



Emerging Therapeutic Strategies for Visceral Leishmaniasis: A Narrative Review of AI-Guided Drug Discovery, Immunotherapy, and Nanomedicine

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Abstract

Visceral leishmaniasis (VL), also known as kala-azar, is a protozoan infection that the World Health Organization classifies as a major neglected tropical disease. Driven by distinct Leishmania parasites and transmitted via sandfly vectors, this pathogen can induce profound systemic inflammation, progressive hepatosplenomegaly, and fatal organ damage, with mortality rates approaching 100% if left untreated. Key factors driving this devastating clinical reality include VL's exceptional capacity for evading the immune system and the severe toxicity of conventional anti-leishmanial therapies. This review paper focuses on the molecular mechanisms underlying VL infection and highlights both current standards of care and emerging therapeutic avenues, including AI-designed therapeutics, immunotherapies, and nanomedicines. By mapping out how these novel interventions target the host-parasite interface, I aim to inspire future therapeutic development and improve clinical outcomes for this critically neglected global disease.

Introduction

What is a Neglected Tropical Disease?

Neglected Tropical Diseases (NTDs) are a group of 21 infectious diseases caused by various pathogens, including viruses, bacteria, parasites, fungi, and toxins, that disproportionately affect impoverished communities in tropical regions (Centers for Disease Control). Compared to other high-profile global health threats such as HIV or Malaria, NTDs face low levels of investment from industrial and governmental programs alike. The lack of funds and research exists despite the fact that over a billion individuals have suffered from NTDs (The END Fund). Beyond the direct health effects, NTDs have been notorious for impacting the quality of life, education, and economic stability of entire communities that have been affected. On an individual level, persistent infection may lead to chronic health complications, disability, and an inability to participate in school or gain employment.

Because of the disease's severity and the stark gap between its burden and current treatment, leishmaniasis stands out among the other 21 NTDs. Leishmaniasis is a group of infectious parasite-borne diseases spread by infected female sandflies (Cleveland Clinic). The disease manifests in three clinical forms: cutaneous leishmaniasis (skin bumps or ulcers), mucosal leishmaniasis (ulcers in orifices), and visceral leishmaniasis (high fever, weight loss,

and abdominal swelling). Visceral Leishmaniasis is the most severe and fatal form (Van Dijk et al.).

Although there is a significant burden associated with visceral leishmaniasis, a significant gap remains between understanding the biological challenges of the disease and developing specific therapeutic strategies with the ability to address them. Current treatments are largely repurposed forms of chemotherapy. Drug repurposing is commonly used for underfunded diseases like visceral leishmaniasis because pharmaceutical companies do not visualize the economic payoff needed to justify advancing a drug through the development pipeline. Current treatments also face limitations related to toxicity, resistance, administration, and accessibility, while the parasite can survive within host cells. Therefore, emerging therapeutic approaches are needed to address the biological complexity of visceral leishmaniasis and overcome the practical barriers that currently limit treatment in endemic regions. This review specifically explores how AI-guided drug discovery, immunotherapy, and nanomedicine may help address these limitations and expand the therapeutic landscape of VL.

What is Visceral Leishmaniasis?

Parasites of the genus *Leishmania* cause Leishmaniasis, which is commonly transmitted to humans by bites from infected female phlebotomine sand flies (Shaw). Leishmaniasis has three clinical forms: cutaneous, mucocutaneous, and visceral. The infecting species and the host's immune response determine the specific form (Georgiadou et al.). Visceral leishmaniasis (VL), or commonly referred to as kala-azar ("black fever"), is the most severe form of the disease. The disease occurs when either *Leishmania donovani* or *Leishmania infantum* parasites enter the host's skin and then circulate through the reticuloendothelial system (networks of immune cells that defend against infection and clear cellular debris), infecting macrophages in the spleen, liver, and even bone marrow (Georgiadou et al.). Clinically, VL commonly manifests as irregular high fevers, extreme enlargement of the spleen and liver (hepatosplenomegaly), excessive weight loss, and pancytopenia, a blood condition that leads to low counts of all three main types of blood cells, leading to anemia, weakness, and susceptibility to secondary infections (Costa et al.). When left untreated, VL is fatal in over 95% of cases, usually within 2 years of symptoms (Yeshaw et al.). Unlike other skin-limited forms of leishmaniasis, VL spreads systemically and evades the immune system. This unique combination makes early diagnosis and treatment critical.

Epidemiology

Historically, VL cases have clustered into three main endemic areas: South Asia (India, Bangladesh, and Nepal), East Africa (Sudan, South Sudan, Ethiopia, Kenya, and Somalia), and South America (Brazil). As of 2024, around 85% of reported cases were in seven nations: Brazil, Ethiopia, India, Kenya, Somalia, South Sudan, and Sudan (Geto et al.). Global case counts

have declined in recent years, largely due to successful elimination programs in South Asia. In fact, Bangladesh became the first country to be validated for eliminating VL as a public health issue in 2023 (World Health Organization). Despite steps in the right direction, VL remains a global public health concern since transmission is largely concentrated in regions with substantial poverty, lacking healthcare infrastructure, and overall barriers to diagnosis and treatment. The disease leads to an estimated 50,000 to 90,000 new cases annually. 73% of the global caseload is found in East Africa, where 50% of those cases are in children under the age of 15 (Geto et al.). Additionally, population displacement, conflict, and environmental changes in these areas disrupt disease control efforts and increase the vulnerability of the endemic communities. The current epidemiology of VL reflects both meaningful progress towards elimination and evidence that the disease's burden persists (Goyal et al.).

Beyond the geographic concentration of endemic areas, VL's burden can be measured in years of healthy life lost: Disability-Adjusted Life Years (DALYs) and Quality-Adjusted Life Years (QALYs). These metrics quantify healthy years of life lost to illness or disability and health gains by quantifying years spent in good health, respectively. A substantial number of DALYs are attributed to NTDs, demonstrating that their devastating impact extends into life beyond infection. Because of its substantial contribution to global DALYs, leishmaniasis has been a particular burden. Leishmaniasis is one of the 21 NTDs officially recognized by the World Health Organization (WHO). This illness stands out when compared to other NTDs due to the stark difference between the disease's burden and the effective treatments on the market. Roughly 350 million individuals are at risk, yet therapeutic development has remained stagnant for the past 15-20 years (Sundar and Singh).

Sandfly-Leishmania Life Cycle and a Disproportionate Global Response

Leishmania parasites alternate between two morphological forms throughout their life cycle: extracellular promastigotes in the sandfly vector (an organism that transmits pathogens), and intracellular amastigotes within the mammalian host's macrophages, a form of white blood cell that engulfs and digests microorganisms and dead cells (Gossage et al.). As seen in Figure 1, when a female phlebotomine sandfly feeds upon an infected reservoir host, it begins to ingest macrophages containing amastigotes, then transforms them into procyclic promastigotes (a stage of active division) in the sandfly's midgut (Bates). Afterward, parasites undergo a complex maturation process in which they change form and adapt to various conditions within the sandfly (see Figure 1). Starting with nectomonad promastigotes, procyclic promastigotes elongate and become motile, moving away from the sandfly midgut and toward the front of the digestive tract (Bates). Afterward, in the leptomonad phase, the promastigotes continue to multiply and produce lipophosphoglycan and proteophosphoglycan (molecules allowing the promastigotes to attach and move through the sandfly's digestive tract). Finally, in the metacyclic promastigote phase, the parasites become smaller, highly motile, and infective parasites, a process called metacyclogenesis (Bates). Finally, the mature parasites migrate to the sandfly's mouth, now

ready to be transmitted during the next bloodmeal. Once metacyclic promastigotes are introduced into the skin of new mammalian hosts, macrophages engulf them, and the parasites revert to amastigotes, reproduce within the macrophages, and prolong the infection (Clos et al.). Infection rates and areas depend on ecological conditions, as sandfly vectors remain most active from dusk to dawn and their range depends on climate.

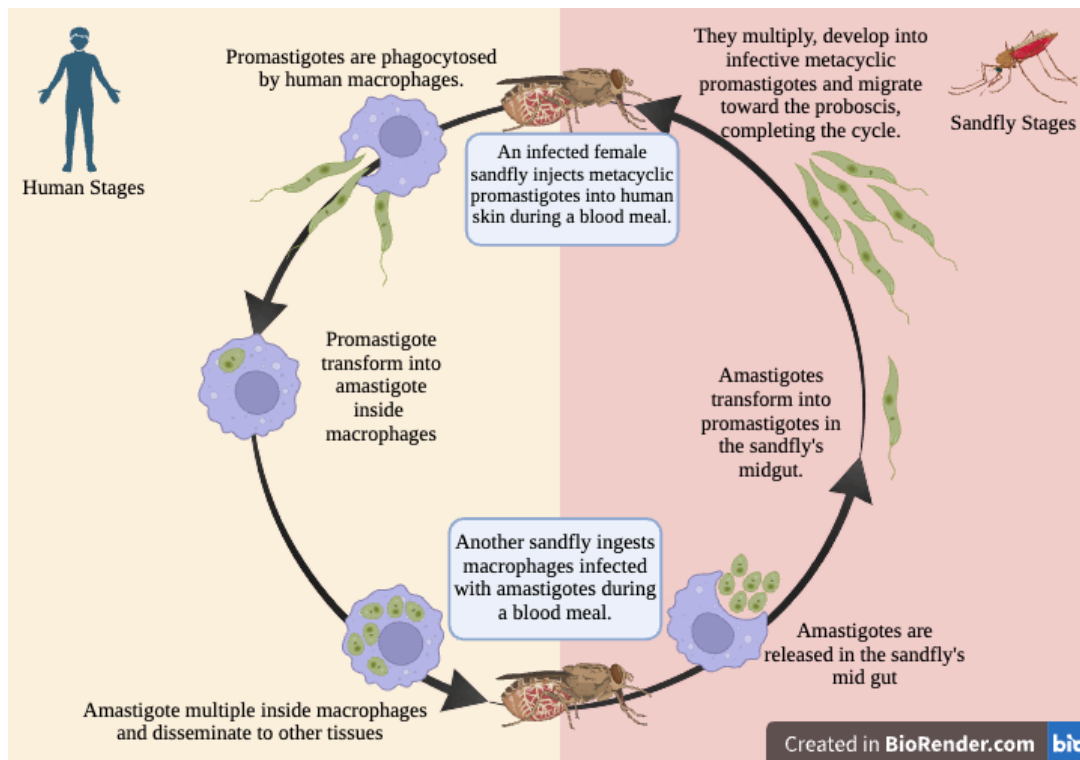


Fig 1: Sandfly-Leishmania Life Cycle in Relation to Human Macrophages

Although VL's transmission biology is well researched and despite its near-total mortality when untreated, the global public health response has been minimal when compared to the disease's severity. No effective vaccine exists, and the therapeutic approach has not changed in decades, a disparity that cannot be attributed to scientific difficulty; instead, it is a direct result of the socioeconomic realities surrounding who the disease affects and the interests of the therapeutics industry.

Socioeconomic Factors and Neglect

VL's classification of an NTD reflects the well-documented relationship the disease has with poverty. Within endemic regions, the risk of infection is substantially higher due to economic factors such as poor housing and sanitation (which directly increase sandfly breeding) and limited protective measures (Alvar et al.). In addition to the environment commonly seen in endemic regions, most communities largely affected by this disease also experience seasonal labor migration, which often brings non-immune populations into contact with infected vectors. Once an individual or community is infected, malnutrition and coexisting infectious diseases

starkly increase the likelihood that exposure to *L. donovani* or *L. infantum* manifests as clinical VL, while limited healthcare access and delays in diagnosis continue to worsen morbidity and mortality—the cycle compounds when community-level finances are analyzed.

Treatment-seeking families in VL-endemic areas often sell assets or take out loans to pay for diagnosis and care, losing as much as 75% of household income to disease, prolonging cyclical poverty (Okwor and Uzonna).

Each of the three major endemic regions reports a different dynamic. In South Asia, coordinated elimination campaigns have been organized and leveraged centralized healthcare systems. This particular form of healthcare system allowed governments to coordinate case detection, treatment plans, and surveillance in areas with high case rates. This centralized approach allowed elimination strategies to be implemented more consistently and deployed on a broader scale, ultimately contributing to a reduction in cases (World Health Organization). In East Africa, chronic conflict, population displacement, and weaker health infrastructure have made driving down cases far more difficult. East Africa has overtaken South Asia in terms of the highest number of VL cases, accounting for 73% of the global caseload (Olliario et al.). In Latin America, VL (primary strain *L. infantum*) is complicated by the local zoonotic transmission cycle, in which domestic dogs serve as reservoir hosts. Therefore, it requires assistance from both veterinary and human public health infrastructure, both of which are lacking in the poorer urban areas of Brazil where the illness is concentrated (Dantas-Torres). Due to VL disproportionately affecting lower-income communities who are already overwhelmed financially, the limited purchasing power has led pharmaceutical and biotechnology companies to have little to no commercial incentive to invest in new therapeutic development. The ultimate outcome is thousands of lives lost due to aging, imperfect therapies.

Current Standard of Care

In the current research landscape, no reliable, effective vaccine exists; pharmacotherapies remain the backbone of current VL treatments, and the main drug varies by region because of differences in cost and available containment infrastructure (Sundar and Chakravarty). Four main treatments are currently available.

Drug Name	Route of Administration	Limitations & Side Effects	Cost of Treatment
Pentavalent antimonials	Intravenous (IV) or Intramuscular (IM), daily for 28 to 30 days	Widespread parasitic resistance, cardiotoxicity, hepatotoxicity, nephrotoxicity, and painful injections that require	Relatively inexpensive compared with newer treatments but varies by region

		hospitalization	
Liposomal amphotericin B	IV infusion in South Asia at a 10mg/kg dose. In East Asia, multiple doses of 30 mg/kg	Infusion reactions, fever, chills, nausea, and electrolyte imbalances; requires IV administration	Historically approximately US\$200 per treatment under a WHO-negotiated access program but can be higher
Amphotericin B Deoxycholate	Slow IV infusion (4-6 hours), daily or alternating days, doses ranging from 15-20 at 0.75 to 1 mg/kg	Significant nephrotoxicity, electrolyte disturbances, fever, chills, anemia, and infusion-related reactions	Generally less expensive than liposomal amphotericin B but requires surrounding monitoring costs increase total treatment cost
Miltefosine	Oral capsules daily for 28 days at 2.5 mg/kg in standard regimens.	Gastrointestinal side effects, including nausea, vomiting, and diarrhea; possible liver and kidney abnormalities. Potential for resistance.	Moderate and variable; oral administration can reduce hospitalization cost
Aminoglycoside Paromomycin	IM injection daily for 21 days at 15 mg/kg in standard regimens.	Pain at injection sites, elevated liver enzymes, and potential kidney or hearing toxicity. Potential for resistance.	Generally relatively inexpensive in endemic countries, although repeated injections add to the cost.

Pentavalent antimonials, a group of heavy metal-based medications, mainly sodium stibogluconate and meglumine antimoniate, have been used for VL since 1945, making them the longest-used therapeutic agents for VL (currently used in East Africa). The route of administration is parenteral, intravenous or intramuscular injection. They are usually administered alongside the aminoglycoside paromomycin for roughly 28 days, which is a significant barrier to effective treatment due to compliance issues and treatment failure (Sundar and Chakravarty). The antimonials have been proven to be inexpensive and effective; however,

they carry a significant risk of toxicity such as cardiotoxicity, hepatotoxicity, and pancreatitis (Kato et al.).

Liposomal amphotericin B (LAmB) is considered the primary treatment of choice in South Asia. Usually given at high doses, LAmB is highly effective and better tolerated than other treatments on the market, but it requires intravenous administration, constant hospital monitoring, and cold-chain storage (Sundar et al.). These requirements severely limit its feasibility in low-resource and rural settings.

Miltefosine is the only oral anti-leishmanial drug commonly used in South Asia and East Africa (Escalera-Lerona et al.). It offers a major practical advantage by eliminating the need for injections or hospitalization, and it can be used as monotherapy or in combination with other therapies. Pitfalls still exist; the drug has a long half-life, increasing the risk of parasite resistance over time, and it is teratogenic (disrupts normal fetal development and can cause structural or functional congenital disabilities) and cannot be utilized in pregnant women or women of childbearing age (Astman et al.). Across all regions, one limitation remains. No single existing therapy offers high efficacy, low toxicity, and worldwide access. Additional factors, including regional drug resistance and cost, further complicate the issue. These regional gaps fragment the standard of care and have done little to address why VL remains one of the deadliest infectious diseases: the parasite's ability to evade and subvert the host's immune system.

Novel Approaches in VL Therapy

Current therapies fail to address the root of the disease: the parasite's immune-subverting survival strategy. Recently, researchers have begun exploring approaches that synergize with the immune dysfunction rather than solely relying on the parasitocidal action of the available drug therapies. Three particular approaches have gained traction in recent years: AI-guided drug discovery, nanomedicine, and immunotherapy. Each of the treatment pathways explores a distinct piece of the underlying problem: VL is one of the deadliest infections largely due to the lack of financial incentive to effectively invest in new pharmaceuticals, and the parasite itself has the ability to manipulate the host's immune response (Tiwari et al.).

AI-Designed Therapeutics

In previous decades, researchers have largely turned to computational approaches such as molecular docking, protein-inhibitor interaction analysis, and quantitative structure-activity relationship (QSAR) models to make drug discovery more efficient and less expensive (Ahmed and Bhat). The next step in computational biology for VL is to incorporate artificial intelligence approaches into VL research in an attempt to completely reshape the economics of discovering new drugs. AI can help bridge funding gaps by enabling large-scale experimental screening

campaigns. An AI-guided approach allows researchers to narrow entire chemical libraries down to a smaller group of high-probability candidate compounds before any biological assays are conducted (Xie et al.).

One of the forebears of this shift involves DeepMind's AlphaFold. Researchers at the Drugs for Neglected Diseases initiative (DNDi) have spent years developing a promising antileishmanial molecule, yet the project was shelved in 2023 since there was no accurate way to visualize the interaction between the drug and its biological target (Schouten et al.). A breakthrough was reached after a scientist on the project utilized metabolomics (the study of small-molecule metabolites left behind by cellular processes) to determine how the drug disrupted the parasite's metabolism, and then identified an enzyme involved in phospholipid production as a target (Lee and Banerjee). The enzyme was infamous for being difficult to experimentally characterize due to being a membrane protein. AlphaFold was used to predict the enzyme's structure directly from its amino acid sequence. The researchers were able to model how the candidate physically bound to the target, turning the seemingly dead end into a tractable solution (Google DeepMind).

This ability has become common in most disease researchers' toolkits. However, the issue becomes more complicated once more than 20 disease-causing *Leishmania* species are introduced (Selvapandiyan et al.). Researchers can now generate structural predictions for the same target gene across various *Leishmania* species to ensure the proteins fold the same way before committing resources to further developing a drug that is hyper-specific to a few species. This same protein-structure database makes it possible to compare the parasite's drug target directly to the human counterpart, allowing researchers to anticipate and counteract any off-target toxicity. Overall, this approach is more financially feasible since the effect can be predicted early in the discovery process rather than later in the expensive animal model studies. A more direct application of AI lies in drug repurposing through machine learning (ML) classifiers. This approach requires ML models to learn statistical patterns of activity across large chemical libraries rather than modeling the specific molecular interactions required for structure-prediction AI (Harigua-Souiai et al.). One research group built an ML pipeline to train both Random Forest and Support Vector Machine. The Random Forest system is an ML algorithm that builds "decision trees" during training and combines each tree's output for accurate predictions. On the other hand, the Support Vector Machine system is an ML algorithm that finds an optimal area to split data into different classes, used as a classifier on large biological screening data that covered over 65,000 chemical compounds (Harigua-Souiai et al.). The compounds were tested against leishmania major promastigote growth. After further pipeline optimization, both classifiers predicted 19 FDA-approved drugs with antileishmanial activity with 90% confidence; seven of the detected drugs had existing scientific literature describing their activity against leishmaniasis.

In a subsequent study, the same group of researchers tested ten previously predicted compounds directly against parasite cultures from three separate *leishmania* strains (Oualha et al.). The study found that five of the ten compounds showed dose-dependent antileishmanial

activity, with a 50% validation rate for the computational screening approach. Three of the five (acebutolol, a beta-blocker used for hypertension; prilocaine, a dental anesthetic; and phenylephrine, a drug used to treat acute hypotension) had never previously been connected to having an effect on leishmania (Oualha et al.). The other two, dibucaine and domperidone, had earlier confirmations of anti-leishmanial activity from veterinary and clinical settings. Most importantly, all five compounds showed antileishmanial effects at concentrations well below levels shown to be toxic to human macrophage cells. In further testing against the intracellular amastigote form of leishmania, the life stage responsible for disease in humans, both dibucaine and domperidone showed potent activity with selectivity index values between 21 and 32 (Oualha et al.). The selectivity index (SI) measures how much more toxic a drug is to the parasite than to the host's own cells, calculated as $SI = CC50/IC50$ —the concentration toxic to human macrophages divided by the concentration needed to kill the parasite (Hasoon and Kadhim). High SI levels mean that the drug is selectively toxic to the parasite and safer for the patient. The SI values of 21-32 mean the drugs killed the intracellular parasite at a concentration around 21 to 32 times lower than the concentration needed to harm the host's own cells. An SI above 10 is generally considered safe to continue further drug development (Afonso and Ricci-Junior). Therefore, this range signals that the compounds are safe and work at doses well below those that would present a risk to the patient. Furthermore, both compounds are already FDA-approved for their own indications, so their human safety and pharmacokinetic profiles are already established.

These individual successes contribute to the overall strategic advantage of AI: allowing researchers to filter enormous chemical libraries down to a high-probability shortlist and converting a previously resource-intensive process into a targeted one. This is a change that is immensely important in a field where large-scale screening campaigns have rarely been financially viable. However, key limitations exist. AI models are only able to provide structural predictions and activity classifiers that can provide promising candidates. They do not have the ability to replace in vitro and in vivo validation that is still required to confirm mechanism, efficacy, and long-term safety. Several of the new hits, including domperidone, showed signs of antiparasitic activity, but research regarding the mechanism is not thorough enough to provide an explanation.

Immunotherapy

Visceral leishmaniasis causes burdens beyond the traditional parasite; at its core, the problem lies in immune regulation. Once *L. donovani* or *L. infantum* amastigotes establish residence inside host macrophages, the parasite actively reprograms the intracellular signaling pathways meant to trigger a protective immune response. This process turns off the macrophages and other cells included in the reticuloendothelial system, the cells responsible for destroying the invaders (Tiwari et al.).

The chronicity usually associated with the disease is tied to the skewing of the host's immunity towards the Th2-dominant state (an immune response associated with antibody production rather than direct cell-killing activities). Therefore, an elevation in Th2 cytokine levels is commonly associated with disease progression, while elevated Th1 cytokine levels (a usually regulated response leading to cell-mediated immunity) are necessary to rehabilitate the host. The main reason for this imbalance is the cytokine interleukin-10 (IL-10), an anti-inflammatory cytokine whose role is to suppress the protective Th1 response and deactivate macrophage functions needed to kill the intracellular parasites (Mosser and Zhang). Because conventional therapies attack the parasite without correcting the underlying immune dysfunction, which causes cellular distress, relapse, and post-kala-azar dermal leishmaniasis (a chronic skin complication that can follow VL treatment) remain persistent problems even among patients who initially respond to treatment (Goyal et al.).

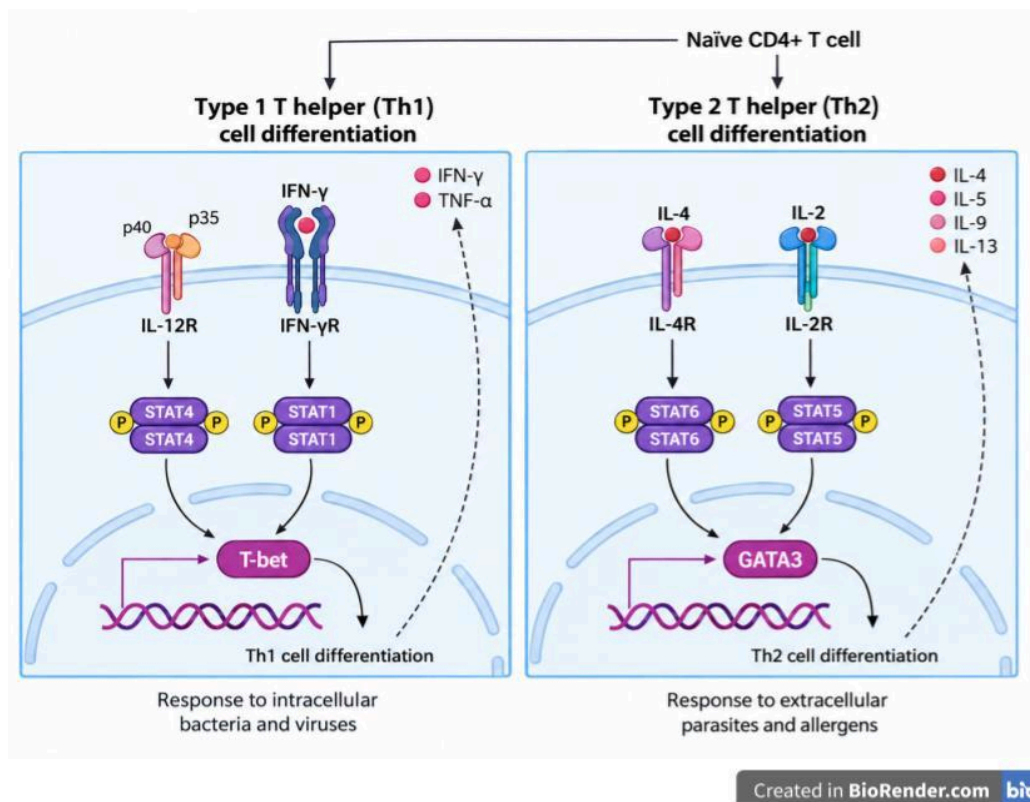


Fig 2: Cytokine Signaling and Th1/Th2 Differentiation in the Immune Response

This gap in care has driven growing interest in immunotherapies, usually used alone or in combination with pharmacotherapies. These treatments are aimed at restoring the protective Th1 response rather than purely relying on antiparasitic drugs alone. Cytokine-based strategies utilizing interferon-gamma (IFN-γ), granulocyte-macrophage colony-stimulating factor (GM-CSF), or interleukin-12 (IL-12) combat the disease by reactivating macrophages, allowing

them to generate nitric oxide and reactive oxygen species, which are both needed to destroy intracellular amastigotes (Yadagiri et al.). Combining IFN- γ with the standard pentavalent antimonials (antimonial sodium stibogluconate) has led to an 87% cure rate in human visceral leishmaniasis patients while simultaneously shortening the duration of treatment (Yadagiri et al.). Similarly, IL-12 has been promising from a mechanistic standpoint. In experimental models, mice were genetically engineered to suppress IL-12; they developed an uncontrollable liver infection, and the disease failed to respond to any standard antimonial treatments, highlighting how vital IL-12 can be to a successful immune response against a parasitic infection (Ullrich et al.).

A complementary strategy was designed to target the immunosuppressive side of the disease directly. Because of IL-10's tendency to actively block macrophage activation, some groups have investigated neutralizing IL-10 itself using either monoclonal antibodies or receptor blockers. Blocking the IL-10 receptor has been shown to reduce liver parasite burden in infected mice by enhancing IL-12 and inducible nitric oxide synthase (iNOS) expression (the enzyme responsible for producing nitric oxide, which helps kill intracellular pathogens). This restores the cytokine signaling pathway that the parasite suppresses (Yadagiri et al.). A recent peptide-drug conjugate encapsulated in nanoparticles has demonstrated how this strategy can be implemented. Researchers conjugated amphotericin B to a synthetic peptide designed to block IL-10. The researchers then encapsulated the complex in cyclodextrin nanoparticles, which are roughly 40 nanometers in diameter. This combined immunomodulatory and antiparasitic nanoparticle reduced parasite burden in infected mice. The dual-action design, where a direct antiparasitic agent is joined with an agent that corrects immune dysfunction, may prove to be more durable than traditional therapies alone, specifically for immunocompromised patients who usually respond poorly to standard regimens.

Despite the high promise exemplified by immunotherapy, utilizing this method for visceral leishmaniasis faces limitations. A large majority of the supporting evidence comes from mouse and hamster models rather than larger human trials (Roatt et al.). Furthermore, immunomodulators carry their own risks. Because they amplify immune activity rather than suppressing the parasite directly, there is a possibility of triggering excessive inflammation or hypersensitivity (Adriaensen et al.). Vaccine development remains an active process but is still an unlicensed frontier in human VL. Top candidates (whole-parasite, recombinant protein, and nucleic acid-based formulations) have shown promising protective efficacy in animal models but have not yet demonstrated efficacy in human clinical trials (Ayala et al.). Cost and formulation stability in the same low-resource, tropical settings where liposomal amphotericin B's reach is already limited remain unresolved barriers, reinforcing the ongoing need for immunotherapies that are not only biologically effective but also affordable and deployable within the fragmented healthcare infrastructure described earlier in this review.

Nanomedicine

Visceral leishmaniasis presents unique delivery challenges that are almost inverse to those faced by many diseases that nanomedicine has usually targeted. Rather than needing to breach the barriers that exclude therapeutics, VL's causative parasite hides inside the macrophages of the spleen, liver, and bone marrow (Scarpini et al.). These are exactly the tissues that macrophages and the entire reticuloendothelial system usually patrol and clear (Singh et al.). Nanomedicine exploits this biology rather than fighting directly against it. Mainly due to nanoparticles' tendency to be captured by phagocytic cells, they can be specially designed to concentrate directly inside the infected macrophages where the parasite resides. In principle, this allows lower drug doses, reduces systemic toxicity, and improves efficacy when compared to free drugs circulating indiscriminately through the body (Singh et al.). The targeting occurs both passively and actively. Passive delivery relies on the natural tendency of nanoparticles to be captured by the mononuclear phagocyte system (the network of immune cells that includes macrophages responsible for clearing foreign particles from the blood). On the other hand, active delivery attaches targeting ligands (examples include D-mannose, lactoferrin, or phosphatidylserine). These ligands bind directly to mannose or scavenger receptors on macrophage surfaces, steering the nanoparticles with greater precision when compared to passive uptake (Singh et al.).

Liposomal formulations have represented the clearest proof of concept for a nanomedicine-based approach, being the only novel treatment currently embedded in standard clinical practice (liposomal amphotericin B). Liposomes themselves are spherical vesicles built from a lipid bilayer that mimics the structure of a natural cell membrane. This structure allows them to encapsulate a drug within the aqueous core while simultaneously remaining biocompatible enough to circulate through the entire body without triggering a significant immune reaction (Jiang et al.). Liposomal amphotericin B takes advantage of this structure to reformulate a drug that previously caused severe nephrotoxicity and led to dangerous infusion reactions in its conventional form into a nanotherapy with a dramatically improved safety profile. Liposomal amphotericin B itself cured over 95% of Indian VL patients within a single 10 mg/kg dose, an efficacy that is comparable to a full month of conventional treatment (Sundar et al.). The liposome's lipid bilayer is thought to reduce the drug's direct interaction with human cell membranes, the main reason behind amphotericin B's toxicity, while its size and surface properties usually direct it toward macrophage uptake (Singh et al.). Looking beyond amphotericin B, researchers have also developed liposomal formulations for artemisinin, a compound that is more commonly associated with antimalarial treatment and that shows superior in vivo antileishmanial activity alongside the restoration of the host's Th1-skewed immune response compared to the free drug, suggesting liposomal encapsulation can extend beyond reengineering existing antileishmanials toward repurposing compounds from entirely different disease areas (Akbari et al.).

When looking beyond lipid-based carriers, polymeric and biodegradable carriers have represented a second major nonmetallic category currently under investigation. PLGA, or poly(lactic-co-glycolic acid), nanoparticles are made from a biodegradable polymer already approved for other pharmaceutical uses. They have been engineered with mannose or lactoferrin ligands attached to their surface for macrophage-specific delivery. They gradually break down in the body into lactic and glycolic acid byproducts that are naturally metabolized; this limits long-term accumulation when compared to other inorganic carriers (an issue commonly associated with metallic nanoparticles). Chitosan is a polysaccharide derived from crustaceans and offers a similarly biodegradable and biocompatible alternative. Mannosylated chitosan nanoparticles loaded with curcumin (a natural compound commonly found in turmeric that has been shown to have antileishmanial and anti-inflammatory properties) have been shown to improve parasite clearance in preclinical models, avoiding the tissue accumulation concerns associated with nanoparticles like silver and gold (Singh et al.). Additionally, gelatin-based nanoparticles, which are derived from denatured collagen, offer a further biodegradable option and are valued for their low toxicity and ease of surface modification with the same macrophage-targeting ligands seen in both liposomal and polymeric systems. Nanotechnology has also begun to transform VL diagnostics as well as treatments, a process that complements the treatment barriers that were described earlier in this review. A lateral flow immunoassay combining chimeric recombinant antigens with gold particles has achieved a sensitivity and specificity of above 98% for canine visceral leishmaniasis. Additionally, quantum dot-based genomic sensors have been pushing detection limits even further, with some platforms even enabling simultaneous detection of the parasite alongside profiling its drug resistance status (Singh et al.). These diagnostic applications remain one of the few areas where metallic nanoparticles continue to retain a clear advantage over nonmetallic alternatives, usually due to gold and quantum dot particles' ability to offer optical and electrochemical signaling properties that biodegradable carriers simply cannot replicate.

A limitation worth exploring across nanocarrier research is that it largely centers around existing antileishmanial and repurposed drugs rather than developing truly novel therapeutic compounds. Encapsulation does meaningfully improve the drugs' delivery, toxicity profile, and macrophage specificity; however, it does not fundamentally change the drugs' mechanism of action. This means any resistance the parasite has already developed toward the drug can persist once the compound is nanoencapsulated, which raises a long-term concern for the field. If nanocarrier innovation alone may not be sufficient to outpace the parasite's demonstrated ability to adapt to existing treatment mechanisms, then continued reliance on the same pool of repurposed drugs could eventually reach diminishing returns, where widespread resistance develops. As a result, it is paramount to simultaneously invest in discovering genuinely new antiparasitic compounds to deliver through liposomal methods (Jamshaid et al.). Another concern has been manufacturing consistency, since batch-to-batch variability in lipid composition and polymer degradation rates can render a nanoformulation partially ineffective or

unexpectedly toxic. Cost also remains a meaningful barrier, where even liposomal amphotericin B (the largest success story in visceral leishmaniasis research) requires cold-chain storage and carries a price point that limits accessibility to the majority of rural and resource-poor endemic regions. The majority of current research relies on intravenous or intraperitoneal administration. Comparatively, an oral nanoparticle formulation developed from the same biodegradable polymers already used in mannosylated and PLGA-based systems would be more practical for a disease concentrated in remote regions where access to injectable treatment infrastructure is extremely limited (Singh et al.).

Discussion

The research presented in this review exemplifies the challenges of researching and treating visceral leishmaniasis. This review makes clear that the issue extends beyond identifying drugs capable of killing the parasite. Modern-day therapies are effective; however, their toxicity, administration requirements, and concerns surrounding resistance have led researchers to believe that no single treatment has adequately addressed the needs of all patients across endemic regions. Additionally, limitations are further complicated by the parasite's biology: the ability to survive within the host's macrophages and manipulate immune outcomes. To combat the disease, it is vital that future therapeutic development not only considers the treatment's ability to eliminate the parasite, but also its efficiency when reaching its target, selectively treating cells, and being integrated into health care systems that face scarce resources.

At the forefront of this frontier is AI-guided drug discovery. It offers one extremely promising way to address the additional barrier created by the lack of financial investment in VL drug development. Computational screening can reduce the number of compounds that must be researched by identifying candidates with a higher predicted likelihood of antileishmanial activity. The drug repurposing studies mentioned in this review demonstrate the potential of this approach: computational models have been utilized to identify compounds that previously demonstrated antileishmanial activity in laboratory experiments. Particular significance should be given to the models' ability to identify FDA-approved drugs because existing information regarding their safety and pharmacokinetics can reduce the many barriers that are often associated with developing an entirely new therapeutic. Yet, it is still key to highlight that computational predictions remain in their infancy and are not a replacement for complete in vivo research, mainly because the activity, mechanisms, and efficacy of predicted candidates must still be established through biological testing and animal models.

