A MEURI-Aligned Emergency Evaluation Protocol for Host-Directed Adjunctive Therapies in Bundibugyo Ebolavirus Disease: A Risk-Benefit Rationale

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Abstract

Background: The escalating outbreak of the Bundibugyo ebolavirus (BDBV) in the Democratic Republic of the Congo (DRC) poses a critical challenge to East African health security. Since approved medical countermeasures (such as ansuvimab-zykl or Inmazeb) are strictly limited to the Zaire ebolavirus due to evolutionary glycoprotein divergence, there is a lack of approved virus-specific therapeutics for BDBV.

Objective: This paper establishes a scientific and ethical rationale for investigating Nitazoxanide (NTZ) as a primary investigational agent and Ivermectin (IVM) as an optional, host-directed adjunctive measure under the WHO Monitored Emergency Use of Unregistered Interventions (MEURI) framework.

Methods & Mechanisms: A risk-benefit analysis compares the historical case fatality rate (CFR) of BDBV of approx. 40% against the established safety profiles of NTZ and IVM in global health programs. Mechanistically, the protocol distinguishes between verified in vitro pathways and clinical hypotheses. NTZ is evaluated for its potential to partially compensate for VP35-mediated immunosuppression by amplifying the upstream mitochondrial RIG-I/MAVS signaling cascade. IVM is introduced via a nuclear transport inhibition hypothesis: It is postulated that Ivermectin could interfere with the VP24-karyopherin axis by modulating the availability of the importin-α ARM domains; however, this requires direct validation.

Conclusion: In the absence of approved virus-specific treatments, the use of highly tolerable, host-directed molecules within a strictly monitored ethical framework offers a pragmatic, risk-minimized strategy for the systematic evaluation of interventions while simultaneously strengthening regional outbreak preparedness.

Keywords: Bundibugyo ebolavirus, Nitazoxanide, Ivermectin, Importin alpha, ARM domains, VP24, MAVS, MEURI, Viral Immune Evasion, Host-Directed Therapy, Drug Repurposing

1. Introduction: The Therapeutic Context in Bundibugyo Ebolavirus

Regional containment of the Bundibugyo ebolavirus (BDBV) remains a priority for health systems in Central and East Africa. Historical outbreaks (e.g., in Uganda) show a case fatality rate (CFR) of approx. 40% in laboratory-confirmed cases (MacNeil et al., 2010). Early supportive intensive care remains the central pillar of survival. Despite significant progress in filoviral therapeutics, approved specific antiviral options for the Bundibugyo species are lacking (WHO, 2026).

Approved antibody cocktails such as Ebanga and Inmazeb bind to highly specific, conserved epitopes of the Zaire ebolavirus glycoprotein. Reviews emphasize that these therapies cannot be considered a universal solution for other species, as BDBV has a structural conformation that limits cross-reactivity (Rijal et al., 2023). Since the development of BDBV-specific vaccines or antibodies requires time, the identification of readily available, heat-stable molecules via host-directed drug repurposing must be scientifically examined.

2. Standard of Care and Risk-Benefit Analysis

It is imperative that investigational drugs complement rather than replace evidence-based supportive care. Strict adherence to guidelines for hydration, electrolyte balance, and organ support in Ebola treatment centers remains the irreplaceable basis of any intervention (Lamontagne et al., 2018; WHO, 2019).

Compared to experimental direct-acting antivirals (e.g., Favipiravir or Remdesivir), which are historically associated with potential hepatotoxicity or transaminitis, NTZ and IVM exhibit highly favorable safety profiles in global use. Given a baseline mortality of 30 to 50% for BDBV, the low risk of severe toxic side effects of these repurposed drugs yields a favorable theoretical risk-benefit ratio for a monitored emergency evaluation.

3. Pharmacological Rationale: Mechanisms and Plausibility

This protocol strictly separates (1) verified host-directed in vitro mechanisms, (2) biological plausibility, and (3) translational limitations. Host-directed therapies (HDTs)

target cellular pathways required by the pathogen, thus offering a theoretical possibility to bypass the structural divergence of the BDBV genome.

3.1 Nitazoxanide: The RIG-I/MAVS Signaling Axis

The pathogenicity of the ebolavirus relies largely on the early suppression of the innate immune response. The main mediator of this immune evasion is the viral VP35 protein, which masks double-stranded viral RNA (dsRNA) and disrupts host cascades, thereby blocking the activation of IRF-3 and the production of interferon-β (Basler et al., 2000; Cárdenas et al., 2006). Furthermore, VP35 antagonizes PACT-induced RIG-I activation (Luthra et al., 2013).

Preclinical data show that, as a primary rationale, NTZ significantly enhances the host's antiviral responses and inhibits EBOV replication in vitro (Jasenosky et al., 2019). Mechanistically, NTZ upregulates the RIG-I pathway and strengthens the RIG-I/MAVS signaling axis, whereby it can partially compensate for VP35-mediated suppression by amplifying upstream signaling pathways.

3.2 Ivermectin: The Importin-α ARM Domain Hypothesis

Besides its established role in dermatological secondary complications, the investigation of IVM is based on a mechanistically plausