



SUDAN VIRUS DISEASE: MOLECULAR PATHOGENESIS, PHARMACOLOGICAL TARGETS AND EMERGING THERAPEUTIC STRATEGIES

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ABSTRACT:

Sudan virus disease (SVD) is a severe, often fatal zoonotic infection caused by Sudan virus (SUDV; *Orthoebolavirussudanense*) and remains a major therapeutic challenge in East and Central Africa. Since its recognition in 1976, recurrent outbreaks, including those in Uganda in 2022 and 2025, have highlighted the absence of licensed SUDV-specific vaccines or therapeutics. This review integrates current understanding of SUDV molecular biology, host–pathogen interactions, and immunopathology with emerging pharmacological opportunities. Key targets include glycoprotein-mediated entry, endosomal trafficking, the RNA-dependent RNA polymerase complex, VP35 and VP24-mediated immune evasion, VP40-mediated assembly, and pathological inflammatory, endothelial, and coagulation pathways. Emerging countermeasures include nucleoside analogues, monoclonal antibodies, RNA-based therapeutics, host-directed agents, and vaccine platforms. However, limited clinical evidence, treatment timing, model-to-human translation, and outbreak-related trial challenges remain significant barriers. Adaptive clinical trials, optimized supportive care, and coordinated outbreak preparedness are essential for advancing effective SUDV countermeasures.

Keywords: Sudan virus; *Orthoebolavirussudanense*; filovirus; viral haemorrhagic fever; antiviral pharmacology; monoclonal antibodies; vaccines; remdesivir

1. INTRODUCTION

Sudan virus disease (SVD) is a severe zoonotic viral infection caused by Sudan virus (SUDV), an enveloped, filamentous, non-segmented, negative-sense single-stranded RNA virus belonging to the genus *Orthoebolavirus* and family *Filoviridae*. SUDV is classified within the species *Orthoebolavirussudanense* and is one of the principal human-pathogenic ebolaviruses. The virus was first recognized in 1976 during simultaneous outbreaks of haemorrhagic fever in southern Sudan and northern Zaire. Since then, recurrent outbreaks have occurred predominantly in Uganda and Sudan, establishing SUDV as an important high-consequence pathogen with substantial implications for global health security.

Filoviruses cause severe systemic diseases characterized by rapid viral replication, dysregulated innate immune responses, endothelial dysfunction, coagulation abnormalities, vascular leakage, fluid and electrolyte disturbances, and progressive multiorgan injury. SVD typically begins with nonspecific febrile manifestations, including fever, headache, fatigue and myalgia, followed by gastrointestinal symptoms such as vomiting and diarrhoea. Severe disease may progress to dehydration, hypotension, hepatic and renal dysfunction, coagulopathy, shock and multiorgan failure. Although the disease is historically described as a haemorrhagic fever, clinically significant bleeding occurs in only a proportion of patients and is generally not the principal determinant of mortality. Instead, systemic inflammation, endothelial dysfunction, vascular leakage, fluid loss and organ injury collectively contribute to poor outcomes. [1]

Despite substantial advances in filovirus research, SUDV remains associated with a major therapeutic gap. Unlike Zaire ebolavirus, for which licensed vaccines and monoclonal antibody therapies have been developed, there is currently no licensed SUDV-specific therapeutic or vaccine routinely available for clinical use. This disparity is particularly important because antigenic differences among ebolaviruses can substantially influence antibody recognition and protective efficacy. Consequently, countermeasures developed specifically against Zaire ebolavirus cannot automatically be considered effective against SUDV. At the same time, the identification of conserved glycoprotein epitopes and shared viral mechanisms has created opportunities for developing broadly active monoclonal antibodies and antiviral agents.

The molecular biology of SUDV provides several potential pharmacological targets. Its approximately 19-kb genome encodes nucleoprotein, VP35, VP40, VP30, VP24, glycoprotein and the large polymerase protein. Glycoprotein is responsible for viral attachment, endosomal entry and membrane

fusion, whereas the nucleoprotein, VP35, VP30 and polymerase coordinate viral RNA replication and transcription. VP40 is the principal matrix protein and regulates virion assembly and budding. VP35 and VP24 also contribute to immune evasion by interfering with interferon production and signalling. These proteins therefore represent potential targets for direct-acting antiviral development.

Viral entry is particularly attractive for pharmacological intervention because SUDV glycoprotein interacts with host-cell factors, including the endosomal receptor Niemann–Pick C1, to facilitate membrane fusion. Structural characterization of this interaction has provided new opportunities for rational drug and antibody design. Similarly, the viral polymerase represents a highly conserved and essential target for nucleoside analogue development. Experimental studies have demonstrated activity of agents such as remdesivir, favipiravir and obeldesivir against SUDV in relevant preclinical models. RNA-based approaches directed against essential viral proteins and monoclonal antibodies targeting conserved glycoprotein epitopes have also produced encouraging experimental results.

SVD pathogenesis, however, cannot be explained solely by viral replication. Disease severity results from a complex interaction between viral factors and host responses. Infection of macrophages and dendritic cells, suppression of innate antiviral signalling, excessive inflammatory mediator production, endothelial barrier disruption and abnormalities of coagulation collectively contribute to systemic disease. Consequently, therapeutic development is increasingly moving toward strategies that combine direct viral inhibition with carefully selected modulation of pathological host responses.

The therapeutic window represents another major challenge. Patients frequently seek medical attention after substantial viral replication and systemic inflammation have already developed. Experimental studies demonstrating efficacy following delayed treatment are therefore particularly important for translational development. Combination therapy involving neutralizing antibodies and polymerase inhibitors may be especially valuable in advanced disease because it can simultaneously reduce infectious virus and suppress ongoing replication. [2]

From a pharmacological perspective, SVD represents an important model for integrating molecular virology, structural biology, medicinal chemistry, antibody engineering, pharmacokinetics, immunology and clinical therapeutics. Continued investigation of viral entry, replication, immune evasion, endothelial injury and inflammatory pathways is essential for identifying interventions that can be translated into effective outbreak treatments. This review therefore examines the molecular pathogenesis of SVD, evaluates major viral and host pharmacological targets, and discusses emerging therapeutic strategies and future directions for the development of effective SUDV-specific countermeasures.

2. EPIDEMIOLOGY

SUDV has caused recurrent outbreaks since its first recognition in 1976. The initial outbreaks occurred in Nzara and Maridi in southern Sudan and were associated with substantial mortality and healthcare-associated transmission. Subsequent outbreaks occurred in Sudan and Uganda, with the largest historically documented outbreak occurring in Uganda during 2000–2001, involving more than 400 cases. Uganda experienced additional outbreaks in 2011, 2012 and 2022. The 2022 outbreak, centred initially in Mubende and subsequently involving several districts including Kampala, resulted in more than 160 confirmed and probable cases and numerous deaths before being declared over in January 2023.

In January 2025, Uganda reported another SVD outbreak. Although the outbreak was comparatively limited and was controlled within approximately three months, it demonstrated the continuing capacity of SUDV to re-emerge and cause community and healthcare-associated transmission. It was also notable for the rapid implementation of an investigational SUDV vaccine trial, representing an important advance in outbreak preparedness.

Historically reported case-fatality ratios for SVD have generally ranged from approximately 30% to more than 50%, although mortality varies considerably according to outbreak, case ascertainment, healthcare access and supportive management. Transmission occurs primarily through direct contact with infected blood or body fluids and contaminated materials, with healthcare workers and caregivers at increased risk. Persistent viral infection in immunologically privileged sites may contribute to rare post-recovery transmission. The precise natural reservoir of SUDV remains uncertain, although bats and other wildlife are considered important areas for continued ecological investigation. The sporadic nature of outbreaks, limited case numbers and high-containment requirements continue to complicate epidemiological surveillance and therapeutic clinical trials. [3,4]

3. MOLECULAR PATHOGENESIS OF SUDAN VIRUS DISEASE

Genome Organization and Viral Replication: Sudan virus (SUDV) is an enveloped, filamentous, non-segmented, negative-sense RNA virus with a genome of approximately 19 kb. Its genome contains seven major genes arranged in the order 3′-NP–VP35–VP40–GP–VP30–VP24–L-5′, encoding nucleoprotein (NP), VP35, VP40, glycoprotein (GP), VP30, VP24 and the large polymerase protein (L). These proteins coordinate viral entry, genome replication, transcription, assembly, budding and immune evasion. Because the genomic RNA is negative-sense and cannot function directly as messenger RNA, the incoming virion must deliver an active ribonucleoprotein complex containing genomic RNA associated with NP, VP35, VP30 and L. Following entry into the cytoplasm, the viral polymerase complex initiates sequential transcription of viral genes, producing capped and polyadenylated messenger RNAs. The L protein provides RNA-dependent RNA polymerase activity, whereas VP35 functions as an essential

polymerase cofactor. NP encapsidates viral RNA and protects it during replication, while VP30 regulates transcription. Full-length antigenomic RNA serves as an intermediate for production of progeny genomes. Viral replication occurs within cytoplasmic inclusion bodies that function as specialized viral replication compartments. The GP gene is particularly important because it produces multiple glycoprotein products through transcriptional editing. The membrane-associated GP forms the principal viral entry protein, whereas secreted GP and other glycoprotein products may influence antibody responses and host-cell interactions. The abundance of secreted GP may contribute to immune modulation by functioning as an antigenic decoy and potentially influencing vascular and inflammatory responses. The essential role of the L polymerase, NP and VP35 in RNA synthesis makes the replication complex an important target for direct-acting antiviral agents.

Attachment, Entry and Endosomal Trafficking: SUDV entry is primarily controlled by its surface glycoprotein, which forms trimeric complexes consisting of GP1 and GP2. GP1 participates in attachment and receptor recognition, whereas GP2 contains the fusion machinery required for merging the viral and endosomal membranes. The heavily glycosylated regions of GP facilitate interactions with cellular attachment factors, while additional host receptors can recognize phosphatidylserine exposed on the viral envelope through an apoptotic-mimicry mechanism. After attachment, SUDV particles are internalized through endocytic mechanisms, including macropinocytosis. The virus subsequently traffics through increasingly acidic endosomal compartments. Host proteases, particularly cathepsins, process GP and remove structural domains that initially conceal the receptor-binding region. This processing exposes the portion of GP required for interaction with the intracellular receptor Niemann–Pick C1 (NPC1). NPC1, a membrane protein involved physiologically in intracellular cholesterol trafficking, is essential for productive ebolavirus infection. Interaction between processed GP and NPC1 triggers conformational changes in GP2, exposing the fusion machinery and enabling fusion between viral and endosomal membranes. The nucleocapsid is then released into the cytoplasm, where viral transcription and replication begin. The dependence of SUDV on conserved host-cell entry mechanisms creates opportunities for pharmacological intervention using antibodies, peptides or small molecules directed against viral GP or selected host factors. However, because proteins such as NPC1 and endosomal proteases have important physiological functions, therapeutic strategies must achieve sufficient antiviral activity without producing unacceptable host toxicity.

Cellular Tropism and Systemic Dissemination: Following infection, SUDV targets monocytes, macrophages and dendritic cells, which are important components of innate and adaptive immune regulation. Infection of these cells facilitates viral dissemination through lymphatic tissues and the bloodstream. Macrophage and dendritic-cell infection also alters cytokine production, antigen presentation and immune activation, allowing viral replication to progress while effective antiviral immunity remains delayed. As infection becomes systemic, the liver, spleen, lymphoid tissues, adrenal glands and kidneys become important sites of pathology. Hepatic involvement may contribute to hepatocellular injury and impaired synthesis of coagulation proteins. Adrenal dysfunction can contribute to hypotension and disturbances in fluid and electrolyte homeostasis, whereas renal injury may result from a combination of systemic inflammation, hypoperfusion and tissue damage. Gastrointestinal involvement produces vomiting and diarrhoea, which can markedly worsen dehydration and electrolyte imbalance. Severe disease therefore reflects both viral dissemination and progressive disruption of multiple physiological systems.

Innate Immune Evasion: A central feature of SUDV pathogenesis is suppression of innate antiviral immunity. Viral RNA is normally recognized by intracellular sensors such as RIG-I and MDA5, initiating signalling through mitochondrial antiviral signalling pathways, TBK1 and related kinases. Activation of interferon regulatory factors subsequently induces type I and type III interferons and establishes an antiviral state. SUDV has evolved mechanisms that interfere with several stages of this response. VP35 is a major interferon antagonist. It can bind viral double-stranded RNA intermediates and prevent their recognition by intracellular RNA sensors. VP35 also interferes with signalling pathways required for activation of interferon regulatory factors. This dual role is particularly significant because VP35 is also essential for viral replication. Consequently, pharmacological disruption of VP35 could theoretically impair both viral RNA synthesis and immune evasion. VP24 provides a complementary mechanism of immune suppression. It interacts with host karyopherin proteins involved in nuclear transport and interferes with the movement of activated STAT proteins into the nucleus. As a result, even when interferon receptors are activated, downstream interferon-stimulated gene expression can be substantially impaired. These mechanisms create an intracellular environment that favours rapid viral amplification during the early phase of infection.

Immunopathology, Coagulopathy and Vascular Dysfunction: Severe SVD results from the interaction between high viral burden and dysregulated host responses. Infected macrophages and other immune cells release cytokines and chemokines that promote inflammation, endothelial activation and tissue injury. Mediators such as interleukin-6, interleukin-8 and tumour necrosis factor can contribute to vascular permeability and systemic inflammatory responses. However, the inflammatory response should not be regarded simply as an uncontrolled cytokine surge. The timing, magnitude and coordination of immune responses are important determinants of disease progression and survival. Adaptive immunity is also impaired during severe infection. Lymphopenia and apoptosis of lymphocytes can occur despite limited evidence that lymphocytes are major sites of productive viral replication. Dysfunction of dendritic cells further compromises antigen presentation and the development of effective antiviral T-cell and antibody responses. Patients who control infection are more likely to develop coordinated adaptive immune responses, supporting the concept that successful therapy should reduce viral burden sufficiently early to permit endogenous immune recovery. Coagulation abnormalities constitute another important component of SVD. Infection and activation of monocytes and macrophages can increase tissue-factor expression, promoting activation of the extrinsic

coagulation pathway. Thrombocytopenia, consumption of coagulation factors, hepatic dysfunction and endothelial injury can subsequently produce a complex haemostatic disturbance. Although haemorrhagic manifestations may occur, severe disease can also involve microvascular thrombosis and impaired tissue perfusion. This explains why empirical anticoagulation or procoagulant therapy may be inappropriate without careful assessment of the patient's coagulation status. Endothelial dysfunction contributes substantially to vascular leakage, hypotension and shock. Inflammatory mediators, viral proteins, oxidative stress and altered endothelial signalling can disrupt intercellular junctions and increase vascular permeability. The RhoA/Rho-associated kinase pathway is one potential regulator of this process because excessive RhoA/ROCK activity can promote actomyosin contraction and endothelial barrier disruption. ROCK inhibition is therefore an interesting experimental host-directed strategy, although its therapeutic relevance specifically in SVD requires further investigation.

Organ Injury and Disease Progression: Progressive organ dysfunction reflects the combined effects of viral replication, inflammatory injury, vascular leakage, hypovolaemia, metabolic disturbances and impaired tissue perfusion. Hepatic injury contributes to altered metabolism and coagulation abnormalities, while renal dysfunction may exacerbate electrolyte and acid-base disturbances. Gastrointestinal fluid losses can rapidly worsen intravascular depletion. Adrenal involvement may contribute to vascular instability and impaired stress responses. Viral burden is closely linked to disease severity in experimental filovirus models, supporting early use of direct antiviral therapies. However, once extensive endothelial damage, inflammation and organ dysfunction have developed, suppression of viral replication alone may be insufficient. This provides a strong pharmacological rationale for combination approaches incorporating antiviral agents, neutralizing antibodies and, where appropriate, carefully selected host-directed therapies. [5-7]

Molecular Features Relevant to Pharmacological Targeting: Although SUDV and Zaire ebolavirus share fundamental mechanisms of replication and pathogenesis, substantial differences in glycoprotein sequence and antigenic architecture influence therapeutic cross-reactivity. Consequently, antibodies developed specifically against Zaire ebolavirus cannot automatically be expected to neutralize SUDV. Conserved regions of GP, including portions of the receptor-binding and fusion machinery, remain attractive targets for broadly neutralizing antibodies. The major pharmacological targets emerging from SUDV pathogenesis therefore include GP-mediated entry, the NPC1-dependent entry pathway, the L polymerase complex, NP, VP35, VP24, viral assembly mediated by VP40, and selected host pathways involved in inflammation, endothelial permeability and coagulation. The relative importance of these targets is likely to vary according to disease stage. Entry inhibitors may have their greatest value early after infection, polymerase inhibitors can directly suppress ongoing viral replication, antibodies can neutralize extracellular virus and enhance immune clearance, while host-directed therapies may become increasingly relevant when inflammatory and vascular injury dominate the clinical phenotype. This stage-dependent framework provides an important foundation for rational development of combination therapies against SVD.

4. PHARMACOLOGICAL TARGETS

The molecular mechanisms underlying SVD provide a diverse range of potential pharmacological targets that can be broadly categorized into virus-directed targets, antibody-based therapies, nucleic-acid therapeutics, host-cell factors, and pathways involved in pathological inflammation, vascular dysfunction, and coagulation. An important principle in SUDV drug development is the balance between antiviral potency, breadth of activity, therapeutic window, and safety. Highly conserved viral proteins such as the RNA-dependent RNA polymerase, nucleoprotein, VP35, and VP40 offer opportunities for direct-acting antivirals, whereas the viral glycoprotein (GP) provides a major target for neutralizing antibodies and entry inhibitors. Host-directed approaches may offer broader activity but must be carefully designed because the cellular pathways involved in viral infection also perform essential physiological functions. [8-11]

4.1 Viral Polymerase Complex:

The viral RNA-dependent RNA polymerase complex, comprising the L polymerase and its cofactor VP35, represents one of the most extensively investigated small-molecule targets. Because viral RNA synthesis depends on enzymatic functions that have no direct equivalent in human cells, nucleoside and nucleotide analogues can potentially achieve selective antiviral activity. Remdesivir is a nucleotide analogue prodrug that is intracellularly converted into its active triphosphate form and interferes with viral RNA synthesis through inhibition of the viral polymerase. Experimental studies have demonstrated activity against SUDV, while non-human-primate studies support its potential antiviral effect. Despite this activity, the therapeutic performance of remdesivir may depend strongly on treatment timing. Experimental filovirus studies indicate that late remdesivir monotherapy may provide less protection than highly potent monoclonal antibody therapy. This does not exclude remdesivir as a therapeutic option; rather, it provides a rationale for evaluating it in combination with agents acting through complementary mechanisms.

Obeldesivir represents an important development in polymerase-directed therapy. It is an orally administered prodrug of GS-441524, the parent nucleoside associated with remdesivir. The oral route may provide substantial logistical advantages during outbreaks by reducing dependence on intravenous administration and allowing earlier treatment or post-exposure intervention. Experimental studies in cynomolgus monkeys have demonstrated protection against lethal SUDV infection following oral administration. The potential combination of oral bioavailability, systemic

antiviral activity, and simplified deployment makes this class particularly relevant to outbreak preparedness.

Favipiravir is another polymerase-directed antiviral. Following intracellular conversion to its active ribonucleotide form, it interferes with viral RNA synthesis and may also promote lethal viral mutagenesis. Experimental SUDV studies have demonstrated reductions in viral replication and improved survival under specific post-exposure treatment conditions. However, differences in pharmacokinetics between experimental animals and humans, uncertainty regarding the systemic exposure required for antiviral activity, and limited human evidence restrict direct translation of these findings. Other approaches include non-nucleoside inhibitors capable of binding allosteric sites on the polymerase or interfering with the L–VP35 interaction. Such agents could complement nucleoside analogues and potentially reduce the emergence of resistance by targeting distinct molecular sites.

4.2 Glycoprotein and Viral Entry:

The SUDV GP is a central pharmacological target because it mediates attachment, endosomal entry, receptor engagement, membrane fusion, and viral tropism. Its extracellular location also makes it readily accessible to neutralizing antibodies. Conserved regions within the GP base, receptor-binding region, and fusion machinery represent particularly important targets for broadly neutralizing antibodies. However, antigenic differences between SUDV and other ebolaviruses mean that antibodies developed against Ebola virus (EBOV) cannot automatically be assumed to provide equivalent protection against SUDV.

Pan-ebolavirus monoclonal antibody strategies have therefore attracted considerable interest. MBP134 is a prominent example of a broadly active antibody approach containing complementary specificities against ebolavirus glycoproteins. Experimental studies have demonstrated activity against EBOV, SUDV, and Bundibugyo virus. The engineered MBP134AF formulation additionally seeks to enhance Fc-mediated immune effector mechanisms, including recruitment of natural killer cells. Thus, antibody-mediated protection may involve both direct viral neutralization and Fc-dependent elimination of infected cells or viral particles.

SUDV-specific antibody combinations have also demonstrated promising experimental activity. RIID F6-H2, consisting of antibodies recognizing distinct GP epitopes, protected rhesus macaques following infection. FVM04/CA45 similarly demonstrated complete protection in cynomolgus macaques even when treatment was initiated several days after infection and clinical disease had developed. The ability to retain efficacy following delayed administration is particularly important for outbreak settings, where patients are frequently diagnosed after viral replication and systemic disease have already progressed.

Small-molecule GP-directed entry inhibitors provide another strategy. Selective estrogen receptor modulators such as toremifene and clomiphene have demonstrated anti-filoviral activity through interactions with GP and disruption of the conformational processes required for entry. Although concentrations required experimentally may exceed those achieved during conventional clinical use, these observations demonstrate the potential value of drug-repurposing approaches and structure-guided screening.

4.3 Host Factors Involved in Endosomal Entry:

SUDV entry depends on several host-cell factors, creating opportunities for host-directed antiviral intervention. NPC1 is an essential intracellular receptor involved in productive ebolavirus entry, while endosomal proteases, phosphoinositide-dependent pathways, ion channels, and trafficking machinery contribute to the entry process. The recently resolved SUDV GP–NPC1 structural interaction provides an important framework for rational development of molecules capable of interfering with viral receptor engagement.

PIKfyve, which participates in endosomal maturation, represents another potential target. Its inhibitor apilimod has demonstrated inhibition of filovirus entry in experimental systems. TPC2, an endolysosomal ion channel, can be inhibited by tetrandrine, while cathepsin inhibitors interfere with proteolytic processing of GP required for productive entry. Agents that disrupt macropinocytosis have also demonstrated antiviral activity. The principal limitation of these strategies is that the targeted host pathways have important physiological functions. NPC1, for example, participates in cholesterol trafficking, while endosomal pathways are required for normal intracellular transport. Consequently, systemic and prolonged inhibition may produce unacceptable toxicity. Transient inhibition or targeting of the specific virus–host interaction interface may therefore offer a more practical therapeutic strategy than complete blockade of host proteins.

4.4 Nucleic-Acid Therapeutics and Viral Protein Interactions:

RNA interference provides a highly sequence-specific approach to SUDV therapy. Lipid nanoparticle-encapsulated small interfering RNA directed against VP35 has demonstrated substantial protective activity in experimental non-human-primate studies, including efficacy after the development of fever and detectable viraemia. VP35 is particularly attractive because it performs dual functions in viral replication and innate immune antagonism. Silencing VP35 could therefore suppress viral replication while simultaneously reducing the ability of the virus to inhibit host antiviral responses.

The principal challenges include sequence specificity, viral genetic variation, delivery to relevant tissues, stability, repeated dosing, manufacturing, and

potential innate immune activation. Advances in lipid nanoparticle technology may nevertheless increase the feasibility of RNA-based therapeutics for emerging viral infections.

VP24 represents another target because it interferes with host interferon signalling by affecting STAT-mediated nuclear transport. Pharmacological disruption of the VP24–host transport machinery could potentially restore antiviral signalling. Similarly, compounds targeting the VP35 interferon-inhibitory domain may enhance recognition of viral RNA and restore interferon production. However, therapeutic enhancement of innate immunity must be carefully controlled because excessive inflammatory activation may contribute to tissue injury and shock.

Nucleoprotein assembly also provides an opportunity for intervention. Disruption of NP–VP35 interactions or other protein–protein interfaces required for nucleocapsid formation could interfere with viral replication. Although such interfaces can be challenging targets for conventional small molecules, structural characterization provides a foundation for rational drug discovery.

4.5 VP40-Mediated Assembly and Budding:

VP40 is essential for viral assembly, membrane recruitment, and budding and therefore represents an additional emerging antiviral target. VP40 oligomerization and interaction with host membrane-associated machinery are required for efficient production of infectious progeny. Structural studies have identified distinct oligomeric states associated with its biological functions, while crystallographic screening has identified small-molecule fragments capable of interacting with SUDV VP40. These findings establish an early framework for structure-based development of VP40 inhibitors. Although no clinically validated VP40 inhibitor is currently available, inhibition of assembly and budding could complement polymerase-directed therapy. A combination targeting viral RNA synthesis and production of infectious particles could theoretically suppress infection at multiple stages and reduce the probability that viral escape from one mechanism would lead to treatment failure.