Immunotherapy deals with a gap that neither conventional therapies nor computational screening can tackle: the parasite's manipulation of host immunity. IL-10 steers the host's immune system into a Th2-dominant state, subsequently killing macrophages. Current leading immunotherapies for VL are cytokine therapies such as IFN- γ and IL-12, which aim to restore the protective Th1 response and reactivate macrophages. When IFN- γ is paired with

pentavalent antimonials, they produce an 87% cure rate while shortening the lengthy treatment time (Yadagiri et al.). Immunotherapies show how a single therapy can attack the parasite while simultaneously restoring immune function, which can be beneficial for immunocompromised patients. Still, the majority of this evidence comes from mouse and hamster models; further research in clinical settings must be done before conclusions can be drawn.

A nanomedicine approach provides an advantage since it exploits the same biology that previously made VL difficult to treat. Macrophages naturally capture nanoparticles, so nanomedicine carriers concentrate drugs in the spleen, liver, and bone marrow, allowing for lower doses, less off-target toxicity, increased shelf-stability, and shorter treatment times (Ji et al.). Liposomal amphotericin B is the clearest success story, as it has become the current standard of care for VL. Liposomal amphotericin B has cured over 95% of INdian patients with a single 10 mg/kg dose (Sundar et al.). Other polymers have also shown promise in drug delivery: PLGA, chitosan, and gelatin. It is key to note that nanomedicine is an encapsulation technique and does not address the resistance concerns with current treatments. Another drawback may be the manufacturing consistency and reliance on injectable administration, which may limit the reach in rural endemic regions. Therefore, nanocarriers alone are not sufficient to address current therapeutic challenges and must be paired with novel compounds.

In the broader therapeutic landscape of visceral leishmaniasis, progress will depend on integrating multiple approaches rather than relying on a single technological solution. AI can be used to identify and prioritize potential therapies, but, as previously stated, it cannot completely replace the scientific drug design process. All three approaches are complementary rather than competing or used in isolation: AI optimizes the discovery pipeline, immunotherapies restore degraded immune responses, and nanocarriers offer specific delivery to infected macrophages. This approach may even help overcome the biological barriers that conventional therapy does not adequately address, especially considering the environments in which endemic regions are located. It is additionally extremely important for leishmania parasites because they occupy an intracellular environment within host macrophages, which provides a unique therapeutic challenge that is often not seen in conventional drug discovery. Overall, for innovation to continue, it must connect molecular-level discoveries with the practical realities of patients living in these endemic regions, including affordability, accessibility, infrastructure, and regional differences in treatment.

The persistence of visceral leishmaniasis cases despite years of scientific understanding and discovery illustrates that therapeutic progress does not directly correlate with improving the lives of those suffering from the disease. The concentration of neglected tropical diseases as a whole in economically disadvantaged populations creates a harsh commercial environment for pharmaceutical development, where, due to conflict, displacement, and inadequate healthcare infrastructure, resources are not invested in disease control. Hence, technological advances cannot single-handedly eliminate VL. Instead, sustained investment, accessible healthcare systems, continued research, and treatments particularly designed for the patients who need

them most are all vital aspects of moving forward and translating emerging discoveries into meaningful public-health improvements.

Conclusion

The neglected tropical disease visceral leishmaniasis remains a global health epidemic due to the severity of the disease, accompanied by limitations in the therapeutic landscape. Treatments currently on the market vary across endemic regions, and each presents its own limitations, including toxicity, administration, resistance, cost, or overall accessibility. Simultaneously, the parasite has the ability to survive within host cells and evade immune defenses, creating further biological challenges that conventional therapies do not fully address. Novel therapies, such as AI-guided drug discovery, provide a particular opportunity to revolutionize how VL therapeutics are both identified and developed. ML models are able to rapidly screen large chemical libraries and predict molecular structures. Practically, by identifying potential drug-repurposing candidates, computational methods may also reduce the time and resources required during early-stage drug discovery by providing protein-folding visualization tools, such as DeepMind's AlphaFold 3. However, it is key to underline that these technologies should still be viewed as tools to accelerate and guide experimental research rather than completely replace it, since the most promising computational findings still require laboratory and clinical validation before they can become viable treatments.

Additional treatments, such as immunotherapies and nanomedicine, address the other half of the issue. Cytokine-based IL-10 blocking immunotherapies aim to restore the protective TH1 response relative to the TH2 response, which prevents macrophages from phagocytosing and leaves the immune system unable to destroy *Leishmania* parasites. Nanomedicines are nanocarriers that deliver drugs directly to affected macrophages, reducing common side effects of current therapies, off-target toxicity, lengthy treatment times, and cold-chain supply requirements.

All in all, improving outcomes for patients with VL will require more than just discovering another antiparasitic; it will require future therapies to address the biological complexity of the parasite while also taking into account the socioeconomic and infrastructural conditions that are synonymous with VL treatment. Continued integration of computational biology, immunotherapies, and nanomedicine with therapeutic innovation could help close the gap between VL's global burden and the limited treatment options currently available.

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