WHO GUIDELINE

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

WEB ANNEX B.
Evidence-to-decision tables

World Health Organization

WHO guidelines for the treatment of visceral leishmaniasis in HIV co-infected patients in East Africa and South-East Asia. Web Annex B. Evidence-to-decision tables

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Contents

Web annex B. Evidence review, PICO questions and GRADE summary tables

Appendix B.1 Population, intervention, comparator and outcomes (PICO) 1: East Africa

Should liposomal amphotericin B [L-AMB] (up to 30 mg/kg, at 5 mg/kg on days 1, 3, 5, 7, 9, 11) + miltefosine (100 mg/day for 28 days) vs L-AMB (up to 40 mg/kg, at 5 mg/kg on days 1–5, 10, 17, 24) be used for visceral leishmaniasis (VL) patients co-infected with HIV in East Africa?

PICO question

Population	VL patients co-infected with HIV in East Africa
Intervention	L-AMB (up to 30 mg/kg, at 5 mg/kg on days 1, 3, 5, 7, 9, 11) + miltefosine (100 mg/day for 28 days)
Comparison	L-AMB (up to 40 mg/kg, at 5 mg/kg on days 1–5, 10, 17, 24)
Main outcomes	All-cause mortality; clinical cure; relapse; relapse-free survival; treatment adherence; adverse events (any cause); serious adverse events due to any cause; follow-up of patients
Setting	All-cause mortality; clinical cure; relapse; relapse-free survival; treatment adherence; adverse events (any cause); serious adverse events due to any cause; follow-up of patients
Perspective	
Background	The WHO recommendation (2010) to use L-AMB (up to 40 mg/kg, at 5 mg/kg on days 1–5, 10, 17, 24) in the treatment of VL in HIV-co-infected patients emerged from the evidence in Mediterranean countries where VL is caused by L. infantum. This lacked region-specific treatment recommendations such as in East Africa, where VL is caused by L. donovani, a different parasite species. New evidence is available from a randomized controlled trial in East Africa.
Conflict of interests	None

Assessment

Desirable effects

How substantial are the desirable anticipated effects?

Judgement	Research evidence	Additional considerations
• Trivial • Small • Moderate • Large • Varies • Don't know	See Web annex 1: Systematic review	• Additional desirable effects of combination therapy include o Possible reduction in resistance to L-AMB o Possible reduction in infectivity in anthroponotic transmission • Available evidence is from patients with advanced AIDS disease. • There is evidence of benefits associated with extended treatment in patients with advanced AIDS disease.

Undesirable effects

How substantial are the undesirable anticipated effects?

Judgement	Research evidence	Additional considerations
• Trivial • Small • Moderate • Large • Varies • Don't know	See Web annex 1: Systematic review	• Additional desirable effects of combination therapy include o Possible reduction in resistance to L-AMB o Possible reduction in infectivity in anthroponotic transmission • Available evidence is from patients with advanced AIDS disease. • There is evidence of benefits associated with extended treatment in patients with advanced AIDS disease.

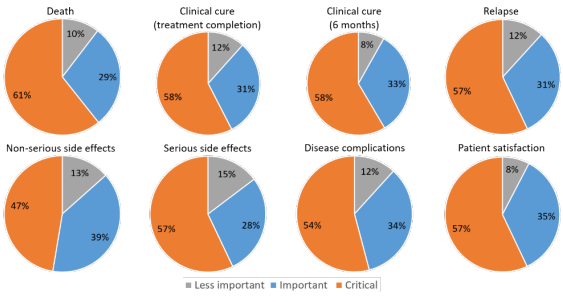
Certainty of evidence

What is the overall certainty of the evidence of effects?

Judgement	Research evidence	Additional considerations
• Very low • Low • Moderate • High • No included studies		

Values

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

Judgement	Research evidence	Additional considerations
• Important uncertainty or variability • Possibly important uncertainty or variability • Probably no important uncertainty or variability • No important uncertainty or variability	Survey results 	

	Interview results Generally consistent with survey results • Mortality, clinical cure at 6 months, relapse, serious side-effects, disease complications: generally valued as critical/important • Clinical cure at treatment completion, patient satisfaction: rating varied • Non-serious side-effects: generally valued as less important	

Balance of effects

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

Judgement	Research evidence	Additional considerations
• Favours the comparison • Probably favours the comparison • Does not favour either the intervention or the comparison • Probably favours the intervention • Favours the intervention • Varies • Don't know		

Resources required

How large are the resource requirements (costs)?

Judgement	Research evidence	Additional considerations
• Large costs • Moderate costs • Negligible costs and savings • Moderate savings • Large savings • Varies • Don't know		• Mandatory contraception plan and pregnancy testing, with use of miltefosine in women of childbearing potential • Cost with hospitalization • Extra toxicity monitoring with miltefosine

	East Africa		Indian subcontinent	
Type of therapy	Treatment regimen	Price per VL treatment	Treatment regimen	Price per VL treatment
Monotherapy	Total dose @40 mg/kg body weight for 35 kg patients = 28-35 vials	US$ 504-630	Total dose @40 mg/kg body weight for 35 kg patients = 28-35 vials	US$ 504-630
Combination therapy	AmBisome®- Total dose @30 mg/kg body weight for 35 kg patients = 21-28 vials Miltefosine- Total dose@100 mg daily x 28 days = 56 capsules	US$ 378- 504 *€ - 75-150 (Price range of miltefosine depends on order volume) Total price- US$ 466.5- 589.7	AmBisome®- Total dose @30 mg/kg body weight for 35 kg patients = 21-28 vials Miltefosine- Total dose@100 mg daily x 14 days = 28 capsules	US$ 378-504 *€- 75-150 (Price range of miltefosine depends on order volume) Total price- US$ 466.5- 589.7

*€ 1 = US$ 1.17 (as of 23 September 2020).
L-AMB is supplied under a donation programme, hence its cost is zero for recipient countries.

