

Online Annex. Evidence to Recommendation

Question 1.

WHAT IS THE EFFICACY AND SAFETY OF THE DIFFERENT SYSTEMIC AND LOCAL TREATMENTS FOR THE MANAGEMENT OF PATIENTS DIAGNOSED WITH CUTANEOUS LEISHMANIASIS IN THE AMERICAS?

Assessment

Problem Is the problem a priority?		
Judgement	Evidence	Additional considerations
<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know		The panel considers the question is a priority given the burden of the disease in the Americas, especially for cutaneous leishmaniasis.
Desirable Effects How substantial are the desirable anticipated effects?		
Judgement	Evidence	Additional considerations
<input type="radio"/> Trivial <input type="radio"/> Small <input checked="" type="radio"/> Moderate <input type="radio"/> Large <input type="radio"/> Varies <input type="radio"/> Don't know	<p>The overall evidence shows a moderate effect of the interventions on adult and pediatric patients for cure at least 3 months after treatment compared with placebo or other treatments:</p> <ul style="list-style-type: none"> • Intralesional antimony, RR 5.00; 95% CI (1.94, 12.89) • Meglumine antimoniate, RR 4.23; 95% CI (0.84, 21.38) • Miltefosine, RR 2.18; 95% CI (1.28, 3.71) • Thermotherapy, RR 0.80; 95% CI (0.68, 0.95) • Paromomycin, RR 2.38; 95% CI (1.50, 3.80). 	

Undesirable Effects

How substantial are the undesirable anticipated effects?

Judgement	Evidence	Additional considerations
<p><input type="radio"/> Large</p> <p><input checked="" type="radio"/> Moderate</p> <p><input type="radio"/> Small</p> <p><input type="radio"/> Trivial</p> <p><input type="radio"/> Varies</p> <p><input type="radio"/> Don't know</p>	<ul style="list-style-type: none">• Severe side effects (SE) in the meglumine antimoniate (MA) group (RR 1.51; 95% CI [1.17, 1.96], 134 patients) compared with placebo.• Miltefosine probably produces more SE (RR 3.96; 95% CI [1.49, 10.48]) compared with placebo.• Four participants developed moderately severe local cellulitis with thermotherapy compared with placebo.• It was reported that 58% of participants who received topical paromomycin had SE that disappeared one week after treatment.	<p>The panel recognizes the toxicity of some drugs as well as the possible side effects. However, there are few options for patients, so clinicians should be careful in the treatment of the patients.</p>

Certainty of Evidence

What is the overall certainty of the evidence of effects?

Judgement	Evidence	Additional considerations
<p><input type="radio"/> Very low</p> <p><input checked="" type="radio"/> Low</p> <p><input type="radio"/> Moderate</p> <p><input type="radio"/> High</p> <p><input type="radio"/> No included studies</p>	<p>The overall certainty of evidence is low and very low due to the risk of bias in the studies (selection bias, lack of blinding, detection bias), very serious imprecision (small sample sizes and confidence intervals exceeding 25% of the estimator) and inconsistency in the findings. Only moderate certainty was reported for the comparison of meglumine antimoniate with placebo for the outcome of cure of at least 3 months and side effects.</p>	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

Judgement	Evidence	Additional considerations
<p><input type="radio"/> Important uncertainty or variability</p> <p><input type="radio"/> Possibly important uncertainty or variability</p> <p><input type="radio"/> Probably no important uncertainty or variability</p> <p><input type="radio"/> No important uncertainty or variability</p>	<p>A qualitative study in three Colombian cities near the Amazon reported that more than 60% of the population had scars consistent with cutaneous leishmaniasis and had not sought treatment in health centers because of lack of knowledge about the possibility of obtaining adequate treatment in a health service institution. Instead they went to pharmacies or neighbors to use topical creams. There is a belief (in conflict zones) that leishmaniasis is the “guerrilla’s disease” and, therefore, that the treatment is controlled by the army, or they may have problems with the authorities (62). Another study reports that as cutaneous leishmaniasis is not a disabling disease, and the injury usually does not hurt (unless infected), affected people do not seek medical attention (63). Several studies also report that many patients go to healers or use traditional medicine with plants or caustic remedies as the first option for cutaneous leishmaniasis treatment, because there is a negative perception of treatment with pentavalent antimonials due to pain, fear of injections, and side effects. Also, they suffer the consequences of social stigma due to their association of leishmaniasis with armed conflict and contexts of poverty and social vulnerability. It is also reported that patients may self-medicate when they have access to medications, which can lead to using ineffective therapeutic doses and to increased side effects (63). Another reason for not attending health services as a first option is the difficulty of access in terms of distance, costs, and bad experiences reported by family members or neighbors (62).</p>	<p>The panel considers that patients would prefer oral drugs in lower dose, especially children.</p> <p>Experts report that children present pain, fear of injections, and crying, so it is recommended that the first option be oral treatment and not systemic treatments (62).</p>

Balance of Effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

Judgement	Evidence	Additional considerations
<p><input type="radio"/> Favors the comparison</p> <p><input type="radio"/> Probably favors the comparison</p> <p><input type="radio"/> Does not favor either the intervention or the comparison</p> <p><input type="radio"/> Probably favors the intervention</p> <p><input type="radio"/> Favors the intervention</p> <p><input type="radio"/> Varies</p> <p><input type="radio"/> Don’t know</p>		<p>The panel considers that the benefits outweigh the risks.</p>

Resources Required
How large is the resource requirements (costs)?

Judgement	Evidence	Additional considerations
<input type="radio"/> Large costs <input checked="" type="radio"/> Moderate costs <input type="radio"/> Negligible costs and savings <input type="radio"/> Moderate savings <input type="radio"/> Large savings <input type="radio"/> Varies <input type="radio"/> Don't know	<p>A 2017 cost-analysis study compared systemic pentavalent antimonials with intralesional antimonials as the first line of cutaneous leishmaniasis treatment in Bolivia. Intralesional pentavalent antimonials presented a saving of US\$ 248 per patient treated according to the payment made by the Ministry of Health and US\$ 688 saved from the society point of view (59).</p>	<p>The panel reports that the management of leishmaniasis can involve significant costs for patients due to multiple and expensive trips to the health service for the administration of medications, given the long duration of treatment.</p> <p>Sometimes, systemic treatment is not administered in rural health centers, so patients and their companions must incur higher costs, which can lead to less adherence to treatment. For institutions providing health services, costs arise in the payment of fees for trained personnel or investment in training, as well as inputs such as syringes to provide adequate care to patients. It was identified that there is a high turnover of health personnel, so training of new professionals is necessary, increasing the costs of providing services.</p>

Certainty of Evidence of Required Resources
What is the certainty of the evidence of resource requirements (costs)?

Judgement	Evidence	Additional considerations
<input type="radio"/> Very low <input checked="" type="radio"/> Low <input type="radio"/> Moderate <input type="radio"/> High <input type="radio"/> No included studies	<p>The certainty of the evidence is low.</p>	

Cost-Effectiveness
Does the cost-effectiveness of the intervention favor the intervention or the comparison?

Judgement	Evidence	Additional considerations
<input type="radio"/> Favors the comparison <input checked="" type="radio"/> Probably favors the comparison <input type="radio"/> Does not favor either the intervention or the comparison <input type="radio"/> Probably favors the intervention <input type="radio"/> Favors the intervention <input type="radio"/> Varies <input type="radio"/> No included studies	<p>Another cost-effectiveness study evaluated intralesional meglumine antimoniate therapy compared to intravenous therapy in the Brazilian health system, reporting that the costs per cured patient were US\$ 330.81 for intralesional and US\$ 494.16 for intravenous per patient in 2018. The incremental cost-effectiveness ratio showed that intralesional meglumine antimoniate can result in a US\$ 864.37 saving for each additional patient cured (60). One study evaluated the cost-effectiveness of thermotherapy compared to meglumine antimoniate in cutaneous leishmaniasis treatment. It was found that the cost of meglumine antimoniate per patient was \$66,807 Colombian pesos compared to \$14,079 for thermotherapy (61).</p>	

Equity
What would be the impact on health equity?

Judgement	Evidence	Additional considerations
<input type="radio"/> Reduced <input checked="" type="radio"/> Probably reduced <input type="radio"/> Probably no impact <input type="radio"/> Probably increased <input type="radio"/> Increased <input type="radio"/> Varies <input type="radio"/> Don't know		Some interventions such as thermotherapy would be available mainly in large and medium-sized cities, and access would be more limited for people in remote areas.

Acceptability
Is the intervention acceptable to key stakeholders?

Judgement	Evidence	Additional considerations
<input type="radio"/> No <input type="radio"/> Probably no <input checked="" type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know		Most interventions would be accepted by the guideline users.

Feasibility
Is the intervention feasible to implement?

Judgement	Evidence	Additional considerations
<input type="radio"/> No <input type="radio"/> Probably no <input checked="" type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know		Most interventions could be implemented.

QUESTION 2.

WHAT IS THE EFFICACY AND SAFETY OF THE DIFFERENT PHARMACOLOGICAL TREATMENTS FOR THE MANAGEMENT OF PATIENTS DIAGNOSED WITH MUCOSAL LEISHMANIASIS IN THE AMERICAS?

Assessment

Problem Is the problem a priority?		
Judgement	Evidence	Additional considerations
<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know		The panel considers the question is a priority given the burden of the disease in the Americas.
Desirable Effects How substantial are the desirable anticipated effects?		
Judgement	Evidence	Additional considerations
<input type="radio"/> Trivial <input type="radio"/> Small <input checked="" type="radio"/> Moderate <input type="radio"/> Large <input type="radio"/> Varies <input type="radio"/> Don't know	<p>The overall evidence shows a moderate effect of the interventions on adult and pediatric patients.</p> <ul style="list-style-type: none"> • Pentavalent antimonial: we identified two studies with 89 participants with no differences in cure rates, doses, or effect on any form of leishmaniasis ($p > 0.05$). • Oral pentoxifylline had a significant synergistic effect with IV sodium stibogluconate (IV SS) of 20 mg/kg/day for 30 days in <i>L. braziliensis</i> (RR 1.66; 95% CI [1.03, 2.69], 23 patients). • Miltefosine versus pentavalent antimonials in participants with mucosal leishmaniasis without reporting differences in cure rates at 3 months (RR 1.04; 95% CI [0.81, 1.34]). 	

Undesirable Effects How substantial are the undesirable anticipated effects?		
Judgement	Evidence	Additional considerations
<input type="radio"/> Large <input checked="" type="radio"/> Moderate <input type="radio"/> Small <input type="radio"/> Trivial <input type="radio"/> Varies <input type="radio"/> Don't know	<ul style="list-style-type: none"> • IV sodium stibogluconate (IV SS) for 28 days with IV SS for 40 days. No discontinuation of treatment was reported. Side effects were arthralgias, myalgias, itching, rash, nausea, anorexia, abdominal pain, cough, and headache in patients treated for 40 days. • Gastrointestinal effects (nausea, vomiting, and epigastric pain) were higher in patients receiving miltefosine (RR 2.97; 95% CI [1.05, 8.38]) compared with meglumine antimoniate. • Mild adverse effects were most frequently observed in the pentoxifylline group. 	<p>The panel recognizes the toxicity of some drugs as well as the possible side effects. However, there are few options for patients, so clinicians should be careful in the treatment of the patients.</p>
Certainty of Evidence What is the overall certainty of the evidence of effects?		
Judgement	Evidence	Additional considerations
<input type="radio"/> Very low <input type="radio"/> Low <input type="radio"/> Moderate <input type="radio"/> High <input type="radio"/> No included studies	<p>The overall certainty of evidence is low and very low due to the risk of bias in the studies (selection bias, lack of blinding, detection bias), and very serious imprecision (small sample sizes and confidence intervals exceeding 25% of the estimator).</p>	
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
Judgement	Evidence	Additional considerations
<input type="radio"/> Important uncertainty or variability <input type="radio"/> Possibly important uncertainty or variability <input type="radio"/> Probably no important uncertainty or variability <input type="radio"/> No important uncertainty or variability	<p>Patients with mucosal or mucocutaneous leishmaniasis report feeling low self-esteem because this clinical form can cause deformities or mutilations, so they prefer treatments that are shorter, and it is important to consider the patient's acceptance so that adherence to treatment is increased. A few studies also report that many patients go to healers or use traditional medicine with plants or caustic remedies as the first option for leishmaniasis treatment, because there is a negative perception of pentavalent antimonials treatment due to pain, fear of injections, and side effects (61, 68).</p>	<p>The panel considers that patients would prefer oral drugs in lower dose, especially children.</p>

Balance of Effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

Judgement	Evidence	Additional considerations
<input type="radio"/> Favors the comparison <input type="radio"/> Probably favors the comparison <input type="radio"/> Does not favor either the intervention or the comparison <input checked="" type="radio"/> Probably favors the intervention <input type="radio"/> Favors the intervention <input type="radio"/> Varies <input type="radio"/> Don't know	<p>Experts considered the combination of pentavalent antimonials with pentoxifylline to be a good alternative for patients. Also, it is recognized that there is very little evidence in mucosal leishmaniasis, but the therapeutic options are those currently used in the Region with better results.</p>	<p>The panel considers that the benefits outweigh the risks.</p>

Resources Required

How large are the resource requirements (costs)?

Judgement	Evidence	Additional considerations
<input type="radio"/> Large costs <input checked="" type="radio"/> Moderate costs <input type="radio"/> Negligible costs and savings <input type="radio"/> Moderate savings <input type="radio"/> Large savings <input type="radio"/> Varies <input type="radio"/> Don't know		<p>Experts report that liposomal amphotericin B is expensive in the countries of the Region, when not acquired with subsidized prices from the agreement with the World Health Organization. Therefore, along with the availability of other alternatives and evidence, it is currently not recommended for patients with mucosal leishmaniasis. Pentavalent antimonials and pentamidine isethionate are included in the benefit plans of most countries. Costs may be incurred for patients, especially in rural areas, because they must make several trips outside their geographic area to receive the treatment, which generally requires hospitalization.</p>

Certainty of Evidence of Required Resources

What is the certainty of the evidence of resource requirements (costs)?

Judgement	Evidence	Additional considerations
<input type="radio"/> Very low <input type="radio"/> Low <input type="radio"/> Moderate <input type="radio"/> High <input type="radio"/> No included studies		

Cost-Effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

Judgement	Evidence	Additional considerations
<input type="radio"/> Favors the comparison <input type="radio"/> Probably favors the comparison <input type="radio"/> Does not favor either the intervention or the comparison <input type="radio"/> Probably favors the intervention <input type="radio"/> Favors the intervention <input type="radio"/> Varies <input type="radio"/> No included studies		

Equity

What would be the impact on health equity?

Judgement	Evidence	Additional considerations
<input type="radio"/> Reduced <input checked="" type="radio"/> Probably reduced <input type="radio"/> Probably no impact <input type="radio"/> Probably increased <input type="radio"/> Increased <input type="radio"/> Varies <input type="radio"/> Don't know		Some interventions (systemic delivery) would be available mainly in large and medium-sized cities, and access would be more limited for people in remote areas.

Acceptability
Is the intervention acceptable to key stakeholders?

Judgement	Evidence	Additional considerations
<input type="radio"/> No <input type="radio"/> Probably no <input checked="" type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know		Most interventions would be accepted by the guideline users.

Feasibility
Is the intervention feasible to implement?

Judgement	Evidence	Additional considerations
<input type="radio"/> No <input type="radio"/> Probably no <input checked="" type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know		Most interventions could be implemented.

QUESTION 3.

WHAT IS THE EFFICACY AND SAFETY OF THE DIFFERENT PHARMACOLOGICAL TREATMENTS FOR THE MANAGEMENT OF NON-IMMUNOCOMPROMISED PATIENTS DIAGNOSED WITH VISCERAL LEISHMANIASIS IN THE AMERICAS?

Assessment

Problem Is the problem a priority?		
Judgement	Evidence	Additional considerations
<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know		The panel considers the question is a priority given the burden of the disease in the Americas.
Desirable Effects How substantial are the desirable anticipated effects?		
Judgement	Evidence	Additional considerations
<input checked="" type="radio"/> Trivial <input type="radio"/> Small <input type="radio"/> Moderate <input type="radio"/> Large <input type="radio"/> Varies <input type="radio"/> Don't know	<p>No differences were reported between the groups compared with meglumine antimoniate: LAB (9.7%; 95% CI [-0.28, 19.68]; p = 0.06) and liposomal amphotericin B plus meglumine antimoniate (6.4%; 95% CI [-3.93, 16.73]; p = 0.222) regarding differences in cure rate.</p> <p>An open randomized controlled trial evaluated the efficacy and safety of N-methyl glucamine antimoniate (20 mg/kg/day for 20 days) and amphotericin B deoxycholate (1 mg/kg/day for 14 days) in 101 pediatric patients (6 months to 12 years old) and adults newly diagnosed with visceral leishmaniasis (VL) without signs of severe disease. No differences in complete cure were found between the groups (RR 1.00; 95% CI [0.91, 1.10]) nor for relapse at 180 days (RR 7.54; 95% CI [0.15, 378]).</p>	

Undesirable Effects How substantial are the undesirable anticipated effects?		
Judgement	Evidence	Additional considerations
<input type="radio"/> Large <input type="radio"/> Moderate <input type="radio"/> Small <input checked="" type="radio"/> Trivial <input type="radio"/> Varies <input type="radio"/> Don't know	<p>High toxicity was reported in amphotericin B deoxycholate (1 mg/kg/day for 14 days) that led to the end of the study for this group of patients.</p> <p>Liposomal amphotericin B monotherapy has a lower frequency of side effects.</p>	<p>The panel recognizes the toxicity of some drugs as well the possible side effects. However, there are few options for patients, so clinicians should be careful in their treatment.</p>
Certainty of Evidence What is the overall certainty of the evidence of effects?		
Judgement	Evidence	Additional considerations
<input type="radio"/> Very low <input type="radio"/> Low <input type="radio"/> Moderate <input type="radio"/> High <input type="radio"/> No included studies	<p>The overall certainty of evidence is low and very low due to the risk of bias in the studies (selection bias, lack of blinding, detection bias), and very serious imprecision (small sample sizes and confidence intervals exceeding 25% of the estimator).</p>	
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
Judgement	Evidence	Additional considerations
<input type="radio"/> Important uncertainty or variability <input type="radio"/> Possibly important uncertainty or variability <input type="radio"/> Probably no important uncertainty or variability <input type="radio"/> No important uncertainty or variability	<p>We found no evidence of visceral leishmaniasis patient preferences in non-immunocompromised patients in the Americas.</p>	<p>The Guideline Development Group panel considers that patients would prefer the most effective therapeutic alternative with fewer side effects and shorter treatment.</p>

Balance of Effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

Judgement	Evidence	Additional considerations
<input type="radio"/> Favors the comparison <input type="radio"/> Probably favors the comparison <input type="radio"/> Does not favor either the intervention or the comparison <input checked="" type="radio"/> Probably favors the intervention <input type="radio"/> Favors the intervention <input type="radio"/> Varies <input type="radio"/> Don't know	The evidence supports the use of liposomal amphotericin B for being safer, which also helps to decrease the number of treatment interruptions. It is important to note that, once toxicity has been overcome, patients are completely cured.	The panel considers that the benefits outweigh the risks.

Resources Required

How large are the resource requirements (costs)?

Judgement	Evidence	Additional considerations
<input type="radio"/> Large costs <input checked="" type="radio"/> Moderate costs <input type="radio"/> Negligible costs and savings <input type="radio"/> Moderate savings <input type="radio"/> Large savings <input type="radio"/> Varies <input type="radio"/> Don't know		The Guideline Development Group panel considers that liposomal amphotericin B is expensive when acquired nationally and still with little access in the countries of the Region, but it is the best therapeutic strategy for adult and pediatric patients in the Americas.

Certainty of Evidence of Required Resources

What is the certainty of the evidence of resource requirements (costs)?

Judgement	Evidence	Additional considerations
<input type="radio"/> Very low <input type="radio"/> Low <input type="radio"/> Moderate <input type="radio"/> High <input type="radio"/> No included studies		

Cost-Effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

Judgement	Evidence	Additional considerations
<input type="radio"/> Favors the comparison <input type="radio"/> Probably favors the comparison <input type="radio"/> Does not favor either the intervention or the comparison <input checked="" type="radio"/> Probably favors the intervention <input type="radio"/> Favors the intervention <input type="radio"/> Varies <input type="radio"/> No included studies	A cost-effectiveness study conducted in Brazil evaluated meglumine antimoniate (MA), liposomal amphotericin B (LAB), and their combination for the treatment of visceral leishmaniasis. LAB was more cost-effective, followed by the MA plus LAB combination. When comparing LAB and MA, a saving of US\$ 278.56 was reported for LAB for each therapeutic failure avoided, US\$ 26.88 for each day of hospitalization, and US\$ 89.88 for each visceral leishmaniasis case cured (72).	

Equity

What would be the impact on health equity?

Judgement	Evidence	Additional considerations
<input type="radio"/> Reduced <input checked="" type="radio"/> Probably reduced <input type="radio"/> Probably no impact <input type="radio"/> Probably increased <input type="radio"/> Increased <input type="radio"/> Varies <input type="radio"/> Don't know		Some interventions (systemic delivery) would be available mainly in large and medium-sized cities, and access would be more limited for people in remote areas.

Acceptability
Is the intervention acceptable to key stakeholders?

Judgement	Evidence	Additional considerations
<input type="radio"/> No <input type="radio"/> Probably no <input checked="" type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know		Most interventions would be accepted by the guideline users.

Feasibility
Is the intervention feasible to implement?

Judgement	Evidence	Additional considerations
<input type="radio"/> No <input type="radio"/> Probably no <input checked="" type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know		Most interventions could be implemented.

QUESTION 4.

WHAT IS THE EFFICACY AND SAFETY OF THE DIFFERENT PHARMACOLOGICAL TREATMENTS FOR THE MANAGEMENT OF IMMUNOCOMPROMISED PATIENTS DIAGNOSED WITH VISCERAL LEISHMANIASIS IN THE AMERICAS?

Assessment

Problem Is the problem a priority?		
Judgement	Evidence	Additional considerations
<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know		The panel considers the question is a priority given the burden of the disease in the Americas.
Desirable Effects How substantial are the desirable anticipated effects?		
Judgement	Evidence	Additional considerations
<input checked="" type="radio"/> Trivial <input type="radio"/> Small <input type="radio"/> Moderate <input type="radio"/> Large <input type="radio"/> Varies <input type="radio"/> Don't know	Two clinical trials evaluated high doses of liposomal amphotericin B (3 mg/kg/day) compared with standard doses of pentavalent antimonials in visceral leishmaniasis patients infected with HIV. No differences were reported in overall cure (RR 0.96; 95% CI [0.72, 1.29]).	

Undesirable Effects

How substantial are the undesirable anticipated effects?

Judgement	Evidence	Additional considerations
<input type="radio"/> Large <input type="radio"/> Moderate <input type="radio"/> Small <input checked="" type="radio"/> Trivial <input type="radio"/> Varies <input type="radio"/> Don't know	Two clinical trials evaluated high doses of liposomal amphotericin B (3 mg/kg/day) compared with standard doses of pentavalent antimonials in visceral leishmaniasis patients infected with HIV. No differences were reported in treatment abandonment (RR 1.28; 95% CI [0.02, 69.15]), death (RR 0.57; 95% CI [0.10, 3.36]), or side effects (RR 0.60; 95% CI [0.11, 3.39]).	The panel recognizes the toxicity of some drugs as well as the possible side effects. However, there are few options for patients, so clinicians should be careful in their treatment.

Certainty of Evidence

What is the overall certainty of the evidence of effects?

Judgement	Evidence	Additional considerations
<input checked="" type="radio"/> Very low <input type="radio"/> Low <input type="radio"/> Moderate <input type="radio"/> High <input type="radio"/> No included studies	The certainty of the evidence is very low due to risk of bias, indirect evidence, heterogeneity, and imprecision.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

Judgement	Evidence	Additional considerations
<input checked="" type="radio"/> Important uncertainty or variability <input type="radio"/> Possibly important uncertainty or variability <input type="radio"/> Probably no important uncertainty or variability <input type="radio"/> No important uncertainty or variability	We found no evidence of visceral leishmaniasis patient preferences in immunocompromised patients in the Americas.	The guideline development group panel considers that patients would prefer the most effective therapeutic alternative with fewer side effects and shorter treatment.

Balance of Effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

Judgement	Evidence	Additional considerations
<input type="radio"/> Favors the comparison <input type="radio"/> Probably favors the comparison <input type="radio"/> Does not favor either the intervention or the comparison <input checked="" type="radio"/> Probably favors the intervention <input type="radio"/> Favors the intervention <input type="radio"/> Varies <input type="radio"/> Don't know		The panel considers that amphotericin B has less toxicity than pentavalent antimonials, so these should be used in immunocompromised patients with visceral leishmaniasis.

Resources Required

How large are the resource requirements (costs)?

Judgement	Evidence	Additional considerations
<input type="radio"/> Large costs <input checked="" type="radio"/> Moderate costs <input type="radio"/> Negligible costs and savings <input type="radio"/> Moderate savings <input type="radio"/> Large savings <input type="radio"/> Varies <input type="radio"/> Don't know		The Guideline Development Group panel considers that liposomal amphotericin B is expensive when acquired nationally and still with little access in the countries of the Region, but it is the best therapeutic strategy for adult and pediatric patients in the Americas.

Certainty of Evidence of Required Resources

What is the certainty of the evidence of resource requirements (costs)?

Judgement	Evidence	Additional considerations
<input type="radio"/> Very low <input type="radio"/> Low <input type="radio"/> Moderate <input type="radio"/> High <input type="radio"/> No included studies		

Cost-Effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

Judgement	Evidence	Additional considerations
<input type="radio"/> Favors the comparison <input type="radio"/> Probably favors the comparison <input type="radio"/> Does not favor either the intervention or the comparison <input type="radio"/> Probably favors the intervention <input type="radio"/> Favors the intervention <input type="radio"/> Varies <input type="radio"/> No included studies		

Equity

What would be the impact on health equity?

Judgement	Evidence	Additional considerations
<input type="radio"/> Reduced <input checked="" type="radio"/> Probably reduced <input type="radio"/> Probably no impact <input type="radio"/> Probably increased <input type="radio"/> Increased <input type="radio"/> Varies <input type="radio"/> Don't know		Some interventions would be available mainly in large and medium-sized cities, and access would be more limited for people in remote areas.

Acceptability
Is the intervention acceptable to key stakeholders?

Judgement	Evidence	Additional considerations
<input type="radio"/> No <input type="radio"/> Probably no <input checked="" type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know		Most interventions would be accepted by the guideline users.

Feasibility
Is the intervention feasible to implement?

Judgement	Evidence	Additional considerations
<input type="radio"/> No <input type="radio"/> Probably no <input checked="" type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know		<p>Most interventions could be implemented.</p> <p>Difficulties will be encountered in accessing liposomal amphotericin B, but it is hoped that access can be provided by strengthening drug production and distribution policies.</p>

QUESTION 5.

WHAT IS THE EFFICACY AND SAFETY OF SECONDARY PROPHYLAXIS FOR THE MANAGEMENT OF IMMUNOCOMPROMISED PATIENTS DIAGNOSED WITH VISCERAL LEISHMANIASIS IN THE AMERICAS?

Assessment

Problem		
Is the problem a priority?		
Judgement	Evidence	Additional considerations
<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know		The panel considers the question is a priority given the burden of the disease in the Americas.
Desirable Effects		
How substantial are the desirable anticipated effects?		
Judgement	Evidence	Additional considerations
<input type="radio"/> Trivial <input type="radio"/> Small <input type="radio"/> Moderate <input type="radio"/> Large <input type="radio"/> Varies <input type="radio"/> Don't know	One clinical trial was selected that evaluated the efficacy of liposomal amphotericin B (3 mg/kg/day) compared with not performing secondary prophylaxis treatment in 17 Spanish patients with VL–HIV coinfection. 50% of participants remained free of VL events at one year of follow-up (95% CI [15.7, 84.3]) in the amphotericin B group and 22.2% in the untreated group (95% CI [2.8, 60]) (p = 0.141) (75).	

Undesirable Effects
How substantial are the undesirable anticipated effects?

