

WHO GUIDELINE

for the treatment of visceral leishmaniasis in HIV co-infected patients in East Africa and South-East Asia



World Health
Organization

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Abbreviations and acronyms

ART	antiretroviral therapy
CI	confidence interval
GDG	Guidelines Development Group
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
L-AMB	liposomal amphotericin B
NTD	neglected tropical disease
PICO	population, intervention, comparator and outcomes
PKDL	post-kala-azar dermal leishmaniasis
RDT	rapid diagnostic test
TB	tuberculosis
VL	visceral leishmaniasis
WHO	World Health Organization

Note on terminology: Although it is recognized that visceral leishmaniasis is a disease and HIV is an infectious agent, the term “VL–HIV coinfection” is used in this publication to refer to infection with *Leishmania* that has resulted in visceral leishmaniasis and with HIV

Executive summary

The leishmaniasis are a group of diseases caused by *Leishmania* spp., which occur in cutaneous, mucocutaneous and visceral forms. They are neglected tropical diseases (NTDs), which disproportionately affect marginalized populations who have limited access to health care. HIV co-infected patients with *Leishmania* infection are highly infectious to sandflies, and an increase in the coinfection rate in an endemic area is likely to increase the effective infective reservoir.

Leishmania and HIV reinforce each other, posing clinical and public health problems. In areas where the endemicity of HIV and *Leishmania* overlap, people living with HIV are more likely to develop visceral leishmaniasis (VL), possibly due to reactivation of a dormant infection or clinical manifestation after primary infection. VL is an AIDS-defining condition, as HIV and *Leishmania* both suppress the immune system, resulting in more severe VL disease, higher rates of relapse and treatment failure, more toxicity of drugs and higher mortality rates than from either infection in isolation. Patients characteristically have high disseminated parasite loads. VL negatively affects responses to antiretroviral therapy (ART), and co-infected patients are difficult to cure, especially when their CD4 cell count is < 200 cells/mm³, as they typically relapse.

Leishmania–HIV coinfection was first reported in the mid-1980s in southern Europe and has since been reported in as many as 45 countries.

Target audience

These guidelines are intended primarily for use by national leishmaniasis control programme managers. They will also be of interest to policy-makers in health ministries, national leishmaniasis and NTD control programme managers, national HIV treatment and prevention advisory boards, national tuberculosis (TB) programme managers, subnational NTD programme managers, clinicians, other health service providers, front-line and public health workers, staff at WHO regional and country offices, nongovernmental organizations and other implementing partners, people living with HIV and community based organizations, population networks, international and bilateral agencies and organizations that provide financial and technical support to leishmaniasis and HIV programmes in the relevant regions.

Guideline development

These guidelines were developed according to the standardized operating procedures described in the *WHO Handbook for guideline development* (1). A WHO steering committee defined the scope of the guidelines and formulated the questions to be addressed according to the population, intervention, comparator and outcomes (PICO) format. A specialized external team was commissioned to conduct a systematic review of the literature and to rate the certainty of the evidence according to the grading of recommendations, assessment, development and evaluation (GRADE) method (2). Evidence-to-decision tools were built from following elements: balance between desirable and undesirable effects, certainty of evidence, values, resource implications, equity, acceptability and feasibility. WHO also organized a mixed methods study to assess the views of stakeholders in relation to the importance of treatment outcomes, and impact on equity, accessibility, and feasibility of treatment options. The guideline development group (GDG) consisted of experts with relevant knowledge and experience, appropriate geographical and gender representation and no conflicts of interest. An online meeting of the GDG was convened on 28 September–1 October 2020.

What's new in these guidelines?

This document describes the management of VL caused by *L. donovani* in HIV co-infected patients in East Africa and South-East Asia. The recommendations are also applicable to other areas endemic for *L. donovani*. The guidelines update the recommendations in the report of a meeting of the WHO Expert Committee on the Control of Leishmaniases (WHO Technical Report Series 949) in 2010 (3). Previously, treatment for VL in HIV co-infected patients was based on limited evidence, extrapolated mainly from experience in countries around the Mediterranean Basin, with *L. infantum* as the main species. As parasite virulence and drug susceptibility differ, the optimal treatment regimens for VL in HIV co-infected patients in areas in which VL is caused by *L. donovani* (East Africa and South-East Asia) were not known. The few studies conducted in leishmaniasis-endemic regions other than Europe made it difficult to provide clear, region-specific recommendations. These guidelines, based on recent evidence from clinical trials in Ethiopia and India, fill this gap.

Until now, the generic recommendation for treatment of a VL episode in an HIV co-infected patient was first to consider lipid formulations of amphotericin B, infused at a dose of 3–5 mg/kg daily or in 10 intermittent doses (on days 1–5, 10, 17, 24, 31 and 38) to a total dose of 40 mg/kg. Evidence from clinical trials in Ethiopia and India on the efficacy and safety of combination therapy (liposomal amphotericin B (L-AMB) plus miltefosine) to treat VL in HIV co-infected patients instead of monotherapy has offered new possibilities for case management. Some evidence has emerged for considering secondary prophylaxis after the first episode of VL, with pentamidine in Ethiopia and with amphotericin B or its lipid formulation in India.

WHO recommendations on treatment of visceral leishmaniasis in HIV co-infected patients

Patients	WHO recommendations	Strength of recommendation	Certainty of evidence
VL patients with HIV coinfection in East Africa	Liposomal amphotericin B + miltefosine: L-AMB (up to a total of 30 mg/kg, at 5 mg/kg on days 1, 3, 5, 7, 9 and 11) + miltefosine (100 mg/day for 28 days) over L-AMB: L-AMB (up to a total of 40 mg/kg, at 5 mg/kg on days 1-5, 10, 17 and 24)	Conditional	Very low
VL patients with HIV coinfection in South-East Asia	Liposomal amphotericin B + miltefosine: L-AMB (up to a total of 30 mg/kg, at 5 mg/kg on days 1, 3, 5, 7, 9 and 11) + miltefosine (100 mg/day for 14 days) over L-AMB: L-AMB (up to a total of 40 mg/kg, at 5 mg/kg on days 1-4, 8, 10, 17 and 24)	Conditional	Very low

Considerations

- Determine the HIV status of patients diagnosed with VL. Routinely screen for tuberculosis at visceral leishmaniasis diagnosis and follow-up.
- In patients who do not show a good clinical response, after ruling out other diagnoses, consider providing extended therapy (one repetition of the same therapy, based on evidence from trials in Ethiopia).
- When miltefosine is not available, consider using monotherapy with L-AMB (up to a total of 40 mg/kg) as per the L-AMB regimen.
- Provide comprehensive clinical management, including adequate HIV treatment and nutritional support.
- Ensure access to contraception and pregnancy testing for women of child-bearing potential before administering miltefosine.

WHO recommendation for secondary prophylaxis after recovery from a first episode of visceral leishmaniasis in HIV co-infected patients

In East Africa

Use secondary prophylaxis after recovery from a first episode of VL in HIV co-infected patients in East Africa
(*Conditional recommendation; very-low-certainty evidence*)

In South-East Asia

Use secondary prophylaxis after a first episode of VL in HIV co-infected patients in South-East Asia
(*Conditional recommendation; very-low-certainty evidence*)

Remarks:

- Secondary prophylaxis is recommended in particular for patients at high risk of relapse (e.g., patients not on ART, with a low CD4 cell count (< 200 cells/mm³), multiple previous VL episodes, failure to achieve clinical or parasitological cure during the first episode of VL, no increase in CD4 cell count at follow-up). Patients should be evaluated case by case.
- As the recommendation for secondary prophylaxis applies specifically to HIV-positive individuals, it is important to determine the HIV status of patients diagnosed with VL.
- In East Africa: pentamidine isethionate at 4 mg/kg per day (300 mg for an adult) every 3–4 weeks. In South-East Asia: amphotericin B deoxycholate at 1 mg/kg every 3–4 weeks or Liposomal amphotericin B (L-AMB) at 3–5 mg/kg per day every 3–4 weeks
- Prophylaxis can be stopped if the CD4 cell count is maintained at or > 350 cells/mm³ or the HIV viral load is undetectable for at least 6 months and there is no clinical evidence of VL relapse.
- When choosing a drug for secondary prophylaxis, consider:
 - using drugs that were not used to treat the primary VL episode,
 - the benefits and safety profiles of the proposed drug,
 - potential collateral benefits in terms of prevention of other infections, and
 - potential drug resistance.

For both recommendations, people who manage VL in HIV co-infected patients are urged to:

- Improve access to HIV testing for all patients with VL.
- Ensure uninterrupted, free access to quality-assured medicines.
- Ensure appropriate access to health-care services at the lowest possible direct and indirect cost.
- Extend the supplier base of antileishmanial diagnostic tests and medicines.
- Strengthen the relevant health infrastructure and human resource capacity.
- Improve coordination among HIV, VL and related programmes, such as for pharmacovigilance, TB and vector control.



Nigatu Abebe, a HIV/VL patient at the Leishmaniasis Research and Treatment Centre at the University of Gondar, Ethiopia.

1. Introduction

The leishmaniasis are a group of diseases caused by *Leishmania* spp. transmitted by the bites of female phlebotomine sandflies. The clinical manifestations include cutaneous leishmaniasis, mucocutaneous, visceral leishmaniasis (VL) and post-kala-azar dermal leishmaniasis (PKDL). The importance of VL as a cause of morbidity and mortality in HIV-infected patients is well recognized, and the burden has increased in the past few decades, posing further clinical and public health problems (4). Although progress has been made in the treatment, diagnosis and prevention of VL, the complexity of VL management in HIV co-infected patients remains, and the rising proportions of co-infected patients are a major threat to VL control and to the elimination programmes in South-East Asia and the high-burden region of East Africa.

Technically, *Leishmania* parasite and HIV are both pathogens; therefore, HIV-positive patients may suffer from any clinical form of VL, cutaneous leishmaniasis or mucocutaneous leishmaniasis or even develop PKDL. HIV and leishmaniasis are mutually reinforcing conditions with amplifying effects on each other, and the catastrophic consequences of simultaneous infection with HIV and *Leishmania* has emerged as a critical challenge in VL control and elimination. Coinfection was initially reported in a number of Mediterranean countries in the mid-1980s but has progressively expanded to 45 countries (5). The presence of HIV coinfection not only makes managing individual cases of VL more difficult – with atypical site involvement, unusual presentations, poor treatment outcomes, increased drug toxicity, frequent relapse and high mortality – but co-infected patients carry high parasite loads and are highly infective to sandflies, increasing their transmission potential. Treatment of VL in HIV co-infected patients with repeated regimens of the same medicine may also select for resistant *Leishmania* strains and thereby introduce a risk of transmission of drug-resistant parasites.

To date, there is insufficient evidence from high-burden regions such as East Africa and South-East Asia on addressing these challenges. The World Health Assembly in 2007 adopted resolution 60.13 on control of leishmaniasis (6), which calls on Member States to encourage research to find new, safe, effective and affordable drug combinations for leishmaniasis control. Co-infection with HIV is an important challenge that must be tackled with integrated approaches, aligned with the WHO road map on neglected tropical diseases 2021–2030 (7).

This document addresses the management of HIV co-infected patients with VL caused by *L. donovani* in East Africa and South-East Asia and updates and complements existing WHO guidance and recommendations (3). The aim is to provide up-to-date, evidence-based recommendations on optimal therapeutic choices for VL due to *L. donovani* in HIV co-infected patients, according to various epidemiological, clinical and operational scenarios. The guidelines do not recommend changes to WHO

recommendations for regions in where VL is predominantly caused by *L. infantum*. Current WHO normative documents on leishmaniasis control in Europe (8) and the Americas (9) provide specific recommendations for the treatment of VL in HIV co-infected patients in those regions.

These guidelines are intended for use primarily by national leishmaniasis control programme managers. They will also be of interest to policy-makers in health ministries, national leishmaniasis and NTD control programme managers, national HIV treatment and prevention advisory boards, national TB programme managers, subnational NTD programme managers; clinicians, other health service providers, front-line and public health workers; staff of WHO regional and country offices; nongovernmental organizations and other implementing partners; people living with HIV and community organizations; population networks; and international and bilateral agencies and organizations that provide financial and technical support to leishmaniasis and HIV programmes in the relevant regions.

The document describes the management of VL caused by *L. donovani* in HIV co-infected patients in East Africa and South-East Asia. The recommendations are also applicable to other areas endemic for *L. donovani*. The guidelines update the recommendations in the report of a meeting of the WHO Expert Committee on the Control of Leishmaniases in 2010 (3).

Guiding principles

The guidelines are based on the following principles.

- WHO's objective is the attainment by all individuals of the highest possible level of health. The guidelines were developed in accordance with that objective and those of the United Nations Universal Declaration of Human Rights.
- Implementation of the guidelines should contribute to achievement of the Sustainable Development Goals and WHO's "triple billion" targets (10).
- Effective implementation of the recommendations will require a public health approach to scale up detection of HIV status in VL patients and vice versa. Optimal management of VL and provision of antiretroviral drugs are necessary along the continuum of HIV prevention, treatment, care and support.
- The recommendations in these guidelines should be implemented with a view to strengthening broader health systems, especially primary and chronic care.
- The recommendations should be implemented according to the local context, including the epidemiology of leishmaniasis and its co-endemicity with HIV, the availability of resources, the organization and capacity of the health system and anticipated cost-effectiveness.
- Patients with VL-HIV coinfection are primarily members of vulnerable or marginalized groups with poor access to health care and who face potential discrimination and stigmatization. These guidelines and the policies derived from them therefore stress basic gender equality, human rights and equity, including the right to confidentiality and informed decision-making about whether to be screened and treated for VL and/or HIV.

- The guidelines should promote greater involvement and empowerment of people living with HIV. High-quality care and treatment for VL–HIV patients will require an uninterrupted supply of appropriate medication and adequately trained staff to ensure their complete, correct administration.
 - Health personnel who care for VL–HIV co-infected patients must respect the fundamental ethical principles of good clinical practice (respect for person, beneficence and justice) at all times.
-

2. Methods

These guidelines were developed according to the process recommended by the WHO Guidelines Review Committee, in alignment with the *WHO Handbook for guideline development* (1). The process comprises: detailed planning; identifying the purpose and the target audience; scoping; establishing a steering group; developing PICO questions; identifying funding sources; incorporating relevant aspects of equity, human rights, gender and social determinants; organizing a synthesis of qualitative evidence; commissioning systematic evidence reviews for each PICO question; using the GRADE method to rate the certainty of the evidence; applying formal procedures and rules for selecting experts for the GDG; managing conflicts of interest; and using the GRADE method to formulate recommendations (2).

A systematic review was commissioned to synthesize and appraise existing evidence. The GRADE method was used to rate the certainty of the evidence and determine the strength of the recommendations. This approach, which WHO has adopted, defines the certainty of evidence as the confidence with which the reported estimates of effect (desirable or undesirable) can be considered to be close to the actual effects of interest. The strength of a recommendation reflects the degree to which the GDG is confident that the desirable effects (potential benefits) of the recommendation outweigh the undesirable effects (potential harm). Desirable effects may include beneficial health outcomes (such as reduced morbidity and mortality), reduction of the burden on the individual and/or health services and potential cost savings. Undesirable effects include those that affect individuals, families, communities or health services. Additional considerations include the resource use and cost implications of implementing the recommendations and clinical outcomes (such as drug resistance and drug toxicity). All the systematic reviews followed the PRISMA guidelines (11,12).

Synthesis of qualitative evidence and evidence to recommendations

WHO organized an online stakeholder survey to assess their rating of the importance of outcomes and their views on the equity, feasibility, affordability and acceptability of the outcome. Ethical approval was obtained from the Research Ethics Review Committee at WHO and the local institutional review boards at the University of Gondar in Ethiopia and the Indian Council of Medical Research–Rajendra Memorial Research Institute of Medical Sciences in India. The results are presented in **Annex 1**.

Guideline Development Group

The GDG was composed of individuals with recognized expertise in the management of VL and similar and/or related diseases or in other public health issues in various institutions in endemic countries in East Africa and South-East Asia and those working in national VL control and elimination programmes with experience in managing VL–HIV cases. Geographical representation and gender balance were taken into account when selecting members.

External systematic evidence reviews were commissioned to address the PICO questions. The criteria for inclusion and exclusion of studies (e.g., study design, sample size, duration of follow up) were based on the evidence required to answer the PICO questions. The search strategies and summaries of evidence are reported in **web annex A**. The GRADE method was used to assess the certainty of evidence, which was categorized per outcome and per PICO question as high, moderate, low or very low according to risk of bias, indirectness, imprecision, inconsistency and publication bias.

Then, for each PICO question the GDG reviewed the available evidence and judged each of the following aspects: desirable effects, undesirable effects, certainty of evidence, values, balance of effects, cost-effectiveness and resources required, impact on equity, acceptability and feasibility. The GDG then decided the direction (for or against) and the strength (strong or conditional) of the recommendation. The discussion was guided by GRADE “evidence-to-decision” tables (2). The GDG also used these tables to record additional information, as available, on justification, subgroup considerations, monitoring and evaluation and research priorities.

Because of restrictions due to the COVID-19 pandemic, the GDG met virtually (online) on 28 September–1 October 2020.

Decision-making

Discussions were facilitated by the Chair and co-Chair, giving equal voice to each panel member. The final recommendations were drafted by consensus when possible (indicating full agreement by all members). When consensus was not reached, the GDG used anonymous voting via www.menti.com directly into the GRADEpro Guideline Development Tool, and the disagreements were noted in the evidence-to-decision tables.

Consideration of potential harm and unintended consequences

In developing the PICO questions, the steering committee considered potential harm and unintended consequences as outcomes of interest. Subsequently, the authors of the systematic review searched for, synthesized and rated the certainty of evidence on potential consequences, which was included in the evidence profiles and evidence-to-decision tables. The GDG reviewed the evidence and made judgements about the “undesirable effects” and, later, the “balance of desirable and undesirable effects”. They also discussed mitigation of risks and unintended consequences. Their judgements contributed to the GDG’s decision on the direction and strength of the recommendations.

External peer review

The draft guidelines were circulated for review to members of the GDG and an external review group. The WHO steering group reviewed the comments and incorporated them into the final document, with due consideration of any conflicts of interest of external review group members.

Declaration and management of conflicts of interest

In accordance with WHO policy, all members of the GDG, the external review group, the systematic review team and the writer of the guidelines completed a WHO declaration of interests form to declare participation in any consulting or advisory panel, research support and financial investments. To strengthen public trust and transparency in WHO meetings involving the provision of expert advice in developing technical norms and standards, the names and brief biographies of individuals considered for participation in developing these guidelines, with a description of the objectives of relevant meetings, were published online before the GDG meeting to allow time for “public notice and comment”.

The WHO secretariat assessed the declarations submitted and, having observed no significant financial, commercial or intellectual conflicts of interests, concluded that no member should be excluded from active participation in formulating the recommendations. The WHO secretariat was satisfied that there had been transparent declarations of interests by the external review group, and no case necessitated exclusion from the review. Additionally, at a session convened on the methods of guideline development by the Guideline Review Committee secretariat at the virtual meeting of the GDG in September 2020, each participant verbally disclosed any potential interests.

The evidence review team was contracted by the Cochrane Collaboration, with specific terms of reference. Researchers involved in the review were also required to complete WHO declaration of interests forms, which were assessed and cleared by the WHO secretariat for financial, commercial or intellectual conflicts of interests. Two GDG members who contributed to studies included as evidence to address PICO 2 did not participate in the discussions on PICO 2.

3. Background

3.1 Epidemiology and burden of visceral leishmaniasis–HIV coinfection

VL, or kala-azar, is a systemic protozoan parasitic disease that is the most severe form of leishmaniasis. Without adequate, timely treatment, the condition is fatal. Transmitted by the bite of female sandflies, the disease is typically caused by *L. donovani* in Asia and sub-Saharan Africa and by *L. infantum* in the Mediterranean Basin, the Middle East, Central Asia, South America and Central America. In East Africa and South-East Asia, VL is spread mainly through human-to-human transmission (anthroponotic), as opposed to zoonotic transmission (involving animals as reservoir hosts) in other foci. PKDL, which may occur after successful treatment of VL, occurs in all areas that are endemic for *L. donovani* but is commonest on the Indian subcontinent and in Sudan and, more rarely, in other East African countries (14). The epidemiology of leishmaniasis depends on the characteristics of the parasite species, the local ecology at transmission sites, current and past exposure of the human population to the parasite, and human behaviour. Leishmaniasis can also be transmitted by shared syringes among intravenous drug users, by blood transfusion and congenitally from mother to infant, but these modes of transmission are rarer than vector-borne transmission. VL is therefore known for its high diversity and complexity.

In 2020, more than 90% of the VL cases reported to WHO were in Brazil, Ethiopia, Eritrea, India, Iraq, Kenya, Nepal, Somalia, South Sudan and Sudan. These high-burden countries are among the more than 70 countries in which VL is considered endemic. Estimates of the global incidence show a decrease in the past decade, from 200 000–400 000 new cases in 2012 to 50 000–90 000 in 2016 (15, 16). During the early 2000s, Bangladesh, India and Nepal collectively reported more than 50% of the global burden of VL. In 2005, these countries signed an agreement to eliminate VL as a public health problem by 2015, setting a target of an annual incidence of less than one case per 10 000 people per year at district (Nepal) and subdistrict (India and Bangladesh) levels. The target date was later revised to 2020. While the incidence on the Indian subcontinent has decreased sharply, East Africa has become the largest focus, with an increasing proportion of global VL cases and recurrent epidemics.

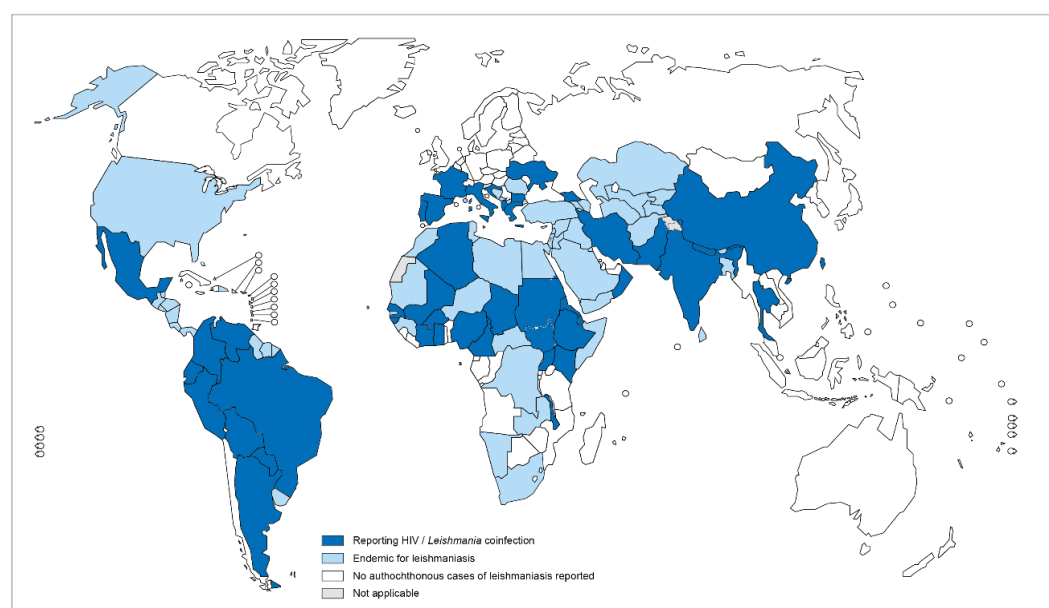
The risk factors for progression to VL and increased spread in all transmission settings include malnutrition, genetic factors, population movement, other infectious diseases and immune suppression – notably HIV infection. HIV continues to be a major global public health problem; it has claimed almost 33 million lives so far, and there were an estimated 38 million people living with HIV at the end of 2019 (17). By mid-2020, 26 million people had access to ART, representing 67% of people living with HIV who knew their status. The prevalence of HIV in the general population of East Africa and South-East Asia is generally low, but increasing numbers of new infections have been reported in some population groups. Early access to ART and support for treatment adherence

are critical, not only to improve the health of people living with HIV but also to prevent HIV transmission. Success has, however, varied by region, country and population, as access to HIV testing, treatment and care is not yet universal. Marginalized population who are at risk of VL, such as migrants and seasonal workers from Ethiopia and India, are even more vulnerable, with few VL and HIV services available to them.

HIV and *Leishmania* reinforce each other in a manner detrimental to the patient. The geographical overlap of endemicity of HIV and *Leishmania* has increased progressively in the past few decades (Fig. 1). As many as 45 countries have reported HIV–*Leishmania* coinfection since the first case was reported in 1985 (5). VL is included in WHO’s clinical staging system for HIV as a stage 4, AIDS-defining condition (atypical disseminated leishmaniasis) (18). In southern Europe, up to 70% of cases of VL in adults are associated with HIV infection, although the number of new cases has decreased since the end of the 1990s, mainly due to access to ART. In other parts of the world, however, where there is limited access to such treatment, the prevalence is rising steadily. The incidence of coinfection increased in Brazil, from 0.7% of VL cases in 2001 to 8.5% in 2012. Northern Ethiopia has a particularly high rate of HIV infection in VL patients, of 15–35% (19). In India, the total number of reported cases of VL–HIV increased from 0.88% in 2000 to 4.19% in 2020. A study in Bihar found that 5.6% of 2077 consecutive confirmed cases of VL in patients aged ≥ 14 years were HIV-positive, of whom half were unaware of their HIV status (20). HIV testing of VL patients in India has recently been scaled up significantly (21).

Data reported to WHO during 2014–2020 showed that > 50 000 people with VL were tested for HIV in 16 countries, and 3070 cases (new and relapses) of VL–HIV coinfection were recorded (22).

Fig. 1. Global distribution of leishmaniasis and of countries that reported HIV–*Leishmania* coinfection, 2021



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement. © WHO 2021. All rights reserved

Data Source: World Health Organization
Map Production: Control of Neglected
Tropical Diseases (NTD)
World Health Organization



3.2 Challenges of visceral leishmaniasis in HIV co-infected patients

VL with HIV coinfection has important epidemiological, clinical and public health implications for patients, their families, clinical services and disease control and elimination programmes alike.

Epidemiological

- In areas endemic for HIV and *Leishmania*, HIV-infected patients are particularly vulnerable to VL as an opportunistic infection and are more likely than individuals without HIV to develop VL from a dormant infection or as a clinical manifestation after primary *Leishmania* infection.
- VL accelerates HIV replication and progression to AIDS.
- As the HIV pandemic extends into rural and remote areas endemic for VL and VL becomes urbanized, the double burden of HIV and VL is expected to increase if no action is taken.
- The estimated incidence of VL in HIV-positive individuals and the incidence of HIV in VL patients differs among countries, regions and districts, over time and among studies, adding complexity to understanding the real burden.
- There are currently limited screening methods for VL in HIV patients in areas endemic for VL.

Clinical and case management

- The virus, HIV, and the parasite, *Leishmania*, have a synergistic effect, as both target macrophages and provoke immunosuppression of the host.

Clinical presentation

- The typical clinical features of VL include fever, splenomegaly or hepatomegaly, loss of appetite and/or weight loss. Although HIV co-infected VL patients also present with these manifestations, splenomegaly may be observed less frequently and, in profoundly immunosuppressed patients, atypical sites may be affected, with involvement of, e.g., the gastrointestinal tract, oral mucosa, peritoneal space, intra-abdominal lymph nodes and skin. Oesophageal involvement can lead to dysphagia and odynophagia, which must be differentiated from other causes of oesophagitis such as candidiasis.
- Involvement of structures of the eye, such as leishmanial uveitis, has also been reported, which includes uveitis as an immune phenomenon and uveitis after treatment for either leishmaniasis or HIV.
- Further exacerbation of symptoms is seen in patients with low CD4 cell counts (< 200 cells/mm³). Diffuse cutaneous and PKDL forms associated with VL have been reported. Antiretroviral treatment in VL coinfection may lead to PKDL due to immune reconstitution inflammatory syndrome.
- The presence of opportunistic infections can complicate a clinical diagnosis at the time of presentation of a patient.

- The clinical presentations of VL relapse in patients co-infected with HIV might be comparable to those of the initial episodes of VL, although the frequency and severity of opportunistic infections depend on ART initiation and maintenance.

Diagnosis

- As both cellular and humoral responses decrease, diagnosis becomes more difficult. Serological tests are less sensitive in co-infected patients, and the results of tests are equivocal due to factors such as test format, region of endemicity and level of immunosuppression. Sequential administration of different serological tests might be necessary to increase sensitivity, e.g. rK39 RDT and the direct agglutination test.
- A substantial proportion of HIV–VL patients may present with other opportunistic infections, which complicate the clinical diagnosis.
- The parasite load is higher and may be found at unusual sites, especially in severely immunosuppressed patients. Therefore, microscopic examination, culture or polymerase chain reaction of blood (plain blood or buffy coat) or bone marrow aspirates might be more sensitive than in immunocompetent patients. *Leishmania* parasites are occasionally found in biopsy samples from skin, gastrointestinal tract or lungs.
- Bone-marrow aspirates from HIV co-infected patients may, however, be paucicellular and contain few parasites, rendering tissue aspirates less reliable, including in relapse.
- HIV co-infected patients are also at higher risk for atypical or more severe presentations of cutaneous and mucosal leishmaniasis.

Treatment and treatment outcome

- There are limited therapeutic options for the treatment of VL in HIV co-infected patients.
- There is a high risk of VL treatment failure, regardless of the drug used, with higher rates of relapse and mortality.
- Antileishmanial drugs, particularly pentavalent antimonials, are more toxic in HIV co-infected patients. As toxicity in general is more frequent, higher doses, combined drug therapy and repetition of drug regimens might be necessary.
- The mortality rate during the first episode is high, with a poor long-term clinical response and a low rate of parasitological cure.
- The lifetime VL relapse rate is 60–100%, depending on the length of follow-up. With time, relapses become more frequent and occur at shorter intervals. Risk factors for relapse include a low CD4 cell count, failure to achieve clinical or parasitological cure during the first episode, absence of secondary prophylaxis and absence of ART.
- VL negatively affects the response to ART, as the baseline CD4 cell count is often lower.

- Reporting systems are often inadequate, such that data on treatment and its outcomes (including death) of VL–HIV co-infected patients are not readily available.

Public health

- Co-infected patients are considered to have increased infectivity, with a high parasite load, serving as human reservoirs of infection for sandflies.
- VL–HIV co-infected patients, especially those with low CD4 cell counts, may have increased transmission capacity, as shown in xenodiagnosis studies.
- Health system resources and capacity are affected by patients who suffer from repeated relapses, prolonged hospital stays and more severe disease.
- VL–HIV co-infected patients are at increased risk of developing drug resistance and could serve as a source of resistant parasites, because of the high rate of treatment failure and of risk of relapse and repeated, prolonged exposure to antileishmanial drug.
- A significant proportion of VL patients are unaware of their HIV status, as systematic screening is not well established, and, in high-VL burden countries, lack of coordination with HIV programmes. As a consequence, most VL episodes in HIV-positive patients are detected late. Clinicians who treat VL alone or HIV alone are insufficiently aware of the link between the two diseases.
- Early HIV diagnosis and adherence to treatment are difficult to assure in highly mobile and difficult-to-reach populations, such as migrants.
- Barriers persist in access to good-quality care, leading to delays in presenting to health-care facilities and high out-of-pocket expenditure. Health services for diagnosis and management of HIV–*Leishmania* coinfection are restricted to a few centres with limited clinical experience. An uninterrupted supply of medicines has also been a challenge, as most antileishmanial medicines are from a single source.
- HIV-related stigmatization persists and contributes to delay in care-seeking. Little is known about patients' perspectives, such as socio-economic aspects and quality of life.
- These factors limit the generation of good-quality evidence, as it is difficult to enrol sufficient numbers of VL-HIV co-infected patients in clinical studies, obviating sufficiently large comparative trials.

3.3 Visceral leishmaniasis–HIV coinfection in East Africa

Eritrea, Ethiopia, Kenya, Somalia, South Sudan, Sudan and Uganda, are countries in East Africa which are highly endemic for VL. Systematic HIV screening and data on VL–HIV coinfection are, however, very limited. In Humera in northwest Ethiopia in 2006, the HIV infection rate among VL patients was as high as 40%, notably in young seasonal workers in VL-endemic lowlands (23). This naive, hard-to-reach population faces many barriers in accessing services for detection and treatment of VL (24). The pooled estimated prevalence of HIV infection among VL-infected people in northwest Ethiopia was 24% according to a recent systematic review and meta-analysis (25). Unpublished data from national and international nongovernmental organizations and research institutes indicated an HIV coinfection rate between 2009 and 2012 of 2% in Gedaref, Sudan, and 2.5% in Greater Upper Nile, South Sudan; and the rate was 1.4% in Kacheliba, Western Pokot, Kenya, during 2006–2012 (19).

The diagnosis of VL in East Africa is guided by an algorithm of clinical suspicion and two serological tests, the rK39 RDT and the direct agglutination test. The accuracy of rK39 RDTs was, however, lower in the general HIV-negative VL patient population than in a similar population on the Indian subcontinent, where *L. donovani* is also endemic. Furthermore, the sensitivity of the rK39 RDT is even lower in VL–HIV patients than in HIV-negative individuals. The test should therefore be used with the direct agglutination test in a serial algorithm for better sensitivity. In patients with advanced HIV, a negative RDT result does not rule out a diagnosis of VL, and diagnosis in such patients relies on invasive procedures for parasitological diagnosis (microscopy and/or culture from spleen, bone marrow or lymph nodes), which also allows monitoring of response to treatment (23). Few hospitals have the capacity to provide these tests, and improved diagnostics for VL–HIV remain a priority.

The first-line treatment of VL in HIV-negative patients in East Africa is parenteral administration of pentavalent antimonials and paromomycin for 17 days. The second-line treatment or the regimen used for complicated cases (26), is liposomal amphotericin B (3–5 mg/kg per daily dose by infusion given over 6–10 days up to a total dose of 30 mg/kg). Overall, the first-line combination therapy is effective and safe in non-HIV–VL patients. In HIV co-infected patients, however, treatment options are more limited, as the rates of toxicity and parasitological failure are higher.

The treatment response of HIV-positive VL patients varies, and they generally require higher doses of paromomycin and L-AMB (27). When L-AMB was administered at a total dose of 30 mg/kg to HIV-positive patients, the cure rate was 60%, while it was 93% in an HIV-negative population (28). A higher dose of 40 mg/kg was reported to result in a 74% cure rate in a first VL episode but only 38% in relapse cases, with failure rates of 16% and 56% in the two groups (28). A retrospective analysis of the records of VL–HIV patients in Ethiopia showed only a 43% cure rate with sodium stibogluconate (29), which is known to be highly toxic in HIV patients. Miltefosine alone was safer (fewer adverse events) than sodium stibogluconate but was less effective, with 17.5% parasitological treatment failure (30). In short, all the drugs lacked efficacy when used as monotherapy. A retrospective study indicated that compassionate use of co-administered L-AMB (at 30 mg/kg total dose) and miltefosine in VL–HIV co-infected patients resulted in a substantially higher cure rates (84%) and lower failure rates in both primary and relapsed

VL-HIV co-infected patients (31). Combination therapy with L-AMB and miltefosine should be assessed to enhance treatment effectiveness, and possibly delay the onset of lack of response.

Although the VL relapse rate in VL-HIV co-infected patients is known to be higher than that of HIV-negative individuals, this is difficult to ascertain, as most patients are lost to follow-up. The risk of relapse is higher for those with a low CD4 cell count (< 200 cells/ μ L) and multiple previous VL episodes who are not receiving ART, those who fail to achieve clinical or parasitological cure during the first episode of VL, those who have no increase in CD4 cell count at follow-up or are not on secondary prophylaxis (32,33). Secondary prophylaxis is generally targeted to those at highest risk of relapse. A study in Ethiopia addressed use of monthly pentamidine, which is currently not used as treatment for VL disease in East Africa but is relatively safe at a low prophylactic dose (34).

3.4 Visceral leishmaniasis-HIV coinfection in South-East Asia

In India, the populous state of Bihar has been the epicentre of VL for over a century. It is also co-endemic for HIV. Although the overall incidence of VL has been falling, 7–20% of reported VL patients aged \geq 18 years are co-infected with HIV, with wide variation among districts. Burza et al. (20) reported that VL with HIV coinfection is “an underdiagnosed and underrecognized emerging public health issue”, which is a critical challenge for VL elimination in this region. Improved surveillance and implementation of the recommendation to offer all VL patients an HIV test may have contributed to increasing the number of reported cases of coinfection. An unpublished study in Nepal showed that 1–5% of VL patients were HIV-positive. Sporadic cases of VL and VL-HIV coinfection have been reported in Thailand.

The complex diagnostic and treatment challenges of VL-HIV coinfection seen in East Africa also prevail in South-East Asia. The outcomes of treating VL in HIV co-infected patients in India with higher doses of L-AMB are far better than those observed in East Africa although still substantially worse than those in HIV-negative patients. Late recognition of co-infected patients is frequent, as not all VL patients are systematically offered HIV testing and counselling. Patients present with more severe morbidity, and a substantial proportion have low CD4 cell counts (< 200 cells/mm³). In Bihar, which has a high economic migration flow, screening of HIV-infected patients for VL in areas not endemic for VL has been advocated, particularly for people who have spent significant time in VL-endemic areas.

TB has been reported as an emerging concomitant infection in VL-HIV co-infected patients in India. The combined immunosuppressive effect of VL and HIV may increase the risk of patients in high-TB burden areas for reactivation of a latent TB infection and hence suffer a triple infection. VL-HIV patients are more likely to develop disseminated TB and are more difficult to diagnose. TB may be a contributing factor to the persistently high mortality rates in VL-HIV coinfection. TB has been reported as an emerging concomitant infection in VL-HIV co-infected patients in India. Screening for TB is rarely done during VL diagnosis, except on clinical indication (e.g., pronounced pulmonary symptoms, marked lymphadenopathy). In contrast, patients who do not respond well to VL treatment are often tested for TB. Screening with a cartridge-based nucleic acid amplification test identified up to 20% of patients with both VL and HIV as having pulmonary TB. These patients are at the highest risk of mortality, and the timing and monitoring of treatment for VL, TB and HIV present many challenges (35).

There is limited evidence on treatment for VL-HIV in India, and case management has been based on evidence from Europe (with *L. infantum* as the causal species instead

of *L. donovani*). There are scant data on the safety of L-AMB (at a dose of 3–5 mg/kg daily or intermittently for 10 doses (days 1–5, 10, 17, 24, 31 and 38 days) in this region, although L-AMB is the treatment of choice for critical VL-HIV patients. High doses of L-AMB are known to be associated with hypokalaemia in treatment of PKDL in Bangladesh in patients with no known HIV infection. Furthermore, long hospitalization is required, increasing the cost and burden for patients. Initially, patients with VL-HIV were treated with a total dose of 20–25 mg/kg L-AMB, which had a good safety profile, although the mortality rate remains high, and relapse occurred in 8–15% of patients (36,37). In a retrospective study of the outcome of L-AMB (up to 30 mg/kg in six equal infusions) combined with 14 days of 100 mg/day oral miltefosine (38), the cumulative incidence of all-cause mortality and VL relapse at 12 months was 14.5% and 6.0%, respectively. Not initiating ART and concurrent tuberculosis were independent risk factors for mortality, whereas no factors were associated with relapse (38). VL-HIV public health experts in India thus recommended a randomized trial with the same regimen.

3.5 Clinical and case management of visceral leishmaniasis in HIV co-infected patients

The pathogenesis of VL and HIV in humans involves complex mechanisms related to dysregulation of host immune responses (cytokine secretion and cell-signalling events), as both HIV and *Leishmania* multiply in cells of myeloid or lymphoid origin. In HIV-infected patients, both the cellular (Th1) and humoral (Th2) responses to *Leishmania* diminish, as the Th1-type response is impaired, and active *Leishmania* infection induces prolonged Th2-type cell activation in HIV-infected patients, which increases viral replication and progressively decreases the CD4 cell count. The Th1-type response, mediated by interleukin-2, interleukin-12 and interferon- γ , leads to activation of macrophages and enhanced intracellular killing of parasites, whereas a predominance of Th2-type cytokines, such as interleukin-4 and interleukin-10, is associated with progressive disease. The link between leishmaniasis and the severity of HIV is a logical consequence of cellular immunodeficiency.

Most cases of VL in HIV co-infected patients present with typical features of VL (e.g., prolonged fever, splenomegaly, anaemia, leukopenia, thrombocytopenia), but atypical presentations occur in severely immunosuppressed patients (39). Usually, (localized) parasites are detected in abnormal tissues such as the intestine, oral cavity, skin and lungs, and these atypical presentations are easily misdiagnosed or mistaken as flare-ups of the underlying disease (40). Furthermore, the clinical presentation of advanced HIV/AIDS (including opportunistic infections) and VL overlap, reducing the likelihood of clinical suspicion. The symptoms and signs of VL must be differentiated from those of conditions such as disseminated mycobacterial infections, lymphoma and disseminated histoplasmosis.

HIV-infected patients appear to have skin manifestations of leishmaniasis more frequently than HIV-negative patients, before, during or after a VL episode. The features of cutaneous involvement vary, particularly in severely immunocompromised patients, and include parasite dissemination, clinical polymorphism with atypical and often more severe clinical forms and even visceralization. Rates of 9–18% of skin lesions and 3% of oral lesions are confirmed as due to leishmaniasis (41). PKDL has also been reported to be more frequent, with a changing clinical presentation, e.g., more nodular lesions containing many parasites. PKDL is the putative reservoir for anthroponotic VL between epidemic cycles, and HIV co-infected VL patients may well play the same role.

Both treatment and the immune response contribute to cure of VL in HIV co-infected patients. The presence of parasites at the end of treatment may imply nonsterile cure, while somewhat higher levels of parasites may result in a slow but progressive increase in parasite numbers and relapse within months of treatment cessation. Serological tests cannot indicate cure or relapse, as antibodies remain detectable for years after a VL episode. The gold standard for VL diagnosis and test of cure is direct parasite visualization by microscopy of tissue aspirate samples (spleen, bone marrow or lymph node). The sensitivity depends on the biological material, i.e., spleen aspirate is more sensitive than bone marrow and lymph node aspirate. Molecular tests, such as polymerase chain reaction on blood, are very sensitive but require trained personnel and laboratory resources that are not available everywhere; furthermore, this method is still not formally validated as a replacement for parasitological visualization. Urine antigen detection tests are highly specific but currently not sensitive enough to be widely used, although they could be considered for use as non-invasive tests of cure (42,43).

3.6 Previous recommendations for treatment of visceral leishmaniasis in HIV co-infected patients

Because of the lack of evidence, there have been no specific guidelines for treatment of VL in HIV co-infected patients in areas where VL is caused by *L. donovani*. Fragmented use of various drugs has been reported in treating episodes of primary VL–HIV and in secondary prophylaxis after the first episode of VL to prevent or delay relapse. Nevertheless, it is difficult to carry out clinical trials, given the dispersed geographical distribution of cases, the concentration of VL in migratory populations and low rates of testing for HIV in VL patients in areas where the two infections are co-endemic. After the studies on VL–HIV in southern Europe in the late 1990s, there was a 20-year gap before research commenced in Ethiopia to assess the efficacy of combination regimens in this patient group. In 2010, a WHO expert committee recommended that countries adopt innovative policies of using drug combinations as they became available and meanwhile adopt the best options for monotherapy with L-AMB (3). In general, because of the risk of resistance in anthroponotic foci, it was recommended that use of monotherapy be limited to L-AMB where possible. Testing of combination regimens in co-infected patients has been encouraged, as they have the potential advantages of better efficacy and lower overall dose, thereby reducing toxic effects. Use of combination regimens is also likely to lower the probability of selection of drug-resistant parasites, thus prolonging the effective life of available medicines (44). Other potential advantages include shorter treatment, better compliance and better treatment completion rates, reducing costs and increasing health service efficiency.

There is therefore a clear rationale for assessing combination treatment. Until now, the recommended treatment has been monotherapy of amphotericin B deoxycholate or its lipid formulations. This recommendation was based mainly on case reports and case series from the Mediterranean Basin during early HIV epidemics, with only a few small trials.

For secondary prophylaxis, most studies have shown its benefit for VL in HIV patients. Secondary prophylaxis is ideally started after a negative test of cure. Potentially, all antileishmanial drugs can be used for this purpose. In anthroponotic transmission regions like East Africa and the Indian subcontinent, however, drugs that are used as first- and second-line therapy are better not used as secondary prophylaxis due

to concern about the development of resistance. In areas endemic for *L. donovani*, secondary prophylaxis is not yet included in any national guidelines for VL–HIV patients.

Several operational and programmatic aspects discussed in the previous guidance (3) are maintained in the current guidelines, where applicable.

3.7 Changes in case management established in these guidelines

These guidelines present a revised therapeutic protocol based on new evidence. They specifically address treatment of VL in HIV co-infected patients. No new medicines are recommended, but rather new recommendations are made for combined use of existing medications. The supporting evidence for combination therapy is described in detail in **web annex A** (systematic evidence reviews). The recommendations of the WHO Guideline Development Group for PICO 1 and 2 can be consulted in full in **web annex B** (evidence-to-decision tables).

3.8 Management of other forms of leishmaniasis and in other endemic regions

The present guidelines address case management and treatment of VL in HIV co-infected patients in East Africa and South-East Asia. For management of other forms of leishmaniasis, including VL in HIV-negative patients, the recommendations of the WHO Expert Committee on the Control of Leishmaniasis (3) should be consulted.

These guidelines do not propose changes to previous WHO recommendations for regions in which VL is predominantly due to *L. infantum*. Current WHO normative documents on leishmaniasis control in Europe (8) and the Americas (9) contain specific recommendations for the treatment of VL in HIV co-infected patients in those regions.

4. Treatment of visceral leishmaniasis in HIV co-infected patients in East Africa and South-East Asia

4.1 Case definition

Visceral leishmaniasis

Clinical description

An illness with prolonged irregular fever, splenomegaly and/or weight loss as its main symptoms. In areas co-endemic for malaria and leishmaniasis, VL should be suspected when fever lasts for more than 2 weeks and no response has been achieved with antimalarial medicines (assuming that drug-resistant malaria has been considered).

Laboratory criteria for diagnosis of VL

- positive parasitology (stained smears from bone marrow, spleen, liver, lymph node, blood or culture of the organism from a biopsy or aspirated material); and/or
- positive serology (immunofluorescence antibody test, ELISA, rK39, direct agglutination test)
- positive polymerase chain reaction and related techniques

HIV case classification (WHO operational definition)

A case of HIV infection is defined as any clinical stage of HIV infection (including severe or stage 4 clinical HIV disease, also known as AIDS) confirmed by laboratory criteria according to national definitions and requirements (18).

Clinical findings in VL–HIV coinfection

- may resemble those in HIV-negative patients, i.e., fever, hepatosplenomegaly and/or weight loss;
- a broad spectrum of atypical sites of *Leishmania* infection possible in severely immunocompromised patients;
- common occurrence of other AIDS-related diseases, such as concomitant opportunistic infections.

Laboratory findings in VL–HIV coinfection

- Serology is usually less sensitive than in HIV-negative individuals. rK39 RDT was less sensitive (77% versus 87%) among parasitologically confirmed cases in a study in Ethiopia. The sensitivity of the direct agglutination test is generally higher than that of rK39 RDTs but still lower among HIV co-infected patients (89% versus 95%) than in HIV-negative patients. Use of rK39 and a direct agglutination test in a serial algorithm can yield a sensitivity of 98% (45). Similar studies have confirmed the low diagnostic accuracy of serological tests (46). Other studies have shown that direct agglutination test titres in HIV-positive and HIV-negative individuals are comparable (47), although the nature of the antigens remains unknown. Lower sensitivity of rK39 RDTs has also been reported in HIV co-infected patients in India.
- Because of the suboptimal sensitivity of rK39 RDTs, parasitological tests continue to be relied upon, and detection of parasites is also the only way to diagnose relapse or cases with atypical clinical signs or negative RDT results but a high index of suspicion of VL. The diagnostic yield is higher from tissue aspirates because of higher tissue parasite densities in HIV co-infected patients. Parasitological confirmation is also useful in assessing treatment response and deciding on treatment extension or change of drugs.
- Pancytopenia is common in VL, but haematological cytopenia is more frequent and pronounced in co-infected patients.
- Hypergammaglobulinaemia secondary to B-cell polyclonal activation is a frequent finding in both VL and HIV infection (limited diagnostic value)

4.2 First choice of treatment: combination therapy

WHO recommendations

In East Africa
<p>The WHO panel suggests L-AMB + miltefosine^a over L-AMB monotherapy^b for individuals with VL–HIV coinfection in East Africa (Conditional recommendation; very-low-certainty evidence)</p> <p>^a Doses when given in combination: L-AMB (up to a cumulative treatment dose of 30 mg/kg body weight, given as 5 mg/kg on each treatment day 1, 3, 5, 7, 9, 11) + miltefosine (100 mg/day for 28 days)</p> <p>^b Dose of L-AMB when used as monotherapy: up to 40 mg/kg, at 5 mg/kg on days 1–5, 10, 17, 24</p>
In South-East Asia
<p>The WHO panel suggests L-AMB + miltefosine^a over L-AMB monotherapy^b for individuals with VL–HIV coinfection in South-East Asia (Conditional recommendation; very-low-certainty evidence)</p> <p>^a Doses when given in combination: L-AMB (≤ 30 mg/kg, at 5 mg/kg on days 1, 3, 5, 7, 9, 11) + miltefosine (100 mg/day for 14 days)</p> <p>^b Dose of L-AMB regimen when used as monotherapy: ≤ 40 mg/kg, at 5 mg/kg on days 1–4, 8, 10, 17 and 24</p>
<p>Remarks:</p> <ul style="list-style-type: none">▪ Determine the HIV status of patients diagnosed with VL. Screen routinely for TB at VL diagnosis and conduct further follow up.▪ Consider extending therapy (same therapy for one additional course) for patients who do not show a good clinical response, after ruling out other diagnoses.▪ When miltefosine is not available or is contraindicated, consider using monotherapy with L-AMB (up to a total of 40 mg/kg).▪ Provide comprehensive clinical management, including adequate HIV treatment and nutritional support.▪ Ensure access to contraception and pregnancy testing for women of childbearing potential.

4.2.1 Rationale

The WHO expert committee report published in 2010 (3) recommended L-AMB for HIV co-infected people, at a high dose of up to 40 mg/kg, given as 5 mg/kg on days 1–5, 10, 17 and 24. ART and secondary prophylaxis were also recommended. Noting the diversity of *Leishmania* parasite strains in different areas of the world, the committee recognized that evidence on region-specific VL treatment regimens was required. Combinations of antileishmanial medicines have been considered beneficial for treatment of VL in people living with HIV because of the high mortality rate and in the risk of relapse, presumed to be due to the synergy between the parasite and the virus in the body. Furthermore, there are limited therapeutic options for co-infected patients (see **Annex 2**), miltefosine being the only oral drug available to treat leishmaniasis.

4.2.2 Recommendations

East Africa

WHO conditionally recommends treatment of VL in HIV co-infected people with a combination of L-AMB and miltefosine at the following doses: L-AMB (total dose of ≤ 30 mg/kg, at 5 mg/kg on days 1, 3, 5, 7, 9, 11) + miltefosine (100 mg/day for 28 days). The therapeutic advantage over monotherapy with L-AMB was considered to be moderate during the deliberations; however, the long-term benefits are potentially important, including a possible reduction in the risk of resistance to amphotericin B. For patients with advanced AIDS, extended treatment is achieved with up to 28 days of oral miltefosine in East Africa and 14 days in South-East Asia. The contraindication of miltefosine in women of childbearing potential must, however, be respected; its embryotoxic and teratogenic potential for this group was considered as the only disadvantage of the combination regimen. The current literature indicates that most cases of VL–HIV coinfection were in males. Although the certainty of the evidence is very low (see **web annex 2**), the consensus of the GDG was that, “for VL in HIV co-infected patients in East Africa, the combination regimen should be used rather than monotherapy with L-AMB”.

During the clinical trials in Ethiopia, the procedures included providing extended combination treatment to slow responders, adding one more cycle of L-AMB and miltefosine, which appeared to be beneficial. Similarly, rescue treatment (sodium stibogluconate or sodium stibogluconate plus paromomycin) was given to non-responders, while routine parasitological test-of-cure on day 29 was implemented to monitor response.

A contraception plan and pregnancy testing must be available before miltefosine is prescribed in females. The cost implications are not necessarily clear; but the total cost of hospitalization might be lower with the combination regimen because it can be taken partly at home. No studies of cost-effectiveness was available. In terms of equity, in a stakeholder survey (**Annex 1**), 60% of respondents considered that the combination therapy would improve health equity, despite the limited use of miltefosine in women of childbearing potential. The stakeholders also considered that combination therapy is both acceptable and feasible if made available free-of-charge. The availability of quality-assured miltefosine might be a challenge and should be considered by national programmes.

South-East Asia

WHO also conditionally recommends treating VL in HIV co-infected patients with L-AMB + miltefosine, at the following doses: L-AMB (≤ 30 mg/kg, at 5 mg/kg on days 1, 3, 5, 7, 9, 11) + miltefosine (100 mg/day for 14 days). Despite the very-low-certainty evidence, the GDG also reached consensus on favouring combination therapy, as the desirable effects appear to outweigh any harm. In this region, experience in the use of miltefosine is better established, as it was offered as first-line treatment for VL in HIV-negative patients since 2007 before a change in 2012–2014 to single-dose L-AMB in this group, miltefosine was the treatment of choice in non-HIV infected PKDL, and the evidence for safety and effectiveness were considered acceptable. Surveys and stakeholder interviews (**Annex 1**) suggest that the outcomes (in terms of mortality, clinical cure at 6 months, relapse, serious side-effects and disease complications) are valued. Equity is not affected, as, at present, treatment for VL is available at no financial cost to the patient. The practicalities of further changes to treatment regimens will depend on medicine donations and governmental decisions.

4.2.3 Summary of data on efficacy and safety to support the changes to recommendations for treatment of VL in HIV co-infected patients

East Africa

A randomized, parallel arm, open-label study in two centres in Ethiopia designed to show the efficacy and safety of combination therapy with L-AMB (≤ 30 mg/kg, at 5 mg/kg on days 1, 3, 5, 7, 9, 11) + miltefosine (100 mg/day for 28 days) as compared with L-AMB monotherapy (≤ 40 mg/kg, at 5 mg/kg on days 1–5, 10, 17, 24) (48). The study had a sequential design, with stopping rules and interim analyses after every 10 participants. In the monotherapy arm, recruitment was stopped after the first 10 participants reached day 29 (total $n = 19$), while recruitment continued in the combination therapy arm. The combination therapy arm stopped recruitment after the first 20 participants reached day 29 (total $n = 39$). Participants were HIV-positive males and females aged 18–60 years with confirmed primary or relapse VL (parasitological diagnosis). The details of all the outcomes assessed are available in **web appendix B**. In this study, extended combination treatment was provided, in which one more cycle was added to the first combination regimen of L-AMB and miltefosine, for slow responders, defined as patients with a positive test of cure at day 29 who were clinically well. Rescue treatment with sodium stibogluconate or sodium stibogluconate plus paromomycin was provided for non-responders.

On day 29, the cure rate with L-AMB monotherapy was 50% (95% confidence interval (CI), 27 ; 73%), increasing at day 58 to 55% (32 ; 78) according to the intention-to-treat analysis and 59% (35 ; 83%) per protocol. With the L-AMB + miltefosine combination treatment, the cure rate at day 29 was 67% (48 ; 82%), increasing to 88% (79 ; 98%; intention to treat) and 91% (82 ; 100%; per protocol) at day 58. The combination of L-AMB + miltefosine showed relatively high efficacy at the end of treatment (day 29) for both primary and relapse cases. The data suggest a good safety profile in a population with a high burden of concomitant illnesses and medications. Extended treatment with L-AMB + miltefosine (with a second cycle for patients with a positive test of cure at day 29) indicated that combination therapy may result in cure of more patients than monotherapy (relative risk, 1.77; 95% CI, 1.08 ; 2.90; 56 participants; low-certainty evidence).

South-East Asia

Data were available from an open label, parallel arm, non-comparative randomized trial of single therapy with L-AMB and combination therapy with L-AMB and oral miltefosine in treating VL in HIV co-infected patients at one site in India (49). L-AMB was given at ≤ 30 mg/kg (at 5 mg/kg on days 1, 3, 5, 7, 9, 11) + miltefosine at 100 mg/day for 14 days. In the parallel arm, L-AMB monotherapy was given at ≤ 40 mg/kg, at 5 mg/kg on days 1–4, 8, 10, 17, 24. There were 75 patients in each arm (total 150). The sample had to be increased by 25% because of an unexpectedly high prevalence of TB coinfection (20%). All patients were to start or be continued on ART (started on day 15). The primary end-point for efficacy was being alive and disease free. This was defined as the absence of signs and symptoms of VL or, if symptomatic, a negative parasitological assessment by tissue aspirate on day 210. In the monotherapy arm, relapse free survival at day 210 was reached by 64 patients (85%) (95% CI, 77.4 ; 100%), while with the combination therapy it was 72 patients (96%) (90.4 ; 100%). Treatment failure by day 29 was reported in four patients (5.3%) in the monotherapy arm and one patient (1.3%) in the combination therapy arm. Five (6.7%) patients in the monotherapy arm died and one (1.3%) relapsed

by day 210, and two (2.7%) in the combination arm died and one (1.3%) relapsed. The outcomes in VL-HIV patients who had concomitant TB were worse than those of other groups. At baseline, 19% of patients (28/150) were TB infected (divided equally between both the arms), which was diagnosed in half of the patients after treatment initiation. Few severe adverse events were seen in either arm, reported for six (10%) patients in the monotherapy arm and four (6%) in the combination therapy arm. All but one of the events occurred in TB patients. The data suggest a good safety profile in a population with a high burden of concomitant illnesses and multiple medications.

4.3 Maintenance therapy/secondary prophylaxis

WHO recommendations

In East Africa
<i>Use secondary prophylaxis</i> after the first episode of VL in HIV co-infected patients (Conditional recommendation; very-low-certainty evidence)
In South-East Asia
<i>Use secondary prophylaxis</i> after the first episode of VL in HIV co-infected patients in South-East Asia (Conditional recommendations; very-low-certainty evidence)
<p>Remarks:</p> <ul style="list-style-type: none"> ▪ Secondary prophylaxis is recommended in particular for patients at higher risk of relapse (e.g., patients not on ART, low CD4 cell count (< 200 cells/mm³), multiple previous VL episodes, failure to achieve clinical or parasitological cure during the first episode of VL, no increase in CD4 cell count at follow-up, patients not on secondary prophylaxis). Patients should be evaluated case by case. ▪ As the recommendation for secondary prophylaxis applies specifically to HIV-positive individuals, the HIV status of individuals with VL must be established. <p>In East Africa: pentamidine isethionate at 4 mg/kg per day [300 mg for an adult]) every 3–4 weeks.</p> <p>In South-East Asia: amphotericin B deoxycholate at 1 mg/kg every 3–4 weeks or Liposomal amphotericin B at 3–5 mg/kg per day every 3–4 weeks.</p> <p>Prophylaxis can be stopped if the CD4 cell count is maintained at > 350 cells/mm³ or an HIV viral load is undetectable for at least 6 months and there is no evidence of VL relapse.</p> <ul style="list-style-type: none"> ▪ When choosing a drug, consider: <ul style="list-style-type: none"> ▪ using drugs that were not used to treat the primary VL episode, ▪ the benefits and safety profiles of the proposed drug, ▪ potential collateral benefits in terms of prevention of other infections and ▪ potential for drug resistance.

4.3.1 Rationale

Currently, no antileishmanial medicine achieves complete clearance of *Leishmania* parasites from the body. The aim of secondary prophylaxis is to avoid or suppress recurrence of VL, thus prolonging the disease-free interval. Critical outcomes for considering secondary prophylaxis are the extent to which the prophylaxis helps attain relapse-free survival, reduces mortality, improves adherence to treatment and is safe. There are, however, few effective drugs for treating VL episodes in co-infected patients that can also be used for secondary prophylaxis. Most of the evidence from Europe and the Mediterranean Basin during early HIV epidemics was in the form of case reports or case series, with a few small trials of low doses of AMB lipid complex (3–5 mg/kg). The existing guidelines are unclear about when to start, when to stop, what medicine to use and the dose and frequency of secondary prophylaxis in VL–HIV co-infected patients. In most anthroponotic transmission areas, such as East Africa and South-East Asia, use of the same drug for first-line regimen and for secondary prophylaxis has raised concern about the development of resistance (50).

In immunocompetent patients, cell-mediated immunity contains the parasites, providing protection against relapse. In HIV patients, however, the remaining parasites continue to multiply, resulting in clinical flare-up and relapse. Successive relapses are less typical and less acute but more frequent. With each relapse, patients become less responsive to treatment, requiring prolonged treatment with highly toxic drugs, high rates of failure of both VL and HIV treatments and increased risk of death.

Adequate HIV treatment is essential to maintain an undetectable viral load. ART contributes to positive VL treatment outcomes in HIV co-infected patients. VL treatment could also result in an increase in HIV viral load, probably as a consequence of the production of activated CD4 T cells, in which the virus replicates more. Therefore, viral replication should be avoided as much as possible with ART, with adequate monitoring, an important consideration in weighing up the benefit of secondary prophylaxis (51,52).

Evidence from zoonotic transmission of *L. infantum* in endemic areas

Most of the data on secondary prophylaxis are from Mediterranean countries, where transmission of VL is zoonotic, with *L. infantum* as the causal species. The data are, however, derived from open-label, uncontrolled studies. Various regimens with several drugs have been used; these were mainly pentavalent antimonials (20 mg/kg per day every 3–4 weeks), amphotericin B (either L-AMB or AmB lipid complex) at 3–5 mg/kg per day for 3–4 weeks or pentamidine (4 mg/kg per day [300 mg for an adult]) given every 3–4 weeks.

The effectiveness of secondary prophylaxis with AmB lipid complex (3 mg/kg per day every 21 days) was addressed in only one prospective randomized study and compared with no secondary prophylaxis (53). The drug was well tolerated, and, after 12 months' follow-up, 22% patients had relapsed, as compared with 50% of patients without secondary prophylaxis. A meta-analysis of the available studies (32) indicated a clear benefit of secondary prophylaxis in reducing VL relapse. The average relapse rate was 67% in patients who did not receive secondary prophylaxis and 31% in the arm that did, although most of the data were from *L. infantum*-endemic areas, where VL transmission is zoonotic.

Data from studies in Europe suggest that a CD4 cell count > 100 cells/mm³ at VL diagnosis reduces the odds of relapse (54). Therefore, the threshold for safe discontinuation of secondary prophylaxis for Spanish patients was suggested to be a

CD4 cell count of 200–350 cells/mm³. Similarly, in the Americas, liposomal amphotericin B is recommended for secondary prophylaxis in patients with VL–HIV coinfection after the first episode of VL, in all patients with a CD4 T cell count < 350/mm³ (strong recommendation, very-low-certainty evidence) (9).

Evidence from anthroponotic transmission of *L. donovani* in endemic areas

In a study in Ethiopia, 11 of 39 patients with relapse had a CD4 cell count > 200 cells/mm³ before relapse (51), whereas in Europe relapse was uncommon in patients with a CD4 cell count > 100 cells/mm³. This suggests that *L. donovani* is more virulent in anthroponotic transmission areas such as East Africa and South-East Asia. Additional reasons for the difference could be the host immune response, which may be reduced by factors such as nutritional status and the presence of other infections and co-morbidities.

Although clinicians and researchers in East Africa have more experience in managing HIV–VL co-infected patients than those in South-East Asia, evidence on secondary prophylaxis is very limited in both areas, and more studies and trials are necessary (23). Medical care for VL in HIV co-infected patients in both areas is severely restricted, as only a few tertiary referral centres manage VL–HIV coinfection. Moreover, health systems, surveillance and medical services for monitoring drug toxicity and patient follow-up are suboptimal. The risk of development of drug resistance must be taken into account in anthroponotic transmission of *L. donovani*, as HIV co-infected patients may become important reservoirs of drug-resistant *L. donovani*. To minimize this risk, a drug different from that used to treat a primary VL episode is generally recommended for secondary prophylaxis.

Further research is necessary to establish criteria for starting and stopping secondary prophylaxis and also to identify the best single-dose drug for secondary prophylaxis in anthroponotic VL due to *L. donovani*.

Physicians in both regions should carefully assess patients at higher risk of relapse, such as those with advanced immunosuppression (e.g., CD4 cell count < 200 cells/mm³) and/or an atypical clinical presentation. Similarly, care should be exercised in assessing patients with a history of treatment for multiple VL episodes before their HIV status was known. In studies of Spanish patients, a positive soluble *Leishmania* antigen-cell proliferation test, indicative of a cell-mediated immune response, was considered a good predictive marker of non-appearance of relapse in HIV patients co-infected with *Leishmania* (55,56). Physicians should also consider factors that affect access to services, such as migratory patients, social and gender barriers and health-seeking behaviour, that might increase the risk that relapses fail to reach clinical attention. Many factors associated with delayed diagnosis and incomplete treatment may also lead to a higher risk of relapse, including non-compliance with treatment or lack of monitoring due to cost.

4.3.2 Summary of data on efficacy and safety to support the recommendations for secondary prophylaxis in VL–HIV co-infected patients

In East Africa

Data were available from two open-label, non-comparative (single-arm) prospective cohort studies conducted in northwest Ethiopia (57,58), in which *pentamidine* was provided as secondary prophylaxis to HIV-positive primary VL patients with CD4

cell counts < 200 cells/mm³ at the end of VL treatment and to relapsed VL patients regardless of their CD4 cell count. Pentamidine prophylaxis was started 1 month after completing VL treatment only for those with no parasites on tissue aspiration post-treatment (or “test of cure” negative). ART and cotrimoxazole prophylaxis were part of routine care.

In the study conducted between November 2011 and September 2013, 74 participants were given monthly infusions of 4 mg/kg pentamidine isethionate diluted in normal saline for 12 months (57). The treatment regimens for primary VL had been sodium stibogluconate alone or in combination with paromomycin or L-AMB alone or in combination with miltefosine. After receiving secondary prophylaxis, 5 of 71 patients died within 2 years of follow-up. The estimated probability of relapse-free survival was 79% (95% CI, 67% ; 87%) at 6 months’ follow-up, 71% (95% CI, 59% ; 80%) at 1 year and 53% at 24–36 months of follow-up. A total of 21 serious adverse events were reported in 17/74 (23%) patients at the 1-year follow-up, two of which may have been related to pentamidine (renal failure in two patients hospitalized with pneumonia), patients who took at least 11 of the 12 doses. The main reasons for discontinuation were relapse (15), death (5) and loss to follow-up (7). More patients with a CD4+cell count ≤ 50 cells/ μ L (5/7; 71.4%) failed than those with counts > 200 cells/ μ L (2/12; 16.7%) ($P < 0.005$).

In the study conducted in 2014–2016 (58), 29 participants were given pentamidine starting 1 month after parasitological cure of a VL episode at a total dose of 40 or 30 mg/kg L-AMB + miltefosine at 100 mg/day for 28 days. By 12 months of follow-up, 12 (41%) participants had relapsed, 5 (17%) patients had died, and 46%, (95% CI, 26 ; 63%) had achieved relapse-free survival. A low CD4 count predicted relapse during the first 12 months of follow up, while VL relapse was an independent risk factor for subsequent relapse or death (adjusted rate ratio: 5.42, 95% CI: 1.1 ; 25.8). Serious adverse events were reported in 8/29 (28%) patients. One death due to acute renal failure in a patient with multiple coexisting diseases that might have affected renal function was considered possibly related to pentamidine.

In another single-arm clinical trial by the same group (59), long-term outcomes were studied in VL–HIV co-infected patients during and after secondary prophylaxis with pentamidine. Outcomes and associated factors were documented for 74 VL–HIV patients in Ethiopia for up to 2.5 years after initiation of pentamidine prophylaxis, including a 1-year follow-up after discontinuation of prophylaxis. The outcomes were: 39 (53%) relapse-free, 20 (27%) relapses, 5 (7%) deaths and 10 (14%) lost to follow-up. The 2-year risk of relapse was 36.9% (95% CI, 23.4 ; 55.0) and was highest for those with a history of VL relapse and a low baseline CD4 count. Forty-five patients were relapse-free and being followed up at month 12 of receiving prophylaxis (including 28 patients with month 12 CD4 counts > 200 cells/ μ L and 17 with CD4 counts < 200 cells/ μ L). The authors concluded that discontinuation of secondary prophylaxis is safe after month 12 if the CD4 count is > 200 cells/ μ L, although long-term management of patients who fail to reach that level remains to be defined. No pentamidine-related serious adverse events were reported during the study or the follow-up period. During the first year of follow-up, however, 42 drug-related adverse events had been reported by 30 (41%) of the 74 participants. The most common were symptoms of the respiratory system (nasal congestion) during pentamidine infusion (14, 19%), hypotension (11, 15%) and renal impairment (5, 6.8%).

In South-East Asia

The only data available on secondary prophylaxis in South-East Asia were from a comparative observational retrospective cohort study in eastern India (2005–2015) to ascertain the protective efficacy and safety of this approach (60). Twenty-seven patients received AMB and L-AMB: 15 received 1 mg/kg L-AMB monthly, and 12 received deoxycholate amphotericin B (1 mg/kg) monthly, and were compared with 24 patients who received no secondary prophylaxis after initial cure with L-AMB or amphotericin B deoxycholate. No relapses or deaths were noted after 6 months in the treated group as follows: relapses: none versus 18/24 (75%); deaths: none versus 11/24 (45.8%) ($P < 0.001$ for both). At the 1-year follow-up, none of the participants but 11/24 of the controls had died. This evidence was considered very uncertain.

In the same study, at 1 year of follow-up, relapse occurred in 0/27 of those receiving secondary prophylaxis and 18/24 (75%) of controls. The authors concluded that secondary prophylaxis with monthly AMB might be effective in preventing relapse and mortality in patients with VL–HIV, although the evidence was again considered very uncertain.

4.3.3 Recommendations

The drugs identified in the systematic review for which there was very-low-certainty evidence for efficacy in secondary prophylaxis were pentamidine in East Africa and low-dose amphotericin B deoxycholate or low-dose L-AMB in India. Further evidence is necessary to establish criteria for using drugs for secondary prophylaxis and in which circumstances (see **section 6**).

WHO conditionally recommends use of secondary prophylaxis after the first episode of VL in HIV co-infected patients in East Africa. One systematic review on predictors of relapse in VL–HIV co-infected patients indicated that secondary prophylaxis reduces the VL relapse rate (32), although the studies considered were conducted only in Europe. Given the specificities of VL–HIV in East Africa (e.g., longer time to relapse than in Europe, anthroponotic transmission), prophylaxis may have a specific altruistic benefit in terms of reducing infectivity (the parasite load) of patients.

Despite the low certainty of evidence (see **web annex A**), the consensus of the GDG was that secondary prophylaxis after a first episode of VL should be recommended for HIV co-infected patients in **East Africa**. The choice of drugs is limited, as the only evidence is on use of pentamidine. The drug has merits, including parallel effectiveness in preventing *Pneumocystis jirovecii* infection and the fact that it is currently not used as the first-line drug for primary VL in areas with anthroponotic VL. In terms of prevention of drug resistance, use of a drug that is not used routinely to treat either primary VL episodes or relapses is theoretically advantageous, as long-term, repeated use of the same drugs (as required for secondary prophylaxis) increases the risk of resistance. In view of the intermittent (monthly) low dose of pentamidine used in the studies (4 mg/kg per month), the risk for adverse effects is likely to be outweighed by the desirable effects of the drug (**Annex 3**). As there is currently no pentamidine donation programme for VL, its cost should be considered, although, in the long run, its use might result in cost savings due to prevention of recurrent disease and associated morbidity and mortality. In East Africa, use of secondary prophylaxis was perceived to increase equity, as prophylaxis is given in various settings, and access to health care might be improved through regularly scheduled visits to health centres. No evidence was found of its

acceptability or feasibility. The consensus of the GDG was that the intervention is likely to be both acceptable and feasible.

For **South-East Asia**, there was general consensus that secondary prophylaxis should be provided after a first episode of VL in HIV co-infected patients. The current evidence is, however, considered to be very uncertain, as it is from a single study, and insufficient for recommending a particular drug. No well-designed studies have been conducted. Several factors should be considered in providing secondary prophylaxis. L-AMB is already used at a single dose of 10 mg/kg as first-line treatment for immunocompetent VL patients. As the half-life of L-AMB that accumulates in the spleen, liver and bone marrow is estimated to be at least 2–3 weeks, a prolonged high-dose regimen is necessary to treat VL in HIV co-infected patients to avoid selection of resistant parasites (61). The long-term impact of use of low-dose amphotericin B is therefore unknown, and more research and trials are necessary.

Physicians should carefully assess patients at higher risk of relapse, such as those with advanced immunosuppression (e.g., CD4 cell count < 200 cells/mm³), who have an atypical clinical presentation. Similarly, care should be exercised in assessing patients with a history of treatment for multiple VL episodes before their HIV status was known.

Physicians should also consider factors that affect access to services, such as migratory patients, social and gender barriers and health-seeking behaviour, that might increase the risk that relapses fail to reach clinical attention. Many factors associated with delayed diagnosis and incomplete treatment may also lead to a higher risk of relapse, including non-compliance with treatment or lack of monitoring due to cost.

4.4 Treatment outcomes, test of cure and follow-up

Cure is considered to have occurred when no signs or symptoms of VL are seen after treatment or there is clinical improvement and a negative test of cure by parasitological assessment of a tissue aspirate. Generally, test of cure by parasitological assessment of a tissue aspirate is not performed in VL patients without HIV because of the invasive nature of the test and the associated risk of complications. HIV co-infected patients should, however, undergo parasitological examination at the end of treatment as a test of cure depending on its feasibility. Some referral centres prefer to conduct a parasitological examination at the time of diagnosis, to provide a baseline for following up patients while on treatment. Repeated tests are very uncomfortable for these patients and should be performed only in referral centres where surgical and blood transfusion services are available.

Once treatment is completed, VL cases are assessed twice to ascertain cure, treatment failure, relapse, death or loss to follow-up. HIV-negative patients are assessed initially at the end of treatment or 15 days after the start of treatment for short regimens (≤ 10 days) and at a final assessment (outcome) 6 months after the last drug was taken. For operational reasons, the same assessment principles are applicable for VL–HIV co-infected patients. At initial assessment, the following outcomes are possible:

- Initial cure: when a full course of drugs has been completed and the patient has improved clinically. The criteria for clinical improvement include no fever, regression of splenomegaly (even partial), return of appetite and/or gain in body weight.