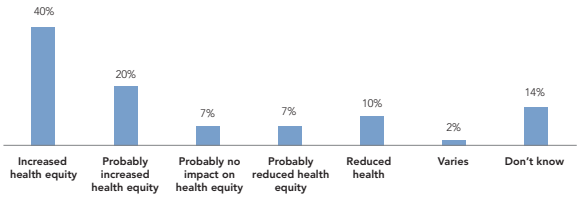
Cost effectiveness

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

Judgement	Research evidence	Additional considerations
• Favours the comparison • Probably favours the comparison • Does not favour either the intervention or the comparison • Probably favours the intervention • Favours the intervention • Varies • No included studies	No evidence identified	

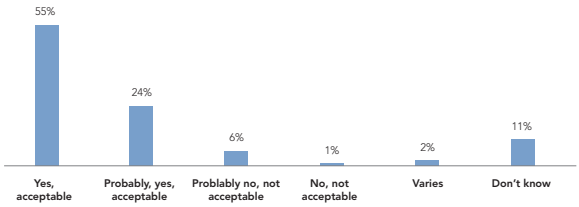
Equity

What would be the impact on health equity?

Judgement	Research evidence	Additional considerations
• Reduced • Probably reduced • Probably no impact • Probably increased • Increased • Varies • Don't know	Survey results  • 2% responded "varies" (depends on availability of treatment facilities providing combination therapy; provision of combination therapy free of cost; while shorter duration of hospitalization is associated with lower cost, availability of quality-assured miltefosine can be a challenge) • 14% responded "don't know" Interview results • Financial aspect: o Cost not an issue as both alternatives available free of cost o Any inequity will depend on donations; governmental decision • Geographical aspect: few health centres providing the treatment (applies to both treatment alternatives of L-AMB monotherapy or combination therapy with L-AMB plus miltefosine) • Contraindication in pregnant females was considered an equity issue (favouring L-AMB monotherapy)	• Combination therapy may disadvantage women of childbearing potential

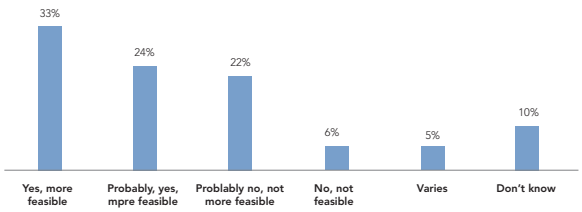
Acceptability

Is the intervention acceptable to key stakeholders?

Judgement	Research evidence	Additional considerations
• No • Probably no • Probably yes • Yes • Varies • Don't know	Survey results  • 2% responded "varies" (depends on doctor's decision; effectiveness of the combination therapy; incidence of adverse effects; information reflected to the patient by the health provider) • 2% responded "other" (non-adherence to non-supervised oral medication is higher; acceptable but treatment schedule is very long so that patients must be treated in the kala-azar HIV sentinel site) • 10% responded "don't know" Interview results Favouring combination therapy: • Shorter duration of hospitalization: generally more acceptable • Other issues related to patient beliefs: fear of intravenous injection; belief that combination therapy is more effective Favouring monotherapy: • Some patients preferred longer duration due to availability of medical supervision at the hospital • Pregnancy test: might be culturally unacceptable among single women of childbearing potential (minority of respondents) • Use of contraceptives (especially injectable): can be an issue (minority of respondents) • Adherence: concern for discontinuation of miltefosine due to side-effects (unless treatment course finished at the hospital) • Other issues related to patient beliefs: belief that oral medication will not cure them	• Combination therapy may disadvantage women of childbearing potential

Feasibility

Is the intervention feasible to implement?

Judgement	Research evidence	Additional considerations
• No • Probably no • Probably yes • Yes • Varies • Don't know	Survey results  • 5% responded "varies" (depends on the availability of infrastructure, human resources and case load; whether staff are trained) • 10% responded "don't know" Interview results Favouring combination therapy: • Longer hospitalization duration generally less feasible Favouring monotherapy: • Some patients preferred longer duration due to poor living conditions not favouring cure, chances of non-adherence (prefer to complete course of miltefosine at the centre) Additional points raised: • Availability of treatment: most mentioned no issues of drug availability; one participant mentioned low stock of L-AMB Availability data	If the donation programme cannot be ensured over the long term, combination therapy will save large amounts of vials per patient

	Miltefosine, 10mg and 50mg capsule	Liposomal Amphotericin B, 50-mg per vial (AmBisome®)
Availability	There is no donation programme and no funding to WHO for its procurement. Endemic countries have to procure it on its own	There is AmBisome® donation programme of Gilead through WHO for free supplies to high priority countries in East Africa (Ethiopia, Kenya, Somalia, Sudan, South Sudan, Uganda) and Indian subcontinent (Bangladesh, India and Nepal)
Buffer stock	None at WHO emergency stock Knight keeps some safety stock	Some 5,000 vials at WHO emergency stock
Any challenge in production and/or supplies	Increased price (3 times) Engagement of potential generic suppliers to enter in 2020	• Obtaining Import permit (when not registered) • Cold chain required (store<25°C) • Unclear status and pricing from generics who may be entering • Request for split delivery not accepted by Gilead (e.g. Brazil)

Summary of judgements

	Judgement						
Desirable effects	Trivial	Small	**Moderate**	Large		Varies	Don't know
Undesirable effects	Large	Moderate	**Small**	Trivial		Varies	Don't know
Certainty of evidence	**Very low**	Low	Moderate	High			No included studies
Values	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
Resources required	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know
Cost-effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
Equity	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	**Probably yes**	Yes		Varies	Don't know
Feasibility	No	Probably no	**Probably yes**	Yes		Varies	Don't know

Type of recommendation

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
⊙	⊙	⊙	⊙	⊙

Conclusions

Recommendation

How substantial are the desirable anticipated effects?

The WHO panel suggests liposomal Amphotericin B + Miltefosine regimen over liposomal Amphotericin B regimen for individuals with HIV-leishmaniasis coinfection in East Africa (Conditional recommendation; very-low-certainty evidence)

Remarks

- Liposomal Amphotericin B + Miltefosine regimen: liposomal Amphotericin B (up to 30 mg/kg, at 5 mg/kg on days 1, 3, 5, 7, 9, 11) + Miltefosine (100 mg/day for 28 days)
- Liposomal Amphotericin B regimen: liposomal Amphotericin B (up to 40 mg/kg, at 5 mg/kg on days 1-5, 10, 17, 24)
- 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.

Justification

Subgroup considerations

Implementation considerations

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.