4.6 Host Response, Vascular Dysfunction and Coagulation:

Pharmacological intervention can also target pathological host responses contributing to severe SVD. Excessive inflammatory signalling, endothelial dysfunction, vascular leakage, coagulation abnormalities, and organ injury collectively contribute to disease progression. Modulation of cytokine signalling and stabilization of endothelial integrity therefore represent potential adjunctive approaches.

Corticosteroids require particular caution because inflammatory responses contribute to both antiviral defence and pathological tissue injury. Although modulation of excessive inflammation has a theoretical therapeutic rationale, indiscriminate immunosuppression could impair viral clearance. Consequently, anti-inflammatory approaches require evaluation through controlled clinical studies rather than empirical administration.

The endothelial barrier represents another potential target. Modulation of RhoA/ROCK signalling, vascular endothelial growth factor pathways, cellular adhesion mechanisms, or endothelial junctional proteins could theoretically reduce vascular leakage. Such approaches would probably function as adjuncts because vascular permeability is only one component of the systemic disease process.

Coagulation-directed treatment also requires individualized consideration. Severe filovirus disease can involve thrombocytopenia, coagulation activation, consumption of clotting factors, bleeding, and potentially thrombotic microvascular abnormalities. Consequently, indiscriminate anticoagulation may be hazardous. Future pharmacological approaches should incorporate biomarkers capable of distinguishing predominant coagulation activation, consumption coagulopathy, and bleeding risk so that haemostatic interventions can be appropriately individualized.

4.7 Antibody Pharmacology and Therapeutic Limitations:

Although monoclonal antibodies currently represent one of the most advanced experimental approaches for SUDV, their clinical deployment presents practical challenges. Intravenous administration, manufacturing complexity, cold-chain requirements, cost, and limited availability may restrict access during large outbreaks. Fc engineering can potentially extend antibody half-life and enhance effector activity, but pharmacokinetic and immunogenicity considerations must be incorporated into development. Viral escape is another concern. Antibody cocktails directed against non-overlapping conserved epitopes may reduce the likelihood of resistance compared with single-antibody therapy. Continued genomic surveillance of SUDV is therefore important for identifying antigenic variation that could influence antibody susceptibility.

4.8 Combination Therapy and Supportive Pharmacology:

Combination therapy represents an important therapeutic concept because SVD involves both active viral replication and progressive systemic pathology. Combining a neutralizing antibody with a polymerase inhibitor allows simultaneous targeting of viral entry or extracellular virus and intracellular viral RNA synthesis. Experimental non-human-primate studies indicate that delayed monotherapy with either remdesivir or a pan-ebolavirus antibody approach may provide limited protection when treatment is initiated late, whereas combined treatment can provide substantially greater protection. These findings support further evaluation of mechanistically complementary combinations.

Sequential treatment strategies may also be explored. An orally available polymerase inhibitor could potentially facilitate early treatment or post-exposure intervention, followed by antibody therapy after infection is confirmed. In severe disease, an antiviral and antibody could potentially be combined with a carefully selected host-directed intervention. Because SVD outbreaks are sporadic and patient numbers are limited, adaptive platform trials may provide a more practical framework for evaluating such combinations than conventional large-scale randomized trials.

Supportive care remains an essential component of pharmacological management. Direct-acting antivirals cannot substitute for correction of severe dehydration, electrolyte disturbances, hypoglycaemia, shock, bacterial coinfection, or organ dysfunction. Appropriate fluid therapy, electrolyte correction, haemodynamic support, treatment of suspected bacterial infections, management of haemorrhagic complications, and structured survivor follow-up are therefore integral to clinical management. Investigational antiviral therapy should be evaluated alongside optimized supportive care rather than as a replacement for it.

5. CLINICAL TRANSLATION, THERAPEUTIC DEVELOPMENT AND PREVENTIVE STRATEGIES

Translation of promising SVD interventions from experimental models to clinical practice remains challenging because outbreaks are sporadic, geographically concentrated, unpredictable, and usually involve relatively small patient populations. Rapid disease progression further limits conventional phase II and III trials. Consequently, therapeutic development requires integrated evidence from validated animal models, pharmacokinetic and pharmacodynamic studies, immunological correlates, and outbreak-based clinical investigations. Guinea pigs, ferrets, rhesus macaques, and cynomolgus macaques remain important for evaluating candidate therapeutics, treatment timing, vaccine platforms, and dosing. However, differences between animal and human pharmacokinetics, immune responses, and disease progression require cautious interpretation. Late-treatment models that initiate therapy after fever, viraemia, or early organ dysfunction are particularly important because the exact time of human infection is rarely known. [12-14]

The therapeutic landscape has expanded considerably, although the absence of an approved SUDV-specific therapeutic highlights the limitations of extrapolating advances achieved against Zaire ebolavirus. Monoclonal antibodies represent one of the most promising biologically specific approaches. SUDV-specific and pan-ebolavirus antibody combinations, including MBP134, have demonstrated protection in experimental models, including following delayed treatment. Future antibody development should prioritize conserved epitopes, complementary antibody specificities, optimized Fc-mediated activity, prolonged half-life, and manufacturing characteristics compatible with outbreak deployment. Intravenous administration, cost, cold-chain requirements, manufacturing complexity, and potential viral escape remain important limitations.

Small-molecule antivirals provide complementary therapeutic opportunities. Remdesivir has demonstrated experimental activity against SUDV, while orally bioavailable approaches such as obeldesivir are particularly attractive because they could simplify early treatment and post-exposure deployment. Favipiravir and other nucleoside analogues remain candidates requiring further translational evaluation, particularly regarding human pharmacokinetics and effective systemic exposure. Combining polymerase inhibitors with monoclonal antibodies may broaden the therapeutic window by simultaneously reducing intracellular viral replication and neutralizing extracellular virus. RNA-based approaches, particularly VP35-targeting siRNA delivered through lipid nanoparticles, provide another promising platform, although delivery, sequence specificity, viral variation, stability, and manufacturing remain challenges.

Host-directed interventions may complement direct antivirals by addressing inflammatory dysregulation, endothelial injury, coagulation abnormalities, and vascular leakage. However, these pathways are also essential for normal physiological functions, creating a narrow therapeutic window. Future studies should therefore incorporate biomarkers of viral burden, endothelial injury, inflammation, and coagulation to identify the disease stages in which host modulation is most appropriate. Such interventions should complement rather than replace antiviral therapy and optimized supportive care.

Preventive strategies are equally important because SVD can spread rapidly through close contact. SUDV-specific vaccine platforms, including recombinant viral vectors, adenovirus-based approaches, DNA vaccines, and newer technologies, have demonstrated varying degrees of experimental immunogenicity and protection. Single-dose vaccines suitable for ring vaccination of contacts and frontline healthcare workers are particularly valuable for outbreak response. However, small outbreaks may not provide sufficient cases to establish conventional vaccine efficacy, increasing the importance of immunogenicity data and validated correlates of protection.

A major lesson from recent outbreaks is that scientific preparedness and clinical-trial preparedness must advance together. Pre-approved adaptive platform protocols, pre-positioned investigational products, standardized endpoints, pharmacokinetic/pharmacodynamic modelling, trained personnel, regulatory pathways, pharmacovigilance systems, and community engagement should be established before outbreaks occur. The 2025 Uganda outbreak demonstrated that candidate products may be available while regulatory and operational barriers can still limit definitive therapeutic evaluation.

Future SVD preparedness should therefore move beyond development of an isolated drug toward a deployable therapeutic and preventive platform integrating rapid molecular diagnosis, early antiviral therapy, pathogen-specific or pan-ebolavirus monoclonal antibodies, vaccination, intensive supportive care, and carefully selected host-directed interventions. Pharmacovigilance, genomic surveillance, and long-term survivor follow-up should

be incorporated from the beginning. Priorities include generating SUDV-specific clinical pharmacology data, strengthening late-treatment models, evaluating combination regimens for pharmacodynamic synergy, developing validated biomarkers, improving orally available therapies, and engineering antibodies with broad activity against genetically diverse SUDV isolates. This integrated approach offers the most practical pathway for translating experimental advances into effective outbreak preparedness and clinical management.

CONCLUSION:

SUDV causes severe disease through viral replication, immune dysregulation, endothelial injury, inflammation, coagulopathy, and multiorgan damage, providing multiple targets for antiviral and host-directed therapies. Despite promising experimental strategies, the absence of licensed SUDV-specific treatment highlights the need for clinical trials, effective vaccines, optimized supportive care, and coordinated outbreak preparedness.

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