoring.

The mainstay of treatment for more than 70 years was sodium stibogluconate (SSG) and meglumine

antimoniate, which are pentavalent antimonial drugs containing an element similar to arsenic.

Other drugs include conventional amphotericin B (an anti-fungal drug which has many side-effects), liposomal amphotericin B (shortened to LAmB, which has relatively fewer side-effects), and Paromomycin.

Miltefosine, which was initially developed as an anti-cancer drug, is the first effective oral drug for VL.

LAmB is now the treatment of choice. The total dose required is different among regions, with a lower dose sufficient in the Indian subcontinent compared to Africa or Latin America. In developing countries, the use of this drug was limited because it is expensive.

Q 16: How was this challenge of cost resolved?

An agreement was reached in 2007 between WHO and Gilead, the manufacturer of LAmB, to reduce the price. It initially cost US$ 2800 per treatment, but now the price is down to US$ 200. Old drugs such as SSG are still inexpensive.

Q 17: How long does the treatment take?

This depends on which drug is used:

- With SSG only, the patient needs a daily injection for 28 days.
- Paromomycin alone needs 21 days.
- Miltefosine alone is typically given for 28 days.
- A recent breakthrough is a single dose of injectable liposomal amphotericin B (LAmB), which significantly improves compliance to treatment.

Multiple studies have confirmed the efficacy of LAmB against VL parasites in the Indian subcontinent. Therefore, single-dose LAmB has been recommended as the first-line VL treatment.

Q 18: Is the treatment safe? What are the possible side-effects?

Side-effects vary.

- Antimonials are toxic drugs with frequent, sometimes life threatening adverse effects such as heart problems and acute pancreatitis.
- Amphotericin B could cause damage to the kidneys or trigger severe allergic reactions. The liposomal form has far fewer side-effects.

- Miltefosine can cause birth defects and cannot be used by pregnant women or women who could become pregnant within two months of treatment. It can sometimes cause gastrointestinal side-effects. It also has a long half-life, meaning it stays in the body for a very long time, which could potentially make the parasite resistant to it.

Q 19: Is there any resistance to this treatment for VL?

Yes. Antimonials (SSG) treatment has been widely misused in the past (by splitting daily doses, using improper dosages and substandard batches of drugs). This has led to the emergence of widespread resistance, sometimes as high as 60–80%. This required a change in drug policy.

In unregulated private health care systems, patients often receive inappropriate treatment courses and this in turn can contribute to the emergence of resistance. This is of particular concern for Miltefosine, as this drug has a long half-life.

Q 20: Is combining different drugs a better option?

Every drug seems to have its drawback. Combination therapy has been advocated as a way to increase treatment efficacy and tolerance, reduce treatment length and cost, and limit the emergence of drug resistance. However, the choice of drugs and the most optimal dosage are still being debated. Several clinical studies are being undertaken to provide more data on the safety and efficacy of different combination therapies.

Regional factors also play a role, with the eastern Africa region still using antimonials as first-line

treatment, while in the Indian subcontinent there are more treatment options. There is scientific evidence that combination therapies are a cost-effective alternative.

Q 21: Given all these complexities regarding VL treatment, what is the status in the Indian subcontinent?

Several breakthroughs in the treatment of VL have been reported over the past decade. In 2010, WHO recommended a treatment regimen for anthroponotic VL caused by *L.donovani* in Bangladesh, Bhutan, India and Nepal. The first line is LAmB, followed by different combinations.

Q 22: Is there any vaccine for VL?

No, not yet. Anti-leishmanial vaccines are still under development.

Q 23: What are the control strategies for VL?

The current control strategies rely on reservoir and vector control – and, of course, early diagnosis and treatment of cases. When the burden of disease is high, active case finding can also be carried out.

Q 24: Can we kill sandflies with insecticide? What are the methods for vector control that are used for VL?

Sandflies are susceptible to the same insecticides as the malaria vector, and residual insecticide spraying of houses and animal shelters has been shown to be successful in India. Another method is environmental control, such as plastering cracks in the house wall and moving away from animal shelters.

Q 25: What about using insecticide-treated nets?

The use of insecticide-impregnated/treated bednets could also prevent VL as well as other vector-borne diseases such as malaria or Japanese encephalitis. However, there is limited evidence that bednets provide protection against VL in particular, as effectiveness of the bednets depends on the sleeping habits of the population and the biting habits of the local vectors.

Q 26: How critical is finding and treating infected patients?

VL can kill if it is left untreated. People who are not treated can also act as a reservoir for parasites and therefore contribute to the spread of the disease. Similarly, PKDL patients are likely to be highly infectious because large numbers of parasites are present in the skin lesions. Therefore, it is critical to identify and treat infected patients.

Q 27: Given the complexities surrounding VL, what can we do to control it?

Early diagnosis and treatment of VL remain very important. Countries that have VL pockets must ensure that diagnostic tests and medicines are available in the health facilities. Vector control is another cornerstone for controlling the disease. With the recent attention on neglected diseases, some national programmes are being boosted to help control the disease.

Q 28: How can it be eliminated in the Indian subcontinent?

Despite the difficulties in controlling VL globally, there are several factors specific to the Indian subcontinent that make elimination feasible.

- Humans are the only reservoir and *Phlebotomus argentipes* sandflies the only known vector for the parasite, so if we can interrupt transmission in humans, it can be eliminated.
- New and more effective diagnostic tests (the rK39 ICTs) and drugs (such as Miltefosine) are available and can be used in the field.
- Most importantly, there is a strong political commitment and intercountry collaboration to check the disease.

The VL elimination initiative was launched in 2005 by the signing of a Memorandum of Understanding among Bangladesh, India and Nepal. The target for elimination is set for 2015.

Q 29: What can cause an increase in cases of VL?

Environmental factors such as deforestation, urbanization and migration of non-immune people to endemic areas have led to an increase in the incidence of VL. In countries with high HIV prevalence (like Ethiopia), the coinfection between HIV and VL is a potential catastrophe, as patients are more difficult to diagnose and treat, and are more likely to relapse.

Q 30: I plan to travel to an area where VL is found. What can I do to prevent infection?

No vaccines or drugs to prevent infection are available at the moment. The best way for travellers to prevent infection is to protect themselves from sandfly bites.

http://www.who.int/leishmaniasis/disease_epidemiology/en/