Monitoring and evaluation

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	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

Research priorities

- Awareness of HIV-VL coinfection and its impact among health-care professionals in East Africa, South-East Asia and beyond.
- 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.
- 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.
- 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.
- Test of cure and for monitoring relapses are urgently needed, including improved antigen detection tests and (bio)markers to link clinical outcome, relapse and parasitological status as well as parasite resistance to medicines.
- 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.
- 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.
- 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

Outcomes	N° of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with liposomal Amphotericin B (up to 40 mg/kg, at 5 mg/kg on days 1-5, 10, 17, 24)	Risk difference with liposomal Amphotericin B (up to 30 mg/kg, at 5 mg/kg on days 1, 3, 5, 7, 9, 11) + Miltefosine (100 mg/day for 28 days)
All-cause mortality (day 86)	59 (1 RCT)	⨁⊙⊙⊙ Very low	RR 0.77 (0.14 to 4.24)	Study population	
				100 per 1,000	23 fewer per 1,000 (86 fewer to 324 more)
Clinical cure assessed with: Treatment success - clinical and parasitological examination, absence of parasites in tissue aspirate (spleen or bone marrow aspiration). Patients with negative parasitology were considered cured of VL (treatment failure = presence of parasites at the D29 assessment, or death prior to the D29 assessment, or no clinical response to treatment requiring rescue medication on or before D29 follow up: 29 days	58 (1 RCT)	⨁⊙⊙⊙ Very low	RR 1.53 (0.80 to 2.93))	Study population	
				368 per 1,000	195 more per 1,000 (74 fewer to 711 more)

Clinical cure assessed with: Treatment success - D58 treatment success was defined as: (i) being parasite free at D29 and no recurrence of symptoms by D58 or (ii) being parasite free at D58 after extended treatment. Thus, D58 failures were patients who (i) received rescue treatment prior to, or at, the D58 visit, or (ii) were confirmed to be parasite positive at D58 or (iii) died up to D58. A patient with detectable parasites at D29 who then received extended treatment would be a treatment failure at D29 but a success at D58 if no parasites were detected at D58 follow up: 58 days	56 (1 RCT)	⨁⨁⊙⊙ Low	RR 1.77 (1.08 to 2.90)	Study population	
				474 per 1,000	365 more per 1,000 (38 more to 900 more)
Relapse follow up: 390 days	51 (1 RCT)	⨁⊙⊙⊙ Very low	RR 0.78 (0.43 to 1.42)	Study population	
				529 per 1,000	116 fewer per 1,000 (302 fewer to 222 more)
Relapse-free survival follow up: 390 days	51 (1 RCT)	⨁⊙⊙⊙ Very low	RR 1.13 (0.62 to 2.04)	Study population	
				471 per 1,000	61 more per 1,000
Treatment adherence follow up: 58 days	59 (1 RCT)	⨁⨁⊙⊙ Low[a,c]	RR 1.26 (0.89 to 1.80)	Study population	
				650 per 1,000	169 more per 1,000 (72 fewer to 520 more)
Adverse events (any cause) follow up: 86 days	58 (1 RCT)	⨁⨁⊙⊙ Low[a,c]	RR 1.00 (0.92 to 1.08)	Study population	
				0 per 1,000	0 fewer per 1,000 (0 fewer to 0 fewer)
Serious adverse events - due to any cause follow up: 86 days	58 (1 RCT)	⨁⊙⊙⊙ Very low[a,b]	RR 1.95 (0.46 to 8.30)	Study population	
				105 per 1,000	100 more per 1,000 (57 fewer to 768 more)
Follow-up of patients	59 (1 RCT)	⨁⨁⊙⊙ Low[a,c]	RR 1.12 (0.88 to 1.43)	Study population	
				800 per 1,000	96 more per 1,000 (96 fewer to 344 more)

[a] Downgraded one level for limitations in study design.

[b] Downgraded two levels for serious imprecision: few events and confidence intervals that encompass no effect, a potential benefit, and a potential harm associated with the intervention; the study was not powered to detect a difference between groups.

[c] Downgraded one level for imprecision: few events; the study was not powered to detect a difference between groups.s

Appendix B.2 Population, intervention, comparator and outcomes (PICO) 1: South-East Asia

Should liposomal Amphotericin B [L-AMB] (up to 30 mg/kg, at 5 mg/kg on days 1, 3, 5, 7, 9, 11) + miltefosine (100 mg/day for 14 days) vs L-AMB (up to 40 mg/kg, at 5 mg/kg on days 1-4, 8, 10, 17, 24) be used for visceral leishmaniasis (VL) patients co-infected with HIV in South-East Asia?

PICO question

Population	Individuals with HIV–VL coinfection in South-East Asia
Intervention	L-AMB (up to 30 mg/kg, at 5 mg/kg on days 1, 3, 5, 7, 9, 11) + miltefosine (100 mg/day for 14 days)
Comparison	L-AMB (up to 40 mg/kg, at 5 mg/kg on days 1–4, 8, 10, 17, 24)
Main outcomes	All-cause mortality; clinical cure; relapse-free survival; relapse; treatment adherence; adverse events - any cause; serious adverse events (any cause)
Setting	South-East Asia
Perspective	
Background	The WHO recommendation (2010) to use L-AMB (up to 40 mg/kg, at 5 mg/kg on days 1–5, 10, 17, 24) in the treatment of VL in HIV-co-infected patients emerged from the evidence in Mediterranean countries where VL is caused by *L. infantum*. This lacked region-specific treatment recommendations such as in South Asia, where VL is caused by *L. donovani*, a different parasite species. New evidence is available from a randomized controlled trial in South Asia.
Conflict of interests	None

Assessment

Desirable effects

How substantial are the desirable anticipated effects?

Judgement	Research evidence	Additional considerations
o Trivial o Small • Moderate o Large o Varies o Don't know	*See Web annex 1: Systematic review*	• Available evidence is from patients with advanced AIDS stage

Undesirable effects

How substantial are the undesirable anticipated effects?

Judgement	Research evidence	Additional considerations
o Trivial o Small • Moderate o Large o Varies o Don't know	*See Web annex 1: Systematic review*	

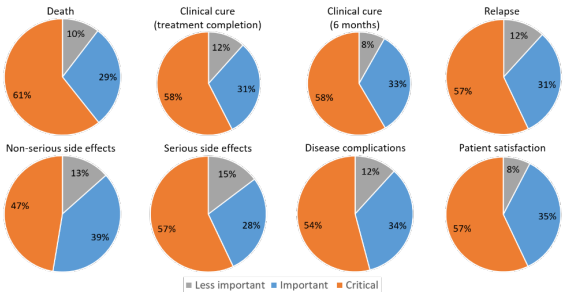
Certainty of evidence

What is the overall certainty of the evidence of effects?

Judgement	Research evidence	Additional considerations
• Very low o Low o Moderate o High o No included studies		

Values

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

Judgement	Research evidence	Additional considerations
o Important uncertainty or variability o Possibly important uncertainty or variability • Probably no important uncertainty or variability o No important uncertainty or variability	Survey results 	
	Interview results Generally consistent with survey results • Mortality, clinical cure at 6 months, relapse, serious side-effects, disease complications: generally valued as critical/important • Clinical cure at treatment completion, patient satisfaction: rating varied • Non-serious side-effects: generally valued as less important	

Balance of effects

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

Judgement	Research evidence	Additional considerations
o Favours the comparison o Probably favours the comparison o Does not favour either the intervention or the comparison • Probably favours the intervention o Favours the intervention o Varies o Don't know		

Resources required

How large are the resource requirements (costs)?

Judgement	Research evidence	Additional considerations
o Large costs o Moderate costs o Negligible costs and savings o Moderate savings o Large savings o Varies o Don't know		

	East Africa		Indian subcontinent	
Type of therapy	Treatment regimen	Price per VL treatment	Treatment regimen	Price per VL treatment
Monotherapy	Total dose @40 mg/kg body weight for 35 kg patients = 28-35 vials	US$ 504-630	Total dose @40 mg/kg body weight for 35 kg patients = 28-35 vials	US$ 504-630
Combination therapy	AmBisome®- Total dose @30 mg/kg body weight for 35 kg patients = 21-28 vials Miltefosine- Total dose@100 mg daily x 28 days = 56 capsules	US$ 378- 504 *€ - 75-150 (Price range of miltefosine depends on order volume) Total price- US$ 466.5- 589.7	AmBisome®- Total dose @30 mg/kg body weight for 35 kg patients = 21-28 vials Miltefosine- Total dose@100 mg daily x 14 days = 28 capsules	US$ 378-504 *€- 75-150 (Price range of miltefosine depends on order volume) Total price- US$ 466.5- 589.7

*€ 1 = US$ 1.17 (as of 23 September 2020).
L-AMB is supplied under a donation programme, hence its cost is zero for recipient countries.

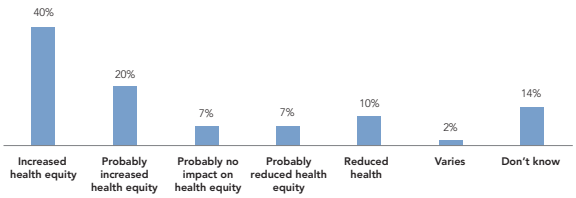
Cost effectiveness

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

Judgement	Research evidence	Additional considerations
o Favours the comparison o Probably favours the comparison o Does not favour either the intervention or the comparison o Probably favours the intervention o Favours the intervention o Varies • No included studies	No evidence identified	

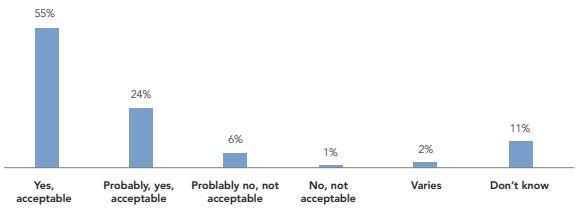
Equity

What would be the impact on health equity?

Judgement	Research evidence	Additional considerations
o Reduced o Probably reduced • Probably no impact o Probably increased o Increased o Varies o Don't know	Survey results  • 2% responded "varies" (depends on availability of treatment facilities providing combination therapy; provision of combination therapy free of cost; while shorter duration of hospitalization is associated with lower cost, availability of quality assured miltefosine can be a challenge) • 14% responded "don't know" Interview results • Financial aspect: o Cost not an issue as both alternatives available free of cost o Any inequity will depend on donations; governmental decision • Geographical aspect: few health centres providing the treatment (applies to both alternatives) • Contraindication in pregnant females was considered as equity issue (favouring monotherapy)	

Acceptability

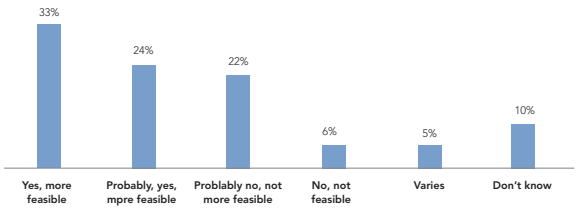
Is the intervention acceptable to key stakeholders?

Judgement	Research evidence	Additional considerations
o No o Probably no • Probably yes o Yes o Varies o Don't know	Survey results  • 2% responded "varies" (depends on doctor's decision; effectiveness of the combination therapy; incidence of adverse effects; information reflected to the patient by thehealth provider) • 2% responded "other" (non-adherence to non -supervised oral medication is higher; acceptable but treatment schedule is very long so that patients must be treated in the kala-azar HIV sentinel site) • 10% responded "don't know" Interview results Favouring combination therapy: • Shorter duration of hospitalization: generally more acceptable • Other issues related to patient beliefs: fear of IV; belief that combination therapy is more effective	• Combination therapy may disadvantage women of childbearing potential

	Favouring monotherapy: • Some patients preferred longer duration due to availability of medical supervision at the hospital • Pregnancy test: might be culturally unacceptable among single women of childbearing potential (minority of respondents) • Use of contraceptives (especially injectable): can be an issue (minority of respondents) • Adherence: concern for discontinuation of miltefosine due to side-effects (unless treatment course finished at the hospital) • Other issues related to patient beliefs: belief that oral medication will not cure them	

Feasibility

Is the intervention feasible to implement?

Judgement	Research evidence	Additional considerations
o No o Probably no • Probably yes o Yes o Varies o Don't know	Survey results  • 5% responded "varies" (depends on the availability of infrastructure, human resources and case load; whether staff are trained) • 10% responded "don't know" Interview results Favouring combination therapy: • Longer hospitalization duration generally less feasible Favouring monotherapy: • Some patients preferred longer duration due to poor living conditions not favouring cure, chances of non-adherence (prefer to complete course of miltefosine at the centre) Additional points raised: • Availability of treatment: most mentioned no issues of drug availability; one participant mentioned low stock of L-AMB Availability data Miltefosine, 10mg and 50mg capsule Availability: There is no donation programme and no funding to WHO for its procurement. Endemic countries have to procure it on its own Buffer stock: None at WHO emergency stock Knight keeps some safety stock Any challenge in production and/or supplies: Increased price (3 times) Engagement of potential generic suppliers to enter in 2020 Liposomal Amphotericin B, 50-mg per vial (AmBisome®) Availability: There is AmBisome® donation programme of Gilead through WHO for free supplies to high priority countries in East Africa (Ethiopia, Kenya, Somalia, Sudan, South Sudan, Uganda) and Indian subcontinent (Bangladesh, India and Nepal) Buffer stock: Some 5,000 vials at WHO emergency stock Any challenge in production and/or supplies: • Obtaining Import permit (when not registered) • Cold chain required (store<25°C) • Unclear status and pricing from generics who may be entering • Request for split delivery not accepted by Gilead (e.g. Brazil)	If the donation programme cannot be ensured over the long term, combination therapy will save large amounts of vials per patient

Summary of judgements

	Judgement						
Desirable effects	Trivial	Small	**Moderate**	Large		Varies	Don't know
Undesirable effects	Large	Moderate	**Small**	Trivial		Varies	Don't know
Certainty of evidence	**Very low**	Low	Moderate	High			No included studies
Values	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
Resources required	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know
Cost-effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
Equity	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	**Probably yes**	Yes		Varies	Don't know
Feasibility	No	Probably no	**Probably yes**	Yes		Varies	Don't know

Type of recommendation

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
⊙	⊙	⊙	⊙	⊙

Conclusions

Recommendation

The WHO panel suggests L-AMB + miltefosine rather than L-AMB monotherapy for individuals with VL–HIV coinfection in South-East Asia (conditional recommendation; very-low-certainty evidence)

Remarks

- L-AMB + miltefosine regimen: L-AMB (up to 30 mg/kg, at 5 mg/kg on days 1, 3, 5, 7, 9, 11) + miltefosine (100 mg/day for 14 days)
- L-AMB regimen: L-AMB (up to 40 mg/kg, at 5 mg/kg on days 1–4, 8, 10, 17, 24)
- Determine the HIV status of patients diagnosed with VL. Screen routinely for TB at VL diagnosis and conduct follow-up.
- Consider extending therapy (same therapy for one additional course, based on evidence from trials in Ethiopia) in 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) 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 childbearing potential before administering miltefosine.

Justification

Subgroup considerations

Implementation considerations

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; and
- improve coordination among HIV, VL and related programmes, such as for pharmacovigilance, TB and vector control.

Monitoring and evaluation

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

Research priorities

- Awareness of HIV–VL coinfection and its impact among health-care professionals in East Africa, South-East Asia and beyond.
- 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.
- Given the very low certainty of the currently available evidence, further clinical trials of the use of combination therapy in VL–HIV coinfection remain 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 are 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.
- 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.
- Test of cure and for monitoring relapses are urgently needed, including improved antigen detection tests and (bio)markers to link clinical outcome, relapse and parasitological status as well as parasite resistance to medicines.
- Long-term follow-up of treated patients will help to understand the development of post-kala-azar dermal leishmaniasis.
- 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.
- 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.
- 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.

Outcomes	N° of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with L-AMB (up to 40 mg/kg, at 5 mg/kg on days 1–4, 8, 10, 17, 24)	Risk difference with L-AMB (up to 30 mg/kg, at 5 mg/kg on days 1, 3, 5, 7, 9, 11) + miltefosine (100 mg/day for 14 days)
All-cause mortality follow up: 58 days	150 (1 RCT)	⨁⨁⊙⊙ Low[a,b]	RR 0.50 (0.05 to 5.40)	Study population	
				27 per 1000	13 fewer per 1000 (25 fewer to 117 more)
All-cause mortality follow up: 210 days	150 (1 RCT)	⨁⨁⊙⊙ Low[a,b]	RR 0.20 (0.02 to 1.67)	Study population	
				67 per 1000	53 fewer per 1000 (65 fewer to 45 more)
All-cause mortality follow up: 390 days	150 (1 RCT)	⨁⨁⊙⊙ Low[a,b]	RR 0.17 (0.02 to 1.35)	Study population	
				80 per 1000	66 fewer per 1000 (78 fewer to 28 more)
Clinical cure follow up: 29 days	150 (1 RCT)	⨁⨁⊙⊙ Low[c,d]	RR 1.04 (0.98 to 1.11)	Study population	
				947 per 1000	38 more per 1000 (19 fewer to 104 more)

Relapse-free survival assessed with: Being alive and disease free (defined as absence of signs and symptoms of VL or if symptomatic, a negative parasitological assessment by tissue aspirate) at day 210 follow up: 210 days	150 (1 RCT)	⊕⊕⊙⊙ Low[c,d]	RR 1.13 (1.01 to 1.25)	Study population	
				853 per 1000	111 more per 1000 (9 more to 213 more)
Relapse-free survival assessed with: Relapse-free survival at 12 months as defined as: the patient is alive and disease-free (defined as absence of signs and symptoms of VL or if symptomatic, a negative parasitological assessment by tissue aspirate) from day 210 (if initially cured) and remains disease-free until the last follow up assessment (i.e. day 390). follow up: 390 days	150 (1 RCT)	⊕⊕⊙⊙ Low[c,d]	RR 1.05 (0.91 to 1.21)	Study population	
				813 per 1000	41 more per 1000 (73 fewer to 171 more)
Relapse follow up: 210 days	150 (1 RCT)	⊕⊙⊙⊙ Very low[b,c]	RR 0.50 (0.05 to 5.40)	Study population	
				27 per 1000	13 fewer per 1000 (25 fewer to 117 more)
Relapse follow up: 390 days	150 (1 RCT)	⊕⊙⊙⊙ Very low[b,c]	RR 2.25 (0.72 to 6.99)	Study population	
				53 per 1000	67 more per 1000 (15 fewer to 319 more)
Treatment adherence – not reported					
Adverse events – any cause follow up: 58 days	150 (1 RCT)	⊕⊕⊙⊙ Low[c,d]		Intervention group: 324 events in 75 participants Control group: 300 events in 75 participants	
Serious adverse events (any cause) follow up: 58 days	150 (1 RCT)	⊕⊙⊙⊙ Very low[b,c]	RR 0.75 (0.27 to 2.06)	Study population	
				107 per 1000	27 fewer per 1000 (78 fewer to 113 more)

[a] Note that this is an open-label study; however, we have not downgraded for risk of bias..

[b] Downgraded two levels for serious imprecision: few events and confidence intervals that encompass no effect, a potential benefit, and a potential harm associated with the intervention.

[c] Downgraded one level for limitations in study design: due to limitations in the study design and execution.

[d] Downgraded one level for imprecision: few events; the study was not powered to detect a difference between groups.

Appendix B.3 Population, intervention, comparator and outcomes (PICO) 2: East Africa

Maintenance therapy/secondary prophylaxis

Should pentamidine vs no intervention be used for secondary prophylaxis after the first episode of visceral leishmaniasis (VL) in HIV–VL co-infected patients?

PICO question

Population	Secondary prophylaxis after the first episode of VL in HIV–VL co-infected patients
Intervention	Pentamidine
Comparison	No intervention
Main outcomes	All-cause mortality; relapse; relapse-free survival; treatment adherence; serious adverse events; adverse events; follow-up of participants; patient satisfaction
Setting	East Africa
Perspective	
Background	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 liposomal amphotericin B [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]) every 3–4 weeks. Data from studies in Europe suggest that a CD4 cell count > 100 cells/mm3 at VL diagnosis reduces the odds of relapse. New evidence has emerged from anthroponotic transmission of L. donovani in endemic areas of East Africa.
Conflict of interests	None. One member of the Guideline Development Group who authored one of the evidence studies under discussions did not participate in the recommendations.

Assessment

Desirable effects

How substantial are the desirable anticipated effects?

Judgement	Research evidence	Additional considerations
o Trivial o Small • Moderate o Large o Varies o Don't know	*See Web annex 1: Systematic review*	• Systematic review on secondary prophylaxis from Europe • Time to relapse is longer in Europe • Given the anthroponotic nature there might be benefit in terms of infectivity • Pentamidine helps with preventing pneumocystis jiroveci infection • In term of prevention of drug resistance, one can also favour the use of a drug such as pentamidine that is not used to treat relapses • One of the reasons to opt for pentamidine was that it was argued not to use any of the first-line drugs for secondary prophylaxis in areas with anthroponotic VL • Use of the same drugs repeatedly and over the long term (as required for secondary prophylaxis) increases resistance to the limited antileishmanial drugs

Undesirable effects

How substantial are the undesirable anticipated effects?

Judgement	Research evidence	Additional considerations
o Large o Moderate • Small o Trivial o Varies o Don't know	*See Web annex 1: Systematic review*	

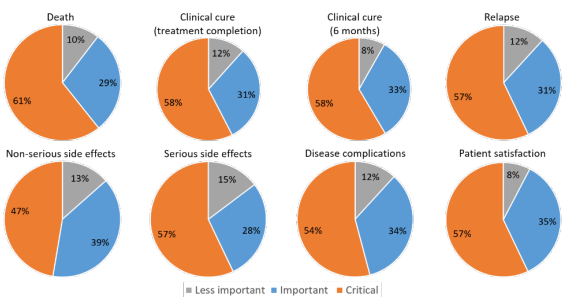
Certainty of evidence

What is the overall certainty of the evidence of effects?

Judgement	Research evidence	Additional considerations
• Very low o Low o Moderate o High o No included studies		

Values

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

Judgement	Research evidence	Additional considerations
o Important uncertainty or variability o Possibly important uncertainty or variability • Probably no important uncertainty or variability o No important uncertainty or variability	Survey results 	

	Interview results Generally consistent with survey results • Mortality, clinical cure at 6 months, relapse, serious side-effects, disease complications: generally valued as critical/important • Clinical cure at treatment completion, patient satisfaction: rating varied • Non-serious side-effects: generally valued as less important	

Balance of effects

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

Judgement	Research evidence	Additional considerations
o Favours the comparison o Probably favours the comparison o Does not favour either the intervention or the comparison • Probably favours the intervention o Favours the intervention o Varies o Don't know		

Resources required

How large are the resource requirements (costs)?

Judgement	Research evidence	Additional considerations
o Large costs • Moderate costs o Negligible costs and savings o Moderate savings o Large savings o Varies o Don't know	<table><tr><th></th><th>Dose for secondary prophylaxis</th><th>Consumption per patient per setting</th><th>Unit cost per vial</th><th>Total cost/patient/year</th></tr><tr><td>Pentamidine, 300 mg per vial</td><td>4 mg/kg once monthly x 12 doses</td><td>1 vial</td><td>Euro[a] 1.3* (USD1.52)</td><td>USD 18.25</td></tr></table> [a] 1 Euro = 1.17 USD (as of 30 September 2020). * This medicine is donated to WHO for the human African trypanosomiasis programme. There is no agreed donation for leishmaniasis. This price is used for WHO internal accounting purposes. The actual cost of medicine could be several times higher in the market, if no donation is received.	Cost could also vary by context • Patient travel to receive the treatment

Cost effectiveness

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

Judgement	Research evidence	Additional considerations
o Favours the comparison o Probably favours the comparison o Does not favour either the intervention or the comparison o Probably favours the intervention o Favours the intervention o Varies • No included studies	No evidence identified	• Likely to be cost-saving due to prevention of recurrent infection and associated morbidity and mortality

Equity What would be the impact on health equity?		
Judgement	Research evidence	Additional considerations
o Reduced o Probably reduced o Probably no impact • Probably increased o Increased o Varies o Don't know	No evidence identified	• Secondary prophylaxis is given in other settings • Access to health care through visit to health centres
Acceptability Is the intervention acceptable to key stakeholders?		
Judgement	Research evidence	Additional considerations
o No o Probably no • Probably yes o Yes o Varies o Don't know	No evidence identified	
Feasibility Is the intervention feasible to implement?		
Judgement	Research evidence	Additional considerations
o No o Probably no • Probably yes o Yes o Varies o Don't know	No evidence identified	

Summary of judgements

	Judgement						
Desirable effects	Trivial	Small	**Moderate**	Large		Varies	Don't know
Undesirable effects	Large	Moderate	**Small**	Trivial		Varies	Don't know
Certainty of evidence	**Very low**	Low	Moderate	High			No included studies
Values	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	**Probably favours the intervention**	Favours the intervention	Varies	Don't know
Resources required	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
Cost-effectiveness	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	**No included studies**
Equity	Reduced	Probably reduced	Probably no impact	**Probably increased**	Increased	Varies	Don't know
Acceptability	No	Probably no	**Probably yes**	Yes		Varies	Don't know
Feasibility	No	Probably no	**Probably yes**	Yes		Varies	Don't know

Type of recommendation

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
⊙	⊙	⊙	⊕	⊙

Conclusions

Recommendation

The WHO panel suggests using secondary prophylaxis after the first episode of VL in HIV–VL co-infected patients in East Africa (conditional recommendation; very-low-certainty evidence).

Remarks

- Secondary prophylaxis is recommended in particular for patients at higher risk of relapse (e.g. patients not on antiretroviral therapy, 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.
- 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 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 > 350 cells/mm3 or an HIV viral load is undetectable for at least 6 months and there is no evidence of VL relapse.
- When choosing a drug, 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 for drug resistance.

Justification

Subgroup considerations

Implementation considerations

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; and
- improve coordination among HIV, VL and related programmes, such as for pharmacovigilance, TB and vector control.

Monitoring and evaluation

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

Research priorities

- Further evidence is required to establish the criteria for use of a drug for secondary prophylaxis.
- Evidence from trials comparing efficacy and safety of different regimens for secondary prophylaxis in East Africa is needed.
- 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.
- 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.

Outcomes	N° of participants (studies) Follow up	Certainty of the evidence (GRADE)	Impact
All-cause mortality follow up: range 12 months to 24 months	0 (2 observational studies)	⨁⊙⊙⊙ Very low[a,b]	At one year follow up, one study reported that 5/29 (17%) participants (with < 200/µL CD4 cells at baseline) died. At two years follow-up, one study reported that 5/74 (7%) participants died.
Relapse follow up: 12 months	0 (1 observational study))	⨁⊙⊙⊙ Very low[c,d]	12/29 (41%) participants (with < 200/µL CD4 cells at baseline) relapsed (two patients that relapsed later died).
Relapse follow up: 24 months	0 (1 observational study)	⨁⊙⊙⊙ Very low[c,e]	20/74 (27%) participants relapsed.
Relapse-free survival follow up: 6 months	0 (1 observational study))	⨁⊙⊙⊙ Very low[c,e]	The estimated probability of relapse free survival at the end of 6 months was 79% (95% CI: 67–87%)
Relapse-free survival follow up: 12 months	0 (1 observational study)	⨁⊙⊙⊙ Very low[c,e]	The estimated probability of relapse free survival at the end of 12 months was 71% (95% CI: 59–80%)
Treatment adherence follow up: 12 months	0 (2 observational studies)	⨁⊙⊙⊙ Very low[a,b]	In one study, 41/74 (55%) completed the follow-up taking at least 11/12 doses without experiencing relapse, death or drug-related serious adverse events. 29 patients discontinued pentamidine permanently; 15 (20.3%) because of relapse, 7 (9.5%) were lost to follow-up, 5 (6.8%) died, one patient had to stop due to hyperglycaemia, and another patient refused to take the study drug. The other study found that 76% (22/29) of patients had 100% compliance for the monthly pentamidine infusions.
Serious adverse events follow up: 12 months	0 (2 observational studies)	⨁⊙⊙⊙ Very low[a,b]	One study reported 21 serious adverse events in 17 (23%) of the 74 patients; and that two events may have been related to pentamidine (renal failure in two patients hospitalized with pneumonia). The other study reported that 8/29 (28%) patients experienced serious adverse events. One death due to acute renal failure in a patient with multiple coexisting diseases that can affect renal status was considered possibly related to pentamidine.
Adverse events follow up: 12 months	0 (1 observational study)	⨁⊙⊙⊙ Very low[c,e]	42 study-drug related adverse events in 30 (41%) of the 74 study participants.
Follow-up of participants follow up: 24 months	0 (2 observational studies)	⨁⊙⊙⊙ Very low[a,b]	One study reported 7/74 (9.5%) lost to follow-up after one year, and 10/74 (14%) after two years. The other study reported all patients were followed-up to the end of the study (n=29).
Patient satisfaction - not measured			

[a] Evidence is considered very-low-certainty, as data are from two non-comparative studies.

[b] 103 participants from two prospective cohort studies.

[c] Evidence is considered very-low-certainty, as data are from one non-comparative study.

[d] 29 participants from one prospective cohort study.

[e] 74 participants from one prospective cohort study.

Appendix B.4 Population, intervention, comparator and outcomes (PICO) 2: South-East Asia

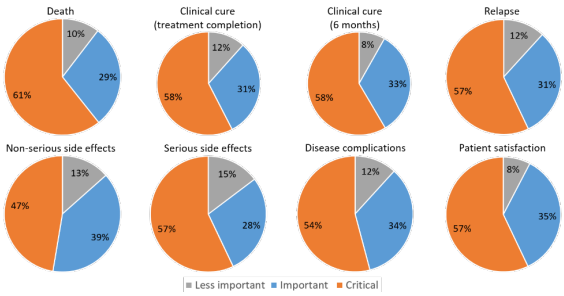
Maintenance therapy/secondary prophylaxis

Should liposomal amphotericin B (L-AMB) or amphotericin B (AMB) deoxycholate vs no intervention be used for secondary prophylaxis after the first episode of visceral leishmaniasis (VL) in HIV–VL co-infected patients?