- Treatment failure or nonresponse: when signs and symptoms persist or recur during treatment or up to initial outcome assessment.
- Death: death of anyone with a diagnosis of VL, regardless of treatment status and cause of death, within the standard post-treatment follow-up (initial assessment). All deaths should be notified, with the cause of death, which could be death due to VL, death due to HIV, death due to another disease or medical condition(s), death due to serious adverse events, death due to non-medical condition or death due to unknown cause.
- Loss to follow-up: the patient did not present for assessment after completion of treatment, or the patient status was not recorded.

At the final assessment, the following treatment outcomes are noted:

- Final cure: a patient who, after initial cure, remains free of symptoms 6 months after the end of treatment.
- Relapse: a patient who experiences recurrence of VL symptoms with parasitological confirmation at any time after initial cure.
- Death: death of anyone with a diagnosis of VL, regardless of treatment status and cause of death, within the standard post-treatment follow-up (final assessment). All deaths should be notified, with the cause of death, which could be death due to VL, death due to HIV, death due to another disease or medical condition(s), death due to serious adverse events, death due to non-medical condition and death due to unknown cause.
- Loss to follow-up: the patient did not present for assessment at 6 months, or the patient status was not recorded.

Once treatment is completed, with clinical improvement and screening and management of other comorbid conditions, secondary infections and complications and nutritional supplementation provided, a patient may be considered for discharge. Details of HIV services and the management of other opportunistic infections are provided in the WHO Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring (62).

Before discharge, all patients should be counselled appropriately about the disease, its treatment, adverse effects of medications, manifestations of possible opportunistic infections and the signs and symptoms that require consultation with health services. Patient treatment cards should contain the essential information, and a copy should be provided to patients. Most patients are referred to referral centres, and provision of information about any centres that are located closer to the patient can save resources.

WHO has signalled the lack of a marker of post-chemotherapeutic cure and called for inclusion of such a biomarker into a point-of-care RDT to improve outcome monitoring and disease control. Ideally, a “test of cure” is used to monitor treatment response. Currently, the test of cure for VL relies on the same method as used for primary diagnosis: parasitological confirmation. Various assays are in the pipeline, pending validation and further evaluation for use in HIV-infected patients. They include an antigen-based test for urine and approaches with IgG subclasses, as it has been shown that high anti-*Leishmania* IgG1 titres are associated with post-treatment relapse in VL (63,64).

As HIV co-infected patients are at higher risk of relapse, their follow-up is critical to detect recurrence of signs and symptoms and provide timely, adequate management. They should be followed up at 6-month intervals (to detect late relapses) or as per national or regional protocols, although other clinical indications may warrant more frequent follow-up, which should be implemented as field conditions allow. Special considerations should be made for migratory patients, depending on resources or the likelihood that patients will be lost to follow-up.

4.5 Treatment for relapse and rescue treatment

Relapse of VL is defined as recurrence of VL signs and symptoms with parasitological confirmation at any time after initial cure. Relapses are an important feature of VL in HIV co-infected patients, and multiple relapses are common. Several studies have identified risk factors for relapse, such as previous VL episodes, a low CD4 cell count ($< 200/\text{mm}^3$), failure to achieve clinical or parasitological cure after the first episode, no increase in CD4 cell count at follow-up and no initiation of ART or secondary prophylaxis (32,33). Many studies in Mediterranean countries suggest that a CD4 cell count $< 100 \text{ cells}/\text{mm}^3$ at the time of primary VL diagnosis is another predictive factor. A cohort study of HIV–VL co-infected patients in India showed that failure to initiate ART and concurrent TB were independent risk factors for mortality and poor treatment outcome; no risk factors associated with relapse were identified (37).

As noted above, VL and HIV target similar immune cells, exerting a synergistic detrimental effect on the cellular immune response. This reduces the therapeutic response and greatly increases the probability of relapse. These cases pose challenges to the control of VL.

A second-choice treatment for relapse is recommended when the first-choice treatment is not available or is not appropriate. This should not be confused with rescue treatment, which is given in cases of treatment failure or non-response. The approach to treating relapse cases is generally at the physician's discretion and may involve repeating the same regimen or treatment with other drugs.

The GDG recommends extending therapy (repeating the same therapy for one more course) when there is no good clinical response after the first course. Patients who receive extended therapy and who still do not show good clinical response should be considered for rescue treatment.

Once test of cure is achieved, secondary prophylaxis can be initiated (in East Africa). In a trial in Ethiopia (48), 19 patients had 29 episodes of relapse during the 12-month follow-up period. Of 29 episodes, 25 were treated with the same combination regimen, 1 was treated with L-AMB alone, and 3 were treated with sodium stibogluconate. As antimonials are more toxic in HIV patients, they must be carefully monitored for pancreatitis and cardiotoxicity. In a trial in India (49), either the same regimen was repeated or monotherapy with L-AMB (up to a total dose 40 mg/kg) was given. Some patients were treated with paromomycin plus miltefosine.

In the case of multiple relapses and/or non-responsiveness, clinicians should decide on the best options for compassionate treatment on an individual basis. They should be aware that repeated exposure to single antileishmanial drugs will inevitably generate

resistance, and patients with incurable VL may develop and transmit drug-resistant parasites. The choice of drug depends on the clinical condition of each patient, the presence of risk factors for relapse, the toxicity of the drug, the tolerability and availability of the drug, access to medical care and opportunities for follow-up.

Clinical and parasitological cure are difficult to achieve in patients who have multiple relapses, who eventually do not respond to all drugs and treatment regimens. These patients require palliative care for multiple opportunistic and terminal complications. WHO defines palliative care as the prevention and relief of suffering of adults and children and their families facing the problems associated with life-threatening illness, including physical, mental, social and spiritual suffering among patients and mental, social and spiritual suffering of family members (64).

4.6 Special situations

Pregnancy

None of the available trials enrolled pregnant or lactating women. Moreover, little information is available on the treatment of VL in pregnant HIV-negative women, limiting the therapeutic options¹. The threat of a fatal outcome of VL for the mother, the foetus and the newborn is much greater than the risk of adverse effects. When VL is untreated, spontaneous abortion, small-for-gestational-age newborns and congenital leishmaniasis have all been described. The decision to treat should be made by both the pregnant woman and her health-care provider with discussing whether the potential benefit justifies the potential risk to the mother and fetus. In general, amphotericin B deoxycholate and lipid formulations have been used. The current literature favours the use of liposomal amphotericin B for the treatment of VL in pregnant women (66,67). The combination regimen used to treat VL in HIV co-infected patients includes miltefosine, which is potentially embryotoxic and teratogenic, and this agent is contraindicated during pregnancy. Few outcomes of VL treatment during pregnancy have been reported; therefore, experts recommend that a pregnancy register be kept to record outcomes for evaluation of the fetotoxicity of the drugs in use.

Children and the elderly

None of the trials enrolled children; therefore, the applicability of combination therapy for children remains uncertain. Even in HIV-negative children, the available treatments may be toxic; furthermore, they are given for a long time and are not easy to administer. L-AMB has the highest therapeutic index and is safe to administer to all age groups. The dose of miltefosine should be 2.5 mg/kg per day for children aged 2–11 years, 50 mg/day for children aged ≥ 12 years weighing < 25 kg and 100 mg/day for those weighing 25–50 kg.

¹ Pentavalent antimonials are contraindicated in pregnancy, as they can result in spontaneous abortion, preterm deliveries and hepatic encephalopathy in the mother and vertical transmission. With paromomycin, ototoxicity in the fetus is the main concern. Insufficient data are available on the use of paromomycin in pregnant women. Pentamidine is contraindicated during the first trimester of pregnancy.

4.7 Recommendations for HIV testing, diagnosis, antiretroviral therapy and advanced disease

See the WHO Consolidated guidelines on HIV (62).

4.7.1 HIV testing and diagnosis

1. Facility-based HIV testing services
1.1 High-HIV-burden settings
HIV testing should be offered to all populations and in all services (for example, services for sexually transmitted infections, hepatitis, TB, children under 5, immunization, malnutrition, antenatal care and all services for priority populations) as an efficient, effective way to identify people with HIV.
1.2 Low-HIV-burden settings
HIV testing should be offered to: <ul style="list-style-type: none">▪ adults, adolescents or children who present in clinical settings with signs and symptoms or medical conditions that could indicate HIV infection, including TB, viral hepatitis and sexually transmitted infections;▪ HIV-exposed children and symptomatic infants and children;▪ priority populations and their partners; and▪ all pregnant women.
2. Community-based HIV testing services
2.1 High-HIV-burden settings
Community HIV testing services are recommended, with linkage to prevention, treatment and care services, in addition to routine testing in facilities, for all populations, particularly priority populations (strong recommendation, low-certainty evidence).
2.2 Low-HIV-burden settings
Community HIV testing services are recommended for priority populations, with linkage to prevention, treatment and care services, in addition to routine testing in facilities (strong recommendation, low-certainty evidence).
3. HIV self-testing
HIV self-testing should be offered (strong recommendation, moderate-certainty evidence).
Remarks
<ul style="list-style-type: none">▪ Provision of HIV self-testing service delivery and support options is desirable.▪ Communities should be engaged in developing and adapting HIV self-testing models.▪ HIV self-testing does not provide a definitive diagnosis of HIV infection. Individuals with a reactive test result must be further tested by a trained tester using the national testing algorithm.
4. HIV partner services
Provider-assisted referral should be offered to people with HIV as part of a comprehensive package of testing and care (strong recommendation, moderate-certainty evidence).

Social network approaches can be offered for HIV testing for priority populations as part of a comprehensive package of care and prevention (conditional recommendation, very-low-certainty evidence).

Good practice statement

In all settings, biological children of a parent living with HIV (or who died from HIV-associated disease) should routinely be offered HIV testing and, if found to be either infected or at high risk of infection through breastfeeding, should be linked to services for treatment or prevention and offered a broader package of voluntary provider-assisted referral.

Note: Partner services include partner notification, contact tracing, index testing and family index case testing for reaching the partners of people living with HIV. These guidelines define partner services as encompassing a range of packages and approaches, including social network approaches.

5. Strategies to make HIV testing services available

Task-sharing

Lay providers who are trained and supervised to use RDTs can conduct safe, effective HIV testing independently (strong recommendation, moderate-certainty evidence).

6. Maintaining the accuracy and reliability of HIV diagnosis

Western blotting

Western blotting and line immunoassays should not be used in national HIV testing strategies or algorithms (strong recommendation, low-certainty evidence).

HIV testing strategy and algorithm

- WHO recommends that all HIV testing algorithms achieve at least 99% positive predictive value and comprise a combination of tests with $\geq 99\%$ sensitivity and $\geq 98\%$ specificity.
- The first test in an HIV testing strategy and algorithm should be the most sensitive, followed by a second and third test with the highest specificity.
- Countries should consider changing to a three-test strategy when HIV positivity in national HIV testing service programmes falls below 5%. Thus, all people who present for HIV testing should have three consecutive reactive test results in order to receive an HIV-positive diagnosis.
- Dual HIV/syphilis RDTs could be the first tests used in HIV testing strategies and algorithms in antenatal care.
- WHO suggests use of a testing strategy for HIV diagnosis that is suitable during surveillance and routine return of the results to participants

Retesting before ART initiation

All people with newly diagnosed HIV should be retested to verify their HIV status before starting ART with the same testing strategy and algorithm as used for the original diagnosis.

Retesting among people with HIV who already know their status, including those on treatment, is not recommended, as incorrect results may be obtained if the person with HIV is on ART.

4.7.2 ART for people living with HIV

1. When to start ART
All populations
HIV testing should be offered to: <ul style="list-style-type: none">▪ Adults (strong recommendation, moderate-certainty evidence)▪ Pregnant and breastfeeding women (strong recommendation, moderate-certainty evidence)▪ Adolescents (conditional recommendation, low-certainty evidence)▪ Children aged ≤ 1–10 years living with HIV (conditional recommendation, low-certainty evidence)▪ Infants in the first year of life (strong recommendation, moderate-certainty evidence).
2. Timing of ART
2.1 Rapid initiation of ART
Rapid initiation ^a should be offered to all people living with HIV after a confirmed HIV diagnosis and clinical assessment (strong recommendation: high-certainty evidence for adults and adolescents; low-certainty evidence for children).
^a Within 7 days of HIV diagnosis; people with advanced HIV disease should be given priority for assessment and initiation.
ART initiation should be offered on the same day to people who are ready (strong recommendation: high certainty evidence for adults and adolescents; low-certainty evidence for children).
Good practice statement
ART should be initiated according to the overarching principles of people-centred care, focused and organized around the health needs, preferences and expectations of people and communities, upholding individual dignity and respect, especially for vulnerable populations, and promoting, engaging and supporting people and families in playing an active role in their own care through informed decision-making. People should be encouraged but not coerced to start ART immediately and should be supported in making an informed choice about when to start ART and the drug regimen to be used.
2.2 Timing of ART for adults, adolescents and children being treated for HIV-associated TB
ART should be started in people living with HIV as soon as possible, within 2 weeks, after initiating TB treatment, regardless of CD4 cell count. ^a
Adults and adolescents (strong recommendation, low- to moderate-certainty evidence)
Children and infants (strong recommendation, very-low-certainty evidence)
^a Except when signs and symptoms of meningitis are present.

<p>3. What to start</p>
<p>3.1 First-line ART</p>
<p>Preferred regimen</p> <p>1. Dolutegravir (DTG) in combination with an nucleoside reverse-transcriptase inhibitor (NRTI) backbone is recommended as the preferred first-line regimen for people living with HIV initiating ART.^a</p> <ul style="list-style-type: none"> ▪ Adults and adolescents (strong recommendation, moderate-certainty evidence) ▪ Infants and children with approved DTG dosing^b (conditional recommendation, low-certainty evidence) <p>^a In settings or populations in which DTG is not accessible or unsuitable because of toxicity and national levels of pretreatment HIV drug resistance are $\geq 10\%$, PI/r-based ARV drugs should be used in first-line ART. The choice of PI/r will depend on the programmatic characteristics. Alternatively, and if feasible, HIV drug resistance testing can be considered to guide the selection of first-line ART regimen (details are given in section 4.9 and table 4.3 of the main HIV guideline)</p> <p>^b As of July 2021, the United States Food and Drug Administration and the European Medicines Agency have approved DTG for infants and children older than four weeks and weighing at least 3 kg.</p>
<p>Alternative regimen (adults and adolescents)</p> <p>2. Efavirenz (EFV) at low dose (400 mg) in combination with an NRTI backbone is recommended as the alternative first-line regimens for adults and adolescents living with HIV initiating ART^a (strong recommendation, moderate-certainty evidence).</p> <p>^a In settings in which pretreatment HIV drug resistance to NNRTIs is $\geq 10\%$, EFV based ART should be avoided. EFV should also be avoided for people initiating or reinitiating first-line regimens with previous ARV drug exposure, regardless if the national prevalence of pretreatment drug resistance.</p>
<p>3.2 Second-line ART</p>
<p>Non-DTG-based regimens</p> <p>DTG in combination with an optimized nucleoside reverse-transcriptase inhibitor backbone may be recommended as a preferred second-line regimen for people living with HIV for whom non-DTG-based regimens are failing.</p> <ul style="list-style-type: none"> ▪ Adults and adolescents (conditional recommendation, moderate-certainty evidence) <p>Children with approved DTG dosing (conditional recommendation, low-certainty evidence)</p>
<p>DTG-based regimens</p> <p>Boosted protease inhibitors in combination with an optimized nucleoside reverse-transcriptase inhibitor backbone are recommended as a preferred second-line regimen for people living with HIV for whom DTG-based regimens are failing (strong recommendation, moderate-certainty evidence).</p>
<p>3.3 Third-line ART</p>
<p>National programmes should develop policies for third-line ART (conditional recommendation, low-certainty evidence).</p>
<p>Third-line regimens should include new drugs with minimal risk of cross-resistance to previously used regimens, such as integrase strand transfer inhibitor (also known as integrase inhibitor) and second-generation non-nucleoside reverse-transcriptase inhibitor and protease inhibitor (conditional recommendation, low-certainty evidence).</p>

People receiving a failing second-line regimen with no new ARV drug options should continue with a tolerated regimen (conditional recommendation, very low-certainty evidence).

Western blotting and line immunoassays should not be used in national HIV testing strategie

As for HIV-TB co-infected patients, ART should be started as soon as possible, within 2 weeks, after initiation of VL treatment, regardless of the CD4 cell count. Starting treatment for both HIV and VL may, however, precipitate immune reconstitution syndrome (IRIS), increasing morbidity and mortality. A 2-week period between starting VL and starting ART will allow immune recovery and prevent IRIS.

Further details of the choice of ART, monitoring and management of advanced HIV disease are available in WHO guidelines (62).

4.8 Management of co-morbid conditions

Various coinfections, co-morbidities and other concomitant health conditions are common among people living with HIV and have implications for their treatment and care, including the timing and choice of antiretroviral drug. Cases of VL and other clinical forms of leishmaniasis have been described in association with immune reconstitution inflammatory syndrome in HIV patients with latent *Leishmania* infection and in patients already treated for VL who have started ART (68).

4.8.1 Tuberculosis

1. Systematic screening for TB among people living with HIV

People living with HIV should be screened for TB disease systematically, at each visit to a health facility (strong recommendation, very-low-certainty evidence).

2. Tools for screening for TB among people living with HIV

Adults and adolescents living with HIV should be screened for TB disease with the WHO-recommended four-symptom screen, and those who report any one of the symptoms of current cough, fever, weight loss or night sweats should be evaluated for TB and other diseases (strong recommendation, moderate-certainty evidence).

In adults and adolescents living with HIV, C-reactive protein with a cut-off of > 5 mg/L may be used to screen for TB disease (conditional recommendation, low-certainty evidence for test accuracy).

In adults and adolescents living with HIV, chest X-ray may be used to screen for TB disease (conditional recommendation, moderate-certainty evidence for test accuracy).

In individuals aged ≥ 15 years in populations in which TB screening is recommended, computer-aided software programmes may be used in place of human readers for interpreting digital chest X-rays for screening and triage for TB disease (conditional recommendation, low-certainty evidence).

In adults and adolescents living with HIV, WHO-recommended molecular RDTs may be used to screen for TB disease (conditional recommendation, moderate-certainty evidence for test accuracy).

Adult and adolescent inpatients with HIV in medical wards in which the prevalence of TB is > 10% should be tested systematically for TB disease with a WHO-recommended molecular RDT (strong recommendation, moderate-certainty evidence for test accuracy).

4.8.2 Management of other co-morbidities

For recommendations on prevention of opportunistic infections in advanced HIV disease, cryptococcal meningitis and other conditions, clinicians may refer to the WHO Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: Recommendations for a public health approach (62). Other coinfections should be treated with appropriate regimens as per national protocols. Attention must be paid to monitoring drug–drug interactions when treating concomitant opportunistic infections.

4.9 Social determinants

Leishmaniasis is a disease of poverty and affects the most marginalized communities. The relation between leishmaniasis and poverty is a vicious cycle: while poverty increases the risk for leishmaniasis and aggravates disease progression, leishmaniasis itself leads to further impoverishment of families due to catastrophic health expenditure, income loss and death of wage earners. As leishmaniasis is an NTD, the significance of *Leishmania* infection in HIV patients is recognized late. The poorest segments of the population, such as migrant daily labourers, are the most severely affected.

4.9.1 Poverty

People living with HIV in VL-endemic areas are at highest risk of acquiring opportunistic VL due to both their decreased immunity and ecological factors associated with poverty that increase the risk of infection, particularly proliferation of vectors and increased human–vector contact. In areas of anthroponotic transmission, poor housing and sanitation, such as the presence of organic matter, damp earthen floors and cracked mud walls, encourage proliferation of vectors, prolong their survival and provide them with resting places during the day.

Poverty also worsens clinical outcomes, as malnutrition and anaemia increase the severity of VL. Long hospital stays and frequent relapses in VL patients result in income loss, with a severe economic impact on families. In Ethiopia, many VL patients are migratory, which further compounds their misery due to delays in diagnosis and treatment and then loss to follow-up.

4.9.2 Gender

VL is reported more frequently in HIV-negative men than in HIV-negative women. Corresponding data on VL–HIV co-infected patients are not available but are expected to show the same trend. Evidence from the Indian subcontinent suggests that biological differences between men and women play a more critical role in the pathogenesis of VL than previously assumed, as the observed male predominance in co-infected cases cannot be explained by socio-cultural factors alone (69). A study on barriers to access in Sudan found a gender bias in accessing care, linked to financial burdens and the general cultural context (70).

4.9.3 Access to health care

A substantial number of VL cases are either not diagnosed or are diagnosed only after a long delay. Surveillance reports to WHO indicate that every third VL–HIV- co-infected patient is unaware of his or her HIV status. Weak health systems are one of the major challenges in the control of leishmaniasis, and lack of coordination between HIV/AIDS and vector-borne/NTD programmes compound the difficulty of screening, detecting and managing VL–HIV co-infected patients. In many settings, the first point of contact is either a health provider outside the formal health system or a private provider, who may not be adequately equipped to manage the syndrome. Low immunity, malnutrition, lack of awareness about HIV, opportunistic infections and delays in seeking care make these patients difficult to treat, further compromising the limited capacities of specialized health centres or hospitals. In several countries, this complex vicious web means that effective management of VL in HIV-infected people is confined to a very few centres.

4.9.3 Sociocultural barriers

Leishmaniasis typically occurs in clusters in marginalized communities. Several published and unpublished reports have shown poor awareness about VL in these communities. Countries should prepare context-specific health messages to improve community participation and thereby maximize the benefits of control strategies. Good community dialogue and display of patient charters and policies for protection of human rights can improve health-seeking behaviour in endemic communities. Some high-VL burden countries, such as India, have adopted incentive approaches, in the form of wage loss compensation, to encourage early reporting and treatment-seeking (21). Such incentives, with respect for the human rights of HIV patients, can be powerful means for reducing barriers to access to medical services and care (71).

5. Operational considerations

5.1 Access to quality-assured medicines

Diagnostics and medicines for VL must be continuously available, affordable and accessible to health systems and to all patients. A functioning supply chain is essential, and all the factors that influence it must be managed (72). Manufacturing capacity determines availability, and most leishmanial medicines are produced by only one or a few producers. Problems of quality, low production capacity and lack of an adequate global forecast regularly result in stock ruptures in endemic countries. Cessation of production is a threat if the supplier base is not expanded, given the small market and the decreasing global case load. Forecasting and quantification of the necessary supplies is based mainly on previous consumption; however, the VL case load can vary considerably from year to year due to inconsistent surveillance, outbreaks or decreases due to ecological conditions.

For manufacturers, the long lead time means that they must complete a full batch production line (minimal order requirement), and national programmes and clinicians might have difficulty in obtaining small quantities of the medicines ad hoc. Suboptimal stock planning and management or complex procurement procedures also result in shortages at health facilities. Supply chains are further strained by lack of registration and importation requirements in endemic countries. Functional drug forecasting and adequate monitoring systems for supply chains and logistics are essential at national level to ensure an uninterrupted drug supply and to minimize delays in importing medicines. The same challenges apply to the supply of diagnostic tools, as the market is relatively small and not profitable. Moreover, diagnostic kits of uncertified quality circulate in endemic regions. Even when medicines to treat VL are available, drugs for the management of cutaneous and mucocutaneous forms of the disease, which might also present in immunocompromised patients and in high-burden countries, are generally not readily available.

Affordability is another crucial issue. The price of these relatively expensive medicines has fallen thanks to negotiations by WHO and other partners; however, there is no drug donation programme for leishmaniasis, except for L-AMB (AmBisome®) through Gilead Sciences for certain low- and middle-income high-VL burden countries in East Africa and South Asia.

After procurement has been negotiated, medicines may still not have been registered in the countries in which they are to be used. If medicines are not registered, special permission for their import is required. Registration is often lacking in countries with very few cases, and medical practitioners in those countries experience great difficulty in obtaining the small quantities of medicines they require.

Access to good-quality antileishmanial medicines has improved in the past decade. WHO supports establishment of an emergency rotating buffer stock to mitigate shortages and promotes pooled procurement through regional approaches. Although all VL medicines are on the WHO Model List of Essential Medicines (73), only a few are either prequalified by WHO or approved by a stringent regulatory authority. Still, manufacturers should engage in procedures to ease procurement in the future (e.g., proper registration, request for pre-qualification), and purchasers could join forces to require that manufacturers exercise stringent quality assurance (i.e., the WHO Prequalification Programme). The cost of registration is an additional disincentive in many countries. In 2021, a generic liposomal amphotericin B was registered by a stringent regulatory authority (74). Overall monitoring of access to leishmanial medicines must be strengthened, with account for pricing, registration and global needs.

5.2 Information on leishmanial medicines

L-AMB was first registered for the treatment of VL in 1996 and miltefosine in 2002. Both drugs are on the WHO Model List of Essential Medicines (73) as antiparasitic drugs. Several lipid formulations of amphotericin B (L-AMB, amphotericin B lipid complex and amphotericin B colloidal dispersion) have been used in the treatment of VL (75), with efficacy similar to that of amphotericin B deoxycholate but which are significantly less toxic. Most clinical trials have been conducted with a reference L-AMB formulation; all other lipid formulations should be evaluated for toxicity, bioequivalence and efficacy before they are used clinically. The information below is a summary of data current at the time of preparation of this document; the latest update should be consulted for further details. (Adverse events of all antileishmanial medicines are summarized in **Annex 3**.)

5.2.1 Liposomal amphotericin B (76)

▪ Administration

- L-AMB is significantly less toxic than amphotericin B deoxycholate; however, adverse events may still occur.
- Like any amphotericin B-containing product, the drug should be administered by medically trained personnel.
- A test dose of 1 mg given by infusion is recommended, followed by a full dose over 2 h. The infusion may be administered over 2 h, if necessary, to prevent or minimize adverse effects.
- Adequate supervision of the infusion rate and monitoring of the patient's status are strongly recommended; proper adjustments, such as reducing the rate or temporary stops while keeping the line open with dextrose solution can be made as required. Physicians should refer to product labels in preparing solutions.
- Serum creatinine levels and, if possible, serum potassium levels should be monitored (once or twice weekly) throughout treatment and adjunctive therapy (potassium and magnesium supplementation) adapted according to the results.
- If renal function deteriorates, the dose should be halved for a few days.
- Renal dysfunction should be checked in newborns if the drug was administered during the last month of pregnancy.
- Breast-feeding should be avoided unless it is vital.

- **Contraindications**
 - Contraindicated in patients who have demonstrated or known hypersensitivity to amphotericin B deoxycholate
- **Warning**
 - Anaphylaxis has been reported after administration of amphotericin B and amphotericin B-containing drugs. In case of a severe anaphylactic reaction, the infusion should be discontinued immediately, and the patient should not receive further infusions.
- **Adverse events**
 - Infusion-related
 - local reaction and pain and thrombophlebitis at injection site, fever (> 1.0 °C increase), chills/rigor, vasodilation, hyperventilation, tachycardia, hypotension
 - Body as a whole:
 - Abdominal pain
 - Asthenia
 - Back pain
 - Blood product transfusion reaction
 - Chills
 - Infection
 - Pain
 - Sepsis
 - Cardiovascular system
 - Chest pain
 - Hypertension
 - Hypotension
 - Tachycardia
 - Digestive system
 - Diarrhoea
 - Gastrointestinal haemorrhage
 - Nausea
 - Vomiting
 - Metabolic and nutritional disorders
 - Increased alkaline phosphatase activity
 - Increased alanine transaminase activity
 - Increased aspartate transaminase activity
 - Bilirubinaemia
 - Increased blood urea nitrogen
 - Increased creatinine
 - Oedema
 - Hyperglycaemia
 - Hyponatraemia
 - Hypervolaemia

- Hypocalcaemia
- Hypokalaemia
- Hypomagnesaemia
- Peripheral oedema
- Nervous system
 - Anxiety
 - Confusion
 - Headache
 - Insomnia
- Respiratory system
 - Increased cough
 - Dyspnoea
 - Epistaxis
 - Hypoxia
 - Lung disorder
 - Pleural effusion
 - Rhinitis
- Skin and appendages
 - Pruritus
 - Rash
 - Sweating
- Urogenital system
 - Haematuria

WHO has issued guidance on the diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children, which includes a minimum package for preventing, monitoring and managing amphotericin B toxicity (77).

5.2.2 Miltefosine (hexadecylphosphocholine)

- **Administration**
 - Oral route (Administer with food to alleviate gastrointestinal adverse reactions.)
 - Dosage depends on body weight.
 - Store at 20–25 °C; excursions permitted to 15–30 °C
 - Protect from moisture.
- **Contraindications**
 - Pregnancy: Miltefosine may harm the fetus and is thus contraindicated in pregnant women.
 - Obtain a urine or serum pregnancy test before giving miltefosine to women of reproductive age.

- Miltefosine should not be prescribed to women of child-bearing potential for whom adequate contraception cannot be assured for the duration of treatment and for 5 months afterwards
- Sjögren-Larsson syndrome
- Hypersensitivity
- **Adverse effects (78)**
 - The most common side-effects of miltefosine are nausea, vomiting and diarrhoea; others include abdominal pain, decreased appetite, dizziness, headache, sleepiness, skin itching and abnormalities in liver or kidney tests.
 - Warnings and caution:
 - Embryo-fetal toxicity: Miltefosine may harm the fetus. Embryo-fetal toxicity, including death and teratogenicity, was observed in animal models at doses below the maximum recommended human dose.
 - It is contraindicated for pregnant women. Women of reproductive age must be tested for pregnancy, and effective contraception must be ensured during therapy and for 5 months after completion of therapy. In lactating mothers, either the drug or nursing should be discontinued after a risk–benefit assessment. Breastfeeding should be avoided for 5 months after treatment.
 - Ophthalmic effects: In preclinical studies, miltefosine showed reversible dose- and duration-dependent retinal atrophy in rats due to effects on retinal epithelial cells. Similar changes were not seen in dogs. The WHO global Individual Case Safety Reports database, Vigibase, however, lists 25 reports of ocular adverse events, with 5 in Bangladesh, 5 in France, 1 in Germany and 15 in India. The ages of the cases ranged from 12 to 70 years (median, 33 years) and the time to onset of 18 events ranged from same day to 110 days (median, 45 days). Causality was assessed in 18 cases and was considered certain in 6 cases, possible in 3 and unlikely in 9. In 14 of the 18 cases of ocular adverse events, the drug was withdrawn or the dose reduced; the symptoms resolved in 9 cases, 8 did not recover and 1 recovered with sequelae (uveitis). Physicians should be capable of proper risk communication and management, so that patients who receive miltefosine are counselled and undergo regular eye examination during and after treatment, as the drug has a long half-life.
 - Reproductive effects: Miltefosine impaired fertility in male and female rats and dogs. Effects on human fertility have yet to be confirmed in formal studies. Nevertheless, at the time of prescription, patients should be given proper advice, informed of the findings in animals and told the potential for impaired fertility in humans has not been adequately evaluated. Scrotal pain, decreased ejaculate volume and absent ejaculation have been reported by male patients.
 - Renal effects: Increased serum creatinine was noted in clinical trials of miltefosine for leishmaniasis treatment. Regular monitoring of renal function is recommended.
 - Hepatic effects: Increased alanine and aspartate transaminases activity and bilirubin were noted in clinical trials of miltefosine in the treatment of VL. Liver transaminases and bilirubin should be monitored.

- Gastrointestinal effects: Vomiting and/or diarrhoea are common during miltefosine administration and may result in volume depletion. Encourage fluid intake to avoid volume depletion.
- Miltefosine causes thrombocytopenia. Platelet counts should be monitored during therapy.
- Absorption of oral contraceptives: Vomiting and/or diarrhoea during miltefosine therapy may affect the absorption of oral contraceptives and therefore compromise their efficacy. Advise women to use additional non-hormonal or alternative method(s) of effective contraception.
- Stevens–Johnson syndrome: Discontinue miltefosine if an exfoliative or bullous rash is noted during therapy

5.2.3 Pentamidine

Pentamidine is supplied in vials containing 300 mg pentamidine isethionate powder, to be reconstituted with 10 mL of water for injection)

▪ Administration

- Pentamidine is administered intramuscularly (in the gluteal region), with strict antiseptic technique and on alternate sides (left–right) each day.
- Patients should be given a source of sugar (e.g., a sweet drink, water with sugar and/or biscuits, bananas, mangos) before injection to prevent hypoglycaemia.
- Patients should lie down for at least 1 h after injection to prevent symptomatic hypotension.
- Vital signs should be checked again 1 h after injection and monitored if the patient is unwell.

▪ Contraindications

- Pentamidine is contraindicated during the first trimester of pregnancy and in patients with known hypersensitivity to pentamidine.

▪ Adverse effects

- Pentamidine is generally well tolerated, although minor adverse reactions are common. Very common ($\geq 1/10$) and common ($\geq 1/100$ to $< 1/10$) undesirable effects are mentioned below. Other uncommon effects are listed in Annex 3.
- Possible immediate reactions include hypotension in about 10% of patients, with dizziness and sometimes collapse and shock; after intravenous injection, hypotension is as frequent as 75% (particularly if infused over < 1 h). Occasional adverse reactions are nausea or vomiting and pain and swelling at the injection site. Sterile abscesses or necrosis may occur at the site of intramuscular injection. Systemic reactions reported include azotaemia due to nephrotoxicity, leukopenia, raised activity of liver function enzymes, hypoglycaemia and hyperglycaemia. Persistent diabetes is a rare but feared event. Severe adverse events such as anaphylaxis and acute pancreatitis are extremely rare.

5.3 Drug interactions

5.3.1 Liposomal amphotericin B

No formal clinical studies have been conducted with the reference L-AMB; however, the following drugs are known to interact with amphotericin B.

Antineoplastic agents: Concurrent use of antineoplastic agents may enhance the potential for renal toxicity, bronchospasm and hypotension. They should be given with caution and with adequate monitoring.

Corticosteroids, corticotropin and other hypokalaemic drugs: Concurrent use of corticosteroids, corticotropin and digitalis may potentiate hypokalaemia and digitalis toxicity, which could predispose patients to cardiac dysfunction. Serum potassium levels and cardiac function should be closely monitored.

Azole group of antifungals (e.g., ketoconazole, miconazole, clotrimazole, fluconazole): Studies of the combination of amphotericin B and imidazoles in experimental animals and in vitro suggest that imidazoles may induce fungal resistance to amphotericin B. Combination therapy should be administered with caution, especially to immunocompromised patients.

Flucytosine: Concurrent use of flucytosine may increase its toxicity by increasing its cellular uptake and/or impairing its renal excretion.

Leukocyte transfusions: Acute pulmonary toxicity has been reported in patients receiving intravenous amphotericin B and leukocyte transfusions simultaneously.

Skeletal muscle relaxants: Amphotericin B-induced hypokalaemia may enhance the curariform effect of skeletal muscle relaxants (e.g., tubocurarine) due to hypokalaemia. When the two are administered concomitantly, serum potassium levels should be closely monitored.

Other nephrotoxic medications: Concurrent use of amphotericin B and other nephrotoxic medications may enhance potential drug-induced renal toxicity. Intensive monitoring of renal function is recommended in patients who require any combination of nephrotoxic medications.

5.3.2 Miltefosine

Studies of metabolism in experimental animals and in vitro have shown that miltefosine does not markedly induce or inhibit the activity of human cytochrome P450 enzymes. Its potential interaction with drug transporters has not been evaluated.

5.3.3 Liposomal amphotericin B, miltefosine and ART

Amphotericin B is neither a substrate nor an inhibitor of the cytochrome P450 enzyme system. Miltefosine also does not inhibit human cytochrome P450 enzymes in vitro or induce cytochrome 3A activity in rats (79). Hence, the pharmacokinetics of these drugs and other antiretrovirals are not expected to interact. Product information labels (76) do not indicate a risk of interaction with ARTs however, additive effects of individual drugs on organs may be observed.

The pharmacokinetics of antiretrovirals were measured in a trial of combination therapy (L-AMB plus miltefosine) in patients co-infected with HIV and VL in Ethiopia

(80). No differences were observed in exposure to efavirenz and nevirapine during VL treatment and follow-up, indicating that antileishmanial drugs have no significant effect. Patients treated with efavirenz, however, had significantly lower exposure to miltefosine at the end of the first cycle of therapy (day 28), which could imply an effect of efavirenz on miltefosine accumulation, although the authors acknowledged the small number of subjects. It was hypothesized that efavirenz competes with miltefosine for binding albumin or increases intracellular accumulation of miltefosine by up-regulating P-glycoprotein. Exposure to amphotericin B on day 1 was similar in patients taking and not taking ART, and no interactions were expected between the antiretroviral drugs administered and amphotericin B. However, study showed low exposure of miltefosine in HIV-VL co-infected patients compared with non-HIV adult VL patients in East Africa. This suggests that miltefosine dosing in adult population should be adjusted by weight to achieve equivalent exposure similar to non-HIV-infected East African adult VL patients.

Similarly, the antileishmanial activity of two protease inhibitors (darunavir and atazanavir) and four non-nucleoside reverse transcriptase inhibitors (tenofovir, efavirenz, nevirapine and delavirdine) was evaluated in VL patients co-infected with HIV due to *L. infantum* (81). Only two non-nucleoside reverse transcriptase inhibitors were active against *L. infantum*. Efavirenz showed the best antileishmanial activity on promastigotes cells, followed by delavirdine mesylate. Nevirapine, tenofovir, atazanavir and darunavir were not active at the concentrations tested. Efavirenz had high antileishmanial activity on intramacrophage amastigotes, and, when used in combination with miltefosine, it improved antileishmanial activity on promastigotes and intracellular amastigotes. Nucleoside reverse transcriptase inhibitors are eliminated by the kidneys. Although there may be no clinically relevant drug–drug interaction with L-AMB, both tenofovir and amphotericin B can be nephrotoxic. Similarly, the combination of zidovudine and amphotericin B may result in additive myelosuppression (anaemia, neutropenia). Close therapeutic monitoring of haematological function is recommended.¹ ARTs should be selected according to national HIV prevention, testing, treatment and monitoring guidelines, and the adverse effects of drugs should be adequately addressed.

5.3.4 Drugs for TB and other comorbid conditions

No data were available on serious drug–drug interactions between antileishmanial and antitubercular medicines. WHO TB treatment guidelines (82), however, include considerations for managing concomitant TB and ART for the prevention of HIV-associated TB, drug-susceptible TB and multidrug-resistant TB. The main contraindicated drug combinations are rifampicin with a protease inhibitor or nevirapine. When people with both HIV and TB receive a boosted protease inhibitor, rifampicin might have to be replaced by rifabutin at a daily dose of 150 mg. If rifabutin is not available, lopinavir/ritonavir can be used for the duration of TB treatment by doubling the standard dose or increasing the boosting dose of ritonavir. When rifampicin is used with dolutegravir, the dose should be raised to 50 mg twice daily in the absence of resistance to integrase strand transfer inhibitor (otherwise this combination should be avoided). In children, twice daily dosing with dolutegravir or raltegravir should be continued for an additional 2 weeks after use of rifampicin has ended. If use of raltegravir is considered (only under special circumstances), doubling of the dosage to 800 mg twice daily is indicated, as recent evidence has shown that standard doses of raltegravir with rifampicin do not meet non-inferiority criteria (83). Rifampicin reduces exposure to tenofovir alafenamide and tenofovir, but recent data showed that intracellular tenofovir diphosphate (active entity) levels were still four times higher than those obtained with tenofovir disoproxil fumarate, even without rifampicin (84),

¹ Retrovir (Zidovudine) Package Insert. Research Triangle Park, NC: Glaxo SmithKline; 2013

suggesting that tenofovir alafenamide at 25 mg once daily with rifampicin may be acceptable when tenofovir alafenamide is considered for use in first-line ART (only under special circumstances).

Currently, there are no data on virological outcomes with either tenofovir alafenamide at 25 mg once or twice daily with rifampicin. In people with HIV and extensively drug-resistant or multidrug-resistant TB who are receiving drugs such as bedaquiline and delamanid, caution should be exercised in co-administering protease inhibitors because of the risk of QT-interval prolongation. Further, as bedaquiline is metabolized primarily by CYP3A4, concomitant use with efavirenz may reduce bedaquiline drug concentrations, resulting in potential loss of activity; therefore, this association should be avoided. Treatment of latent TB infection with isoniazid (300 mg) and rifapentine (600 mg) daily for 4 weeks or isoniazid and rifapentine once weekly for 3 months is not recommended for people receiving protease inhibitors or nevirapine because of the risk of HIV virological failure. There is no evidence to indicate that a change of dosage of rifapentine, dolutegravir or raltegravir is necessary for patients on these regimens. As for rifampicin, the dosages of dolutegravir, raltegravir and tenofovir alafenamide should be doubled with isoniazid (300 mg) and rifapentine (600 mg) daily for 4 weeks, whereas the standard dose can be used with isoniazid and rifapentine once weekly for 3 months. Details of other comorbid conditions, drug–drug interactions and current WHO guidance on management of HIV-associated TB can be found in the Consolidated guidelines (62).

5.4 Pharmacovigilance

Pharmacovigilance systems are usually designed to monitor side-effects, adverse reactions and drug interactions; however, their scope should be broadened to address the growing problem of substandard and counterfeit medicines and to monitor the development of drug resistance. Substandard medicines have led to avoidable deaths and iatrogenic side-effects. Routine monitoring of resistance should be included in the early stages of research and development (85).

A distinction must be made between adverse events and adverse drug reactions when determining the severity of adverse events and their relation to exposure to a product. Once an adverse event has been detected, its maximum severity should be established and graded according to international standards. It should be determined whether the event was caused by the product or by other medicines administered concomitantly or was due to another illness. Serious adverse events should be investigated immediately and reported rapidly. Quality assurance and regulatory mechanisms are critically important.

Pharmacovigilance systems in VL-endemic countries require improvement, with integration of a multi-disease approach. Issues of toxicity, adherence, treatment response and resistance have affected treatment programmes, and programmes for reporting these events should be strengthened. Multidisciplinary national pharmacovigilance centres should be established and their capacity strengthened for regular analysis of data on safety to identify and review signals, generate hypotheses and ensure regular reporting and feedback. Pharmaco-epidemiological methods should include post-licensing clinical trials to assess the effectiveness and safety of medicines, case–control studies and active population-based evaluation of marketed products authorized for use.

The current WHO Drug Monitoring System has an extensive network, with 170 member countries. All countries should establish a national pharmacovigilance centre to record reported adverse drug reactions in order for them to be included in VigiBase, the WHO global database of individual case safety reports. VigiBase has been used to monitor antileishmanial medicines for adverse drug reactions, including those with serious outcomes.

5.5 Indicators for monitoring and evaluation

The main objectives of monitoring and evaluating a leishmaniasis control programme are to:

- collect, process, analyse and report or disseminate information relevant to leishmaniasis;
- verify that activities have been implemented as planned to ensure accountability and address problems in a timely manner;
- provide feedback to relevant authorities to improve future planning; and
- document whether the planned strategies have achieved the expected outcomes.

Monitoring involves routine tracking of programme performance by record-keeping, reporting, surveillance and periodic surveys. The objectives are to verify progress or the status of implementation, ensure accountability, detect problems and constraints, promote evidence-based planning and provide timely feedback so that adjustments can be made as necessary. Monitoring indicators include input, process, output and outcome indicators (Table 1).

Evaluation consists of periodic assessment of changes in targeted outcomes or results that can be attributed to a programme. The objectives are to assess the impact and effectiveness of a control intervention after a certain time. A monitoring and evaluation framework can provide reliable information at local, national or international level. Information on HIV should be integrated into the VL programme data management system and vice versa.

Table 1. Indicators for monitoring VL–HIV coinfection

Type of indicator	Recommended indicators	Source and interval or frequency
Output	Number or proportion of VL cases screened for HIV Number or proportion of HIV-positive VL cases treated Number of relapse cases within 6, 12 or 24 months Number of patients started on secondary prophylaxis	Annual programme reports
Outcome	Proportion of HIV-positive VL cases cured: initial and final cure rates Proportion of HIV-positive VL cases alive at 6 and 12 months	Annual programme reports
Impact	Case fatality rate	Annual programme reports

Surveillance should be strengthened to determine and record cause-specific mortality as part of overall mortality due to VL. The NTD road map 2021–2030 (7) has set an ambitious target of global elimination of VL as a public health problem (defined as < 1% case fatality rate due to primary VL) by 2030. This new target should stimulate national programmes to strengthen leishmaniasis surveillance and extend it to include HIV–VL variables and indicators.

5.5.1 Prevention of antimicrobial resistance

Factors that encourage development of drug resistance include not using the most effective regimen, inadequate dose or duration of treatment, irregular treatment, use of substandard medicines, poor surveillance of treatment outcomes, the lack of biomarkers for parasite resistance and lack of national plans for drug resistance surveillance.

A study in South Asia of the factors that contribute to low treatment efficacy of antimonials for VL in HIV-negative patients showed that, of 312 patients, 73% consulted a local healer and only 27% went to a qualified medical practitioner (86). With regard to treatment, 58% took regular treatment and 42% irregular treatment, with incomplete treatment in almost 50% of patients, such that, in the end, only 26% of patients had received an adequate dose and duration of treatment. This was considered to have played an important role in the development of resistance to antimonials.

Although multidrug therapy has the potential advantage of reducing the probability of selection of drug-resistant parasites, thereby prolonging the life of available medicines, the observation of decreased cure rates could be the first sign of the development of drug resistance. WHO recommends counselling and follow-up of all VL cases and routine monitoring of cure rates. WHO will regularly evaluate treatment efficacy and clinical outcomes to monitor potential drug resistance, as appropriate. Laboratory surveillance for drug resistance should be integrated into the national plan for antimicrobial resistance rather than in a vertical approach. In addition, monitoring of access to leishmanial medicines should be strengthened, with pricing, registration, drug policies and quality assurance at all levels. Uncontrolled access to medicines (e.g., over the counter) could lead to misuse, suboptimal treatment and in the long term, drug resistance.

5.6 National guidelines

National leishmaniasis control programmes should adopt recommendations on VL in relevant policy and guidance. Consultations with stakeholders, including affected patients and communities, will increase uptake and dissemination of guidelines. Every measure should be taken to extend access to treatment and services for VL patients. Delays in diagnosis and lack of proper management (e.g., timely treatment of VL episodes, detection and management of other opportunistic infections, nutritional support, access to ART and follow-up) compound the poor outcomes of these patients. Secondary and tertiary health care facilities should be equipped with the necessary diagnostics and essential medicines and build adequate human resource capacity for managing such patients. HIV–VL management requires a comprehensive, multi-pronged approach among national programmes and joint guidelines for VL and HIV programmes.

5.7 Training material and manuals

Data reported to WHO indicate that, globally, almost every third VL patient is unaware of their HIV status. In Bihar and Jharkhand, two highly VL-endemic states in India, more than 90% of VL patients detected in 2020 knew their HIV status. Health authorities, decision-makers, health staff, community health workers, community leaders, populations at risk and patients should be trained in aspects of VL–HIV coinfection with customized training material.

5.8 Coordination among programmes for HIV, TB and leishmaniasis for neglected tropical disease and vector-borne disease control and national pharmacovigilance

Wherever possible, synergy and coordination should be established between leishmaniasis, NTD, vector-borne disease control and national HIV prevention and control programmes in countries and areas where the conditions overlap. Coordination and synergy are vital to tackle VL–HIV coinfection. Efficient links and integrated programme management should be established at all levels, with continuing work to control both conditions.

The aim of optimal management of VL–HIV coinfection is not only to cure VL but also to achieve an undetectable viral load by early initiation of ART. Uptake of ART in routine programme conditions has progressed, but access remains a challenge in many under-resourced VL-endemic countries. Few health facilities offer services for both diseases, and patients are often referred to specialized centres. VL episodes may impair the response of VL patients to ART, while ART and increased CD4 count positively affect VL treatment outcomes, such as relapse. Therefore, coordination of the two programmes can prolong patient survival and improve their quality of life.

Suggested areas for coordination are screening strategies in high-prevalence areas, increasing awareness and clinical suspicion of VL in health-care workers, follow-up of patients, social benefits or incentives for VL relapse patients, cross-reporting, identifying bottlenecks in integration of VL and HIV programmes and addressing them as required.

As VL–HIV patients act as reservoirs of VL infection, use of insecticide-treated bednets and other personal protection by HIV-positive patients with VL or PKDL could decrease the likelihood that sandflies will feed on infected individuals. Other vector control methods should be implemented as per national protocols through integrated vector management, wherever applicable.

6. Research priorities

VL in HIV co-infected patients is a growing challenge for VL control and elimination. Late diagnosis of leishmaniasis in people living with HIV is difficult, and awareness of this coinfection and its impact must be increased among health-care professionals in East Africa, South-East Asia and beyond. Operational research to develop screening strategies in high-HIV-VL prevalence areas and integration of relevant components of VL and HIV programmes should be explored (87). The disease burden should be estimated in countries and areas where the extent of the coinfection problem is not known.

Serological tests for diagnosis of VL in HIV co-infected patients have poor sensitivity, and cross-reactions are possible. Tests that can be used for accurate confirmation of cure and for monitoring relapses are urgently needed, including improved antigen detection tests and useful (bio)markers to link clinical outcome, relapse and parasitological status as well as to assess parasite resistance to medicines. A better criterion for cure should be established. Long-term follow-up of treated patients will help to understand the development of PKDL. Studies should be performed to define predictors of good treatment outcome (e.g., HIV viral load, nutritional status, diet modification including protein restriction and fatty acid intake, gender).

The importance of other co-morbid conditions in VL-HIV patients, including TB, should be studied further. In a trial on VL-HIV in India, 19% of patients (28/150) were infected with pulmonary TB at baseline (49). The importance of TB as a co-morbid condition in VL-HIV co-infected patients indicates that TB should be excluded in studies of VL-HIV patients. Immune-reconstitution inflammatory syndrome, which appears to be underreported in VL-HIV coinfection, should be addressed in detailed prospective studies to further characterize its clinical features, incidence and, particularly, skin manifestations (88).

Better understanding of the epidemiology and progression of VL in patients with HIV with improved proxy biomarkers will be vital for ensuring earlier detection and better outcomes. The susceptibility of *L. donovani* in South-East Asia to low-dose L-AMB may represent a unique opportunity for primary prophylaxis in asymptomatic *Leishmania*-HIV co-infected patients, potentially reducing progression to symptomatic disease, and should be further explored. Recent evidence shows that, if specific immunity to leishmaniasis is maintained and the HIV viral load remains undetectable, patients are likely to remain asymptomatic for VL (56). Basic research to understand the immunological interaction of the two infections and the immune-modulatory effects of drugs could ultimately improve the management of coinfection.

Given the very low certainty of the currently available evidence, further clinical trials of the use of combination therapy in VL-HIV coinfection remains a necessity. Well-designed studies are urgently needed to strengthen the evidence for this treatment and to improve outcomes in patients in field conditions in East Africa and South-East Asia. Ease

of use remains important, and drug discovery and development of more user-friendly and oral medicines must continue. None of the current antileishmanial medicines is free of significant toxicity. The safety of regimens is one of the most important areas of research, as little information is currently available from traditional pharmacovigilance approaches. Cohort event monitoring may provide reliable, definitive answers on safety. No data on the safety of miltefosine therapy beyond 28 days is available, and studies on the safety of long-term miltefosine treatment is necessary, as VL patients may require extended therapy (repetition of the same regimen for one more cycle) or more cycles in cases of multiple relapses.

Other interventions that could improve the efficacy of antileishmanial treatment are necessary to reduce the number of relapses, prevent resistance and reduce toxicity. Suggested lines of enquiry include studies on early use of ART, use of combined antileishmanial therapies in various scenarios and immune-based co-therapies. To date, there is no clear evidence on the interaction of antiretroviral drugs and antileishmanial medications.

Further evidence is required to establish the criteria for use of a drug for secondary prophylaxis. Secondary prophylaxis with a drug different from that used to treat the primary VL attack is generally recommended to minimize the risk of resistance, with clear starting and stopping criteria. This is required, particularly in South-East Asia, where evidence for secondary prophylaxis is limited. Research on simpler therapeutic and prophylactic regimens for VL–HIV co-infected patients is also necessary. Social determinants of VL in HIV patients remain poorly explored, and more studies are needed.

Given the focal distribution of VL–HIV coinfection and difficulty in accessing often hard-to-reach populations, research is inherently difficult to perform. Operational and implementation research on the best models for systematic screening for VL among HIV patients and vice versa will facilitate both research and implementation of programmes. Scientific research to better understand the impact of VL–HIV coinfection, gains in programme efficiency and reducing mortality would further inform policy-makers. Research to increase understanding of the perspectives of affected communities in order to reduce delay in accessing health-care services remains important.

7. Publication, dissemination & evaluation

7.1 Publication and dissemination

These guidelines will be accessible on the WHO website with links to related websites, and they will be translated into the official United Nations languages pertinent to VL and HIV. Hard copies will be distributed through national leishmaniasis control programmes to health staff working on case management. The WHO regional offices will ensure dissemination to WHO country offices and ministries of health and to key international and national organizations and WHO collaborating centres. Additional tools will be developed to support country implementation. Incorporation of VL into national treatment protocols and field implementation will be monitored through existing support activities and through the annual WHO coordination meeting on VL.

7.2 Evaluation and updating

Use of these guidelines will be evaluated to determine the extent of uptake of the recommendations into national policies and programmes. The results will be published annually in WHO reports, in the leishmaniasis surveillance updates published in the *Weekly Epidemiological Record* and in profiles of countries in East Africa and South-East Asia that are co-endemic for HIV and VL. The results of the evaluation and any new evidence will be taken into account in future updates.

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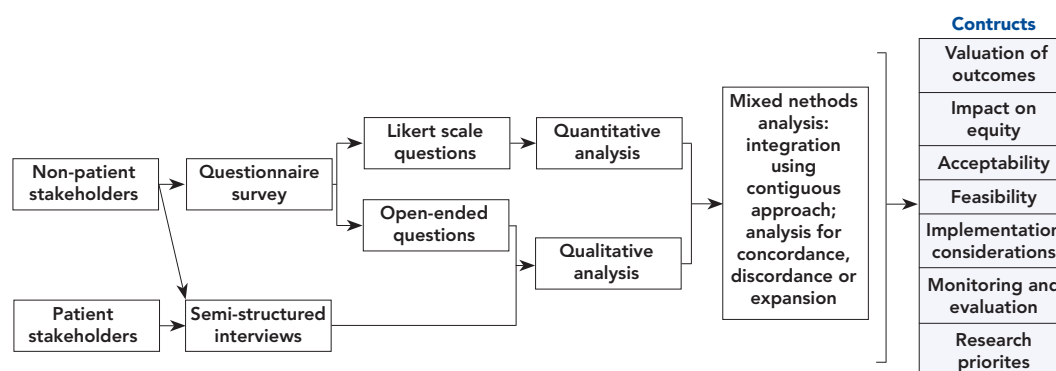
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Annex 1. Evidence for the equity, accessibility, feasibility, affordability and rating of treatment outcomes

Stakeholders' views and perspectives on treatments of visceral leishmaniasis and their outcomes in VL–HIV co-infected patients in East Africa and South-East Asia: a mixed-methods study

A technical team conducted a mixed-methods study (Fig. A4.1) to assess the views of stakeholders in relation to the treatment options for VL in HIV co-infected patients. The study will be published in a peer-reviewed journal and will be available as a web annex for reference. The quantitative objectives were to assess stakeholders' rating of the importance of the outcomes and assess their views on the equity, feasibility, and acceptability of treatment options. The qualitative objectives were to explore the reasons for their rating and views. The mixed-method study objective was to integrate the findings from the quantitative and qualitative components of the study. The study consisted of a survey of "non-patient" stakeholders and interviews with both patients and non-patients. The non-patient stakeholders included national officers of NDT programmes, staff at the ministries of health, subnational programme managers, physicians and nurses at district and referral hospitals, members of nongovernmental organizations, academic researchers, regional and country WHO personnel and members of the WHO's Regional Technical Advisory Group on VL. The survey and interview guide were designed by guideline methodologists at the American University of Beirut, Lebanon, with feedback from the WHO secretariat. The survey was widely disseminated through listserves suggested by WHO headquarters, regional and country offices and WHO partners, including national VL programmes. In order to recruit non-patient stakeholders to the interviews, the research team invited respondents to the online survey who had responded positively to a question about willingness to participate in a semi-structured interview. Physicians at treatment centres in Ethiopia and India assisted in patient recruitment.

Fig. A4.1. Mixed-methods design



The research team received a total of 177 complete survey responses and interviewed 10 non-patient stakeholders and 19 patients (Table A4.1). The evidence-to-decision tables in web annex 2 summarize the results of the survey and interviews.

Table A4.1. Survey participants' characteristics (N=177)

	South-East Asia (N=142)*	East Africa (N=32)*	Other/not specified (N=3)*
Gender			
Female	18 (13)	8 (26)	0 (0)
Male	123 (87)	23 (74)	2 (100)
Age (years)			
18–30	22 (15)	1 (3)	0 (0)
31–50	90 (63)	23 (72)	2 (67)
51–64	22 (15)	8 (25)	1 (33)
> 64	8 (6)	0 (0)	0 (0)
Highest attained educational degree			
Doctoral degree	49 (35)	14 (45)	2 (67)
Master's degree	51 (36)	13 (42)	1 (33)
Bachelor's degree	32 (23)	3 (10)	0 (0)
Certificate or diploma	3 (2)	1 (3)	0 (0)
None of the above	7 (5)	0 (0)	0 (0)
Stakeholder group			
Health providers/clinical officers	51 (36)	11 (34)	0 (0)
National NTD officers/subnational programme managers	43 (30)	8 (25)	1 (33)
Researchers	15 (11)	10 (31)	0 (0)
Nongovernmental organizations	12 (8)	1 (3)	1 (33)
Regional and country office WHO staff	4 (3)	0 (0)	1 (33)
Policy-makers	3 (2)	0 (0)	0 (0)

Members of WHO's Regional Technical Advisory Group on VL	2 (1)	0 (0)	0 (0)
National ministry of health staff	0 (0)	1 (3)	0 (0)
Not specified	12 (8)	1 (3)	0 (0)
Affiliation			
Nongovernmental organization	81 (57)	6 (19)	1 (33)
Governmental organization	29 (20)	18 (56)	1 (33)
International intergovernmental organization	16 (11)	4 (13)	1 (33)
Academic institution	12 (8)	4 (13)	0 (0)
Private for-profit organization	2 (1)	0 (0)	0 (0)
Not specified/other	2 (1)	0 (0)	0 (0)

Abbreviations: NTD: neglected tropical diseases; WHO: World Health Organization; VL: visceral leishmaniasis.

*Numbers do not always add to 177 due to missing data. Percentages represent valid percentages

**Total of 14 countries

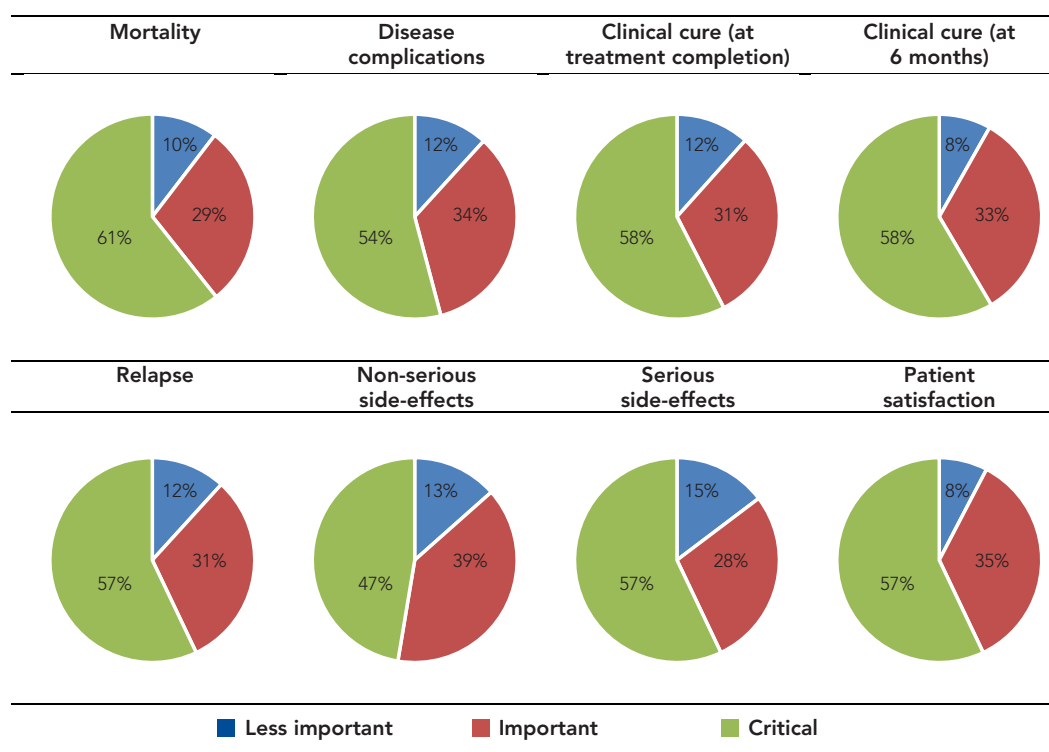
Valuation of the outcomes of interest

The outcome rated as "critical" by most participants (61%) was mortality, followed by clinical cure at 6 months and clinical cure at the time of treatment completion (58%), relapse (57%), serious adverse events (57%), patient satisfaction (57%) and complications (54%). Participants viewed clinical cure as essential for patients to return to their daily life and economic productivity. Non-patient stakeholders emphasized the importance of "sustained" clinical cure.

Impact on equity, acceptability and feasibility of treatment alternatives

Most participants (60%) considered that providing combination therapy would increase health equity (40% "increased", 20% "probably increased"). Most participants (79%) replied that combination therapy is more acceptable (55% "more acceptable", 24% "probably more acceptable") and more feasible than monotherapy (57%; 33% "more feasible", 24% "probably more feasible") (Fig. A4.2).

Fig. A4.2. Valuation of each outcome of interest



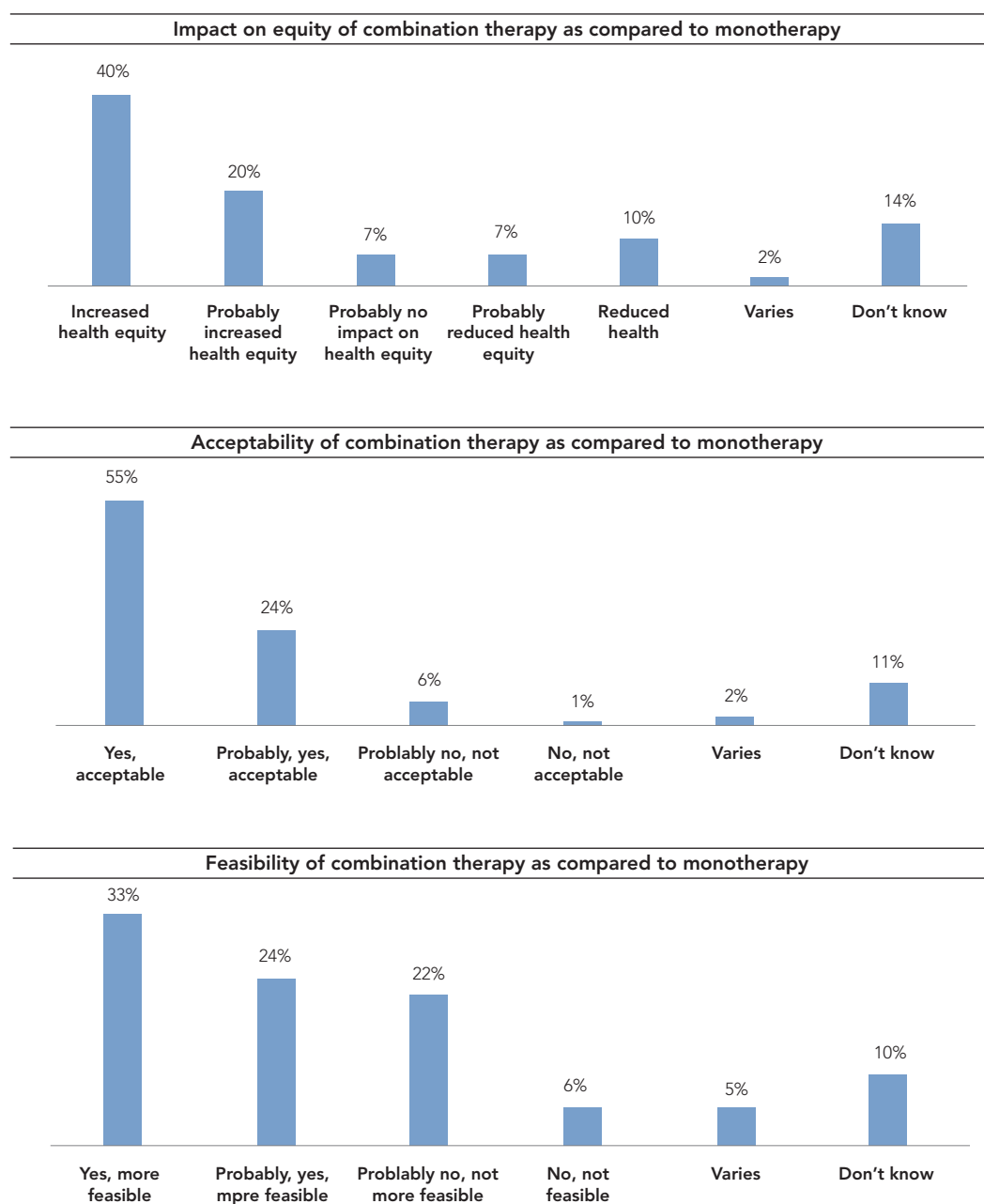
Semi-structured interviews

Both patient and non-patient stakeholders considered a reduction in mortality to be an important outcome. While the non-patient stakeholders highlighted death as a critical outcome for any disease, they noted the particular importance of mortality as an outcome in this population, as coinfection and immunosuppression increase their vulnerability. Patients considered survival to be a “miracle” and recounted the deaths of close relations. All the participants perceived clinical cure as an opportunity for patients to resume their daily activities and become socially and economically productive. Non-patient stakeholders placed a higher value on clinical cure at 6 months than at the time of treatment completion because of the higher risk of these patients for relapse.

Impact on equity, feasibility and acceptability

Most of the participants considered that the two treatments did not have a differential effect on equity, as they are both available for free in public health facilities. A few participants were, however, concerned about the adverse events associated with miltefosine, making pregnant women ineligible for the combination therapy. General issues of equity, such as out-of-pocket expenditure in private health facilities, were mentioned for this group of patients. The interviews revealed that combination therapy was more acceptable than monotherapy, due mainly to the shorter hospitalization. Longer hospital stays were perceived as less feasible and less acceptable by all participants (Fig. A4.3).

Fig. A4.3. Impact on equity, acceptability and feasibility of combination therapy as compared with monotherapy-



Implementation, monitoring and evaluation and research

Participants suggested a number of implementation considerations, notably addressing access to treatment and the importance of counselling and of a holistic approach to treatment. Suggestions for monitoring and evaluation included which parameters to monitor (e.g., adverse events, drug interactions) and the logistics of monitoring (e.g., tools, checklists). The research priorities identified included disease epidemiology, diagnostic aspects, prevention, disease progression and prognosis, acquisition of more data, issues related to treatment, immunology, relation with HIV and health systems

Annex 2. Costs of medicines in current use for the treatment of leishmaniasis

Drug prices (January 2021)

Compound	Commercial name and manufacturer	Unit, administration	Price per unit ^a
Amphotericin B deoxycholate	Different names in different countries	50-mg vial, IV	Variable, but median is US\$ 7.5 per 50-mg vial
Liposomal amphotericin B	AmBisome®: Gilead Sciences, USA	50-mg vial, IV	WHO-negotiated price: US\$ 16.25 ^b
Miltefosine	Impavido®: Knights Therapeutics, Barbados Single source	50-mg and 10-mg capsule, oral	WHO-negotiated prices: € 75–150 ^c per pack of 56 capsules
Paromomycin	Paromomycin, Gland Pharma, India Single source	2-mL vial of 375 mg/mL, IM/IV	WHO-negotiated price: US\$ 1.3/vial
Generic sodium stibogluconate	SSG, Albert David, India Single source	30-mL vial of 100 mg/mL, IM/IV	US\$ 7.25/vial ^d
Meglumine antimoniate	Glucantime®: Sanofi, France Single source	5-mL vial of 81 mg/mL, IM/IV	WHO-negotiated price: US\$ 1.2/vial

IM, intramuscular; IV, intravenous

^a Prices as quoted by manufacturers in the currency as originally quoted

^b This price was offered in 2014; in 2011, an L-AMB donation programme started for selected countries on the Indian subcontinent and East Africa.

^c Prices depend upon the size of order

^d Price valid for governments, United Nations organizations and nongovernmental organizations

Note: costs are given by the companies in the indicated currencies that are maintained to avoid any potential variations

Annex 3. Adverse effects of antileishmanial medicines

Drug	Organ system	Very common side-effects (≥ 1/10 patients)	Common side-effects (≥ 1/100 to < 1/10 patients)	Uncommon (≥ 1/1000 to < 1/100); rare (≥ 1/10 000 to < 1/10000); very rare (< 1/10 000)
Miltefosine	Gastrointestinal disorders	Vomiting, diarrhoea	Anorexia, nausea	Abdominal pain, thrombocytopenia
	Hepatobiliary disorders	Increased activity of liver enzymes		
	Renal and urinary disorders		Increased blood urea nitrogen, creatinine	
	Immune disorders			Steven–Johnson syndrome
Paromomycin	Skin		Pruritus	
	Gastrointestinal disorders		Nausea, metallic taste	Vomiting
	General	Headache, lethargy, mild injection-site pain	Pyrexia, reversible abnormal audiogram	Injection site swelling, abscess, ototoxicity, conductive deafness, proteinuria
	Hepatobiliary disorders		Transient increases in alanine and aspartate transaminases	Increased alkaline phosphatase, blood bilirubin
Liposomal amphotericin B	Skin		Pruritus	
	General and infusion related	Chills/rigor, fever, nausea, vomiting, hypertension, tachycardia, breathlessness, hypoxia, rash, anaemia, insomnia, malaise, fatigue, confusion, muscle weakness or cramps	Chest tightness, chest pain, breathlessness, difficulty in breathing (possibly with wheeze), flushing, vasodilation lowering blood pressure, musculoskeletal pain (described as joint pain, back pain or bone pain), stomach pain, headache, bleeding into skin, unusual bruising and prolonged bleeding after injury, fits or seizures, pain and swelling around the infusion site	Heart attack, severe swelling around lip, eyes or tongue, muscle breakdown, bone and joint pain
	Hepatobiliary disorders	Increased alkaline phosphatase		
	Gastrointestinal disorders	Diarrhoea, nausea, vomiting		

	Blood disorders	High blood sugar, low potassium, low magnesium, low calcium, low sodium		Anaemia with symptoms of excessive fatigue and breathlessness after light activity, a pale complexion, interference in blood phosphorus test results
	Renal and urinary disorders	Increased blood urea nitrogen, increased creatinine		Kidney failure
Amphotericin B deoxycholate	General and infusion related	Fever (sometimes accompanied by shaking chills, usually within 15–20 min of initiation of treatment), malaise, weight loss, hypotension, tachypnoea, pain at the injection site with or without phlebitis or thrombophlebitis, generalized pain, including muscle and joint pains	Flushing, anaphylactoid and other allergic reactions, bronchospasm, wheezing, rash, in particular maculopapular, pruritus	
	Cardiopulmonary		Cardiac arrest, shock, cardiac failure, pulmonary oedema, hypersensitivity pneumonitis, arrhythmia, including ventricular fibrillation, dyspnoea, hypertension	
	Hepatobiliary disorders			
	Gastrointestinal disorders	Anorexia, nausea, vomiting, diarrhoea, dyspepsia, cramping, epigastric pain	Acute liver failure, hepatitis, jaundice, haemorrhagic gastroenteritis, melena	
	Blood disorders	Normochromic, normocytic anaemia	Agranulocytosis, coagulation defects, thrombocytopenia, leukopenia, eosinophilia, leukocytosis	
	Renal and urinary disorders	Decreased renal function and renal function abnormalities, including azotaemia, hypokalaemia, hyposthenuria, renal tubular acidosis and nephrocalcinosis. Usually improves with interruption of therapy but some permanent impairment, especially in patients receiving large amounts (> 5 g) of amphotericin B or other nephrotoxic agents	Acute renal failure, anuria, oliguria	
	Neurological symptoms		Convulsions, hearing loss, tinnitus, transient vertigo, visual impairment, diplopia, peripheral neuropathy, encephalopathy, other neurological symptoms	

Sodium stibogluconate	General and infusion related	Flushing, sweating, fever, rash, yellow skin and eyes, pain and thrombosis on intravenous administration, pain at injection site if given intramuscularly, abdominal pain, anorexia, malaise, myalgia, arthralgia, headache and lethargy		Anaphylaxis, rigor, exacerbation of lesions on the cheek, substernal pain
	Cardiopulmonary	Fatal cardiac arrhythmia, changes in electrocardiogram, including reduction in T-wave amplitude, T-wave inversion and QT prolongation, transient coughing	Pneumonia	
	Hepatobiliary disorders	Transient rise in serum lipase and amylase, symptomatic pancreatitis		
	Gastrointestinal disorders	Bleeding from nose or gums		
	Blood disorders			Transient reductions in platelets, white blood cells and haemoglobin
	Neurological symptoms	Vertigo		
Meglumine antimoniate	General and infusion related	Headache, general malaise, difficulty in breathing, skin rash, facial oedema. Precautions to be taken before systemic administration: a protein-rich diet throughout treatment, correction of iron-deficiency anaemia or specific deficiencies to be corrected before treatment. Cardiac, hepatic and renal functions must be monitored throughout the treatment (instructions from product package insert)		
	Cardiopulmonary	Cardiac changes (dose dependent and generally reversible): T-wave inversion and QT interval prolongation		Cardiac arrhythmia
	Gastrointestinal disorders	Abdominal pain, increased liver enzyme activity		Pancreatitis
	Renal and urinary disorders			Acute renal insufficiency

Pentamidine	General	Local pain at injection site, induration, sterile abscess, nausea, vomiting, abdominal pain, hypotension, syncope, hypoglycaemia, diabetes mellitus		
	Blood and lymphatic system		Leukopenia, thrombocytopenia, anaemia	
	Metabolism and nutrition	Azotaemia	Hypoglycaemia, hyperglycaemia, hyperkalaemia, hypocalcaemia, hypomagnesaemia	
	Nervous system		Syncope, dizziness	
	Vascular		Hypotension, flushing	
	Cardiopulmonary			QT interval prolongation, cardiac arrhythmia
	Gastrointestinal		Nausea, vomiting, taste disturbance	Pancreatitis (rare)
	Hepatobiliary		Abnormal liver function	
	Skin and subcutaneous tissue		Rash	Stevens-Johnson syndrome (frequency unknown)
	Renal and urinary	Acute renal failure, macroscopic haematuria		

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