Judgement	Evidence	Additional considerations
<input type="radio"/> Large <input type="radio"/> Moderate <input type="radio"/> Small <input checked="" type="radio"/> Trivial <input type="radio"/> Varies <input type="radio"/> Don't know	<p>The amphotericin B group had more mild side effects (88%), which were tolerated by participants, compared to the control group (33%) (p = 0.0032). The certainty of the evidence is very low due to risk of bias and inaccuracy (75).</p>	<p>The panel recognizes the toxicity of some drugs as well as the possible side effects. However, there are few options for patients, so clinicians should be careful in their treatment.</p>

Certainty of Evidence
What is the overall certainty of the evidence of effects?

Judgement	Evidence	Additional considerations
<input type="radio"/> Very low <input type="radio"/> Low <input type="radio"/> Moderate <input type="radio"/> High <input type="radio"/> No included studies	<p>The certainty of the evidence is very low due to risk of bias, indirect evidence, heterogeneity, and imprecision.</p>	

Values
Is there important uncertainty about or variability in how much people value the main outcomes?

Judgement	Evidence	Additional considerations
<input checked="" type="radio"/> Important uncertainty or variability <input type="radio"/> Possibly important uncertainty or variability <input type="radio"/> Probably no important uncertainty or variability <input type="radio"/> No important uncertainty or variability	<p>We found no evidence of visceral leishmaniasis patient preferences in immunocompromised patients in the Americas.</p>	<p>The Guideline Development Group panel considers that patients would prefer the most effective therapeutic alternative with fewer side effects and shorter treatment.</p>

Balance of Effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

Judgement	Evidence	Additional considerations
<input type="radio"/> Favors the comparison <input type="radio"/> Probably favors the comparison <input type="radio"/> Does not favor either the intervention or the comparison <input checked="" type="radio"/> Probably favors the intervention <input type="radio"/> Favors the intervention <input type="radio"/> Varies <input type="radio"/> Don't know		The Guideline Development Group panel considers that the benefit of the intervention is greater than the risk, so a strong recommendation was formulated. There was no evidence for patients immunocompromised due to HIV, so the expert panel updated the remarks of the previous version of the Guideline.

Resources Required

How large are the resource requirements (costs)?

Judgement	Evidence	Additional considerations
<input type="radio"/> Large costs <input checked="" type="radio"/> Moderate costs <input type="radio"/> Negligible costs and savings <input type="radio"/> Moderate savings <input type="radio"/> Large savings <input type="radio"/> Varies <input type="radio"/> Don't know		The Guideline Development Group panel considers that liposomal amphotericin B is expensive when acquired nationally and still with little access in the countries of the Region, but it is the best therapeutic strategy for adult and pediatric patients in the Americas.

Certainty of Evidence of Required Resources

What is the certainty of the evidence of resource requirements (costs)?

Judgement	Evidence	Additional considerations
<input type="radio"/> Very low <input type="radio"/> Low <input type="radio"/> Moderate <input type="radio"/> High <input type="radio"/> No included studies		

Cost-Effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

Judgement	Evidence	Additional considerations
<input type="radio"/> Favors the comparison <input type="radio"/> Probably favors the comparison <input type="radio"/> Does not favor either the intervention or the comparison <input type="radio"/> Probably favors the intervention <input type="radio"/> Favors the intervention <input type="radio"/> Varies <input type="radio"/> No included studies		

Equity

What would be the impact on health equity?

Judgement	Evidence	Additional considerations
<input type="radio"/> Reduced <input checked="" type="radio"/> Probably reduced <input type="radio"/> Probably no impact <input type="radio"/> Probably increased <input type="radio"/> Increased <input type="radio"/> Varies <input type="radio"/> Don't know		Some interventions would be available mainly in large and medium-sized cities, and access would be more limited for people in remote areas.

Acceptability
Is the intervention acceptable to key stakeholders?

Judgement	Evidence	Additional considerations
<input type="radio"/> No <input type="radio"/> Probably no <input checked="" type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know		Most interventions would be accepted by the guideline users.

Feasibility
Is the intervention feasible to implement?

Judgement	Evidence	Additional considerations
<input type="radio"/> No <input type="radio"/> Probably no <input checked="" type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know		<p>Most interventions could be implemented.</p> <p>Difficulties will be encountered in accessing liposomal amphotericin B, but it is hoped that access can be provided by strengthening drug production and distribution policies.</p>