PICO question

Population	Secondary prophylaxis after the first episode of VL in HIV–VL co-infected patients
Intervention	L-AMB or AMB deoxycholate
Comparison	No intervention
Main outcomes	All-cause mortality; relapse; relapse-free survival; treatment adherence; serious adverse events; adverse events; follow-up of patients; patient satisfaction
Setting	Southeast Asia
Perspective	
Background	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]) every 3–4 weeks. Data from studies in Europe suggest that a CD4 cell count > 100 cells/mm3 at VL diagnosis reduces the odds of relapse. Very limited evidence is available from anthroponotic transmission of L. donovani in endemic areas of South-East Asia. This evidence is considered very uncertain.
Conflict of interests	

Assessment

Desirable effects How substantial are the desirable anticipated effects?		
Judgement	Research evidence	Additional considerations
o Trivial o Small • Moderate o Large o Varies o Don't know	*See Web annex 1: Systematic review*	
Undesirable effects How substantial are the undesirable anticipated effects?		
Judgement	Research evidence	Additional considerations
o Large o Moderate • Small o Trivial o Varies o Don't know	*See Web annex 1: Systematic review*	
Certainty of evidence What is the overall certainty of the evidence of effects?		
Judgement	Research evidence	Additional considerations
• Very low o Low o Moderate o High o No included studies		
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
Judgement	Research evidence	Additional considerations
o Important uncertainty or variability o Possibly important uncertainty or variability • Probably no important uncertainty or variability o No important uncertainty or variability	Survey results 	
	Interview results Generally consistent with survey results • Mortality, clinical cure at 6 months, relapse, serious side-effects, disease complications: generally valued as critical/important • Clinical cure at treatment completion, patient satisfaction: rating varied • Non-serious side-effects: generally valued as less important	

Balance of effects

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

Judgement	Research evidence	Additional considerations
o Favours the comparison o Probably favours the comparison o Does not favour either the intervention or the comparison • Probably favours the intervention o Favours the intervention o Varies o Don't know		

Resources required

How large are the resource requirements (costs)?

Judgement	Research evidence	Additional considerations
o Large costs • Moderate costs o Negligible costs and savings o Moderate savings o Large savings o Varies o Don't know		

	Dose for secondary prophylaxis	Consumption per patient per setting	Unit cost per vial	Total cost/patient/year
Liposomal amphotericin B, 50 mg per vial	1 mg/kg once monthly x 12	1 vial	USD 18*	USD 216
Amphotericin B deoxycholate, 50 mg per vial	1 mg/kg once monthly x 12	1 vial	USD 7.5**	USD 90

1 Euro = 1.17 USD (as of 30 September 2020).
*WHO preferential price; medicine donated through WHO.
** UNICEF. Sources and prices of selected medicines for children, 2nd ed., 2010.

Cost effectiveness

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

Judgement	Research evidence	Additional considerations
o Favours the comparison o Probably favours the comparison o Does not favour either the intervention or the comparison o Probably favours the intervention o Favours the intervention o Varies • No included studies	No evidence identified	• Likely to be cost-saving due to prevention of recurrent infection and associated morbidity and mortality

Equity What would be the impact on health equity?		
Judgement	Research evidence	Additional considerations
o Reduced o Probably reduced o Probably no impact • Probably increased o Increased o Varies o Don't know	No evidence identified	
Acceptability Is the intervention acceptable to key stakeholders?		
Judgement	Research evidence	Additional considerations
o No o Probably no • Probably yes o Yes o Varies o Don't know	No evidence identified	
Feasibility Is the intervention feasible to implement?		
Judgement	Research evidence	Additional considerations
o No o Probably no • Probably yes o Yes o Varies o Don't know	No evidence identified	

Summary of judgements

	Judgement						
Desirable effects	Trivial	Small	**Moderate**	Large		Varies	Don't know
Undesirable effects	Large	Moderate	**Small**	Trivial		Varies	Don't know
Certainty of evidence	**Very low**	Low	Moderate	High			No included studies
Values	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	**Probably favours the intervention**	Favours the intervention	Varies	Don't know
Resources required	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
Cost-effectiveness	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	**No included studies**
Equity	Reduced	Probably reduced	Probably no impact	**Probably increased**	Increased	Varies	Don't know
Acceptability	No	Probably no	**Probably yes**	Yes		Varies	Don't know
Feasibility	No	Probably no	**Probably yes**	Yes		Varies	Don't know

Type of recommendation

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
⊙	⊙	⊙	⊕	⊙

Conclusions

Recommendation

The WHO panel suggests using secondary prophylaxis after the first episode of VL in HIV–VL co-infected patients in Southeast Asia (conditional recommendations; very-low-certainty evidence).

Remarks

- 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.
- 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 at 3–5 mg/kg per day every 3–4 weeks.
- 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.
- When choosing a drug, 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 for drug resistance.

Justification

Subgroup considerations

Implementation considerations

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; and Improve coordination among HIV, VL and related programmes, such as for pharmacovigilance, TB and vector control.

Monitoring and evaluation

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

Research priorities

- 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.

Outcomes	N° of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no intervention	Risk difference with L-AMB or AMB deoxycholate
All-cause mortality follow up: 12 months	51 (1 observational study)	⨁⊙⊙⊙ Very low[a,b]	HR 0.09 (0.03 to 0.31)	Low	
				0 per 1000	-- per 1000 (-- to --)
Relapse follow up: 6 months	51 (1 observational study)	⨁⊙⊙⊙ Very low[b,c]	RR 0.02 (0.00 to 0.38)	Study population	
				750 per 1000	735 fewer per 1000 (750 fewer to 465 fewer)
Relapse follow up: 12 months	51 (1 observational study)	⨁⊙⊙⊙ Very low[b,c]	RR 0.02 (0.00 to 0.38)	Study population	
				750 per 1000	735 fewer per 1000 (750 fewer to 465 fewer)
Relapse-free survival follow up: 12 months	51 (1 observational study)	⨁⊙⊙⊙ Very low[b,c]	RR 3.78 (1.95 to 7.33)	Study population	
				250 per 1000	695 more per 1000 (238 more to 1583 more)
Treatment adherence - not measured					
Serious adverse events - not measured					
Adverse events - not measured					
Follow-up of patients - not measured					
Patient satisfaction - not measured					

[a] Retrospective cohort study with serious risk of selection bias.

[b] 51 participants from one study.

[c] Retrospective cohort study with serious risk of selection bias and serious risk of bias due to confounding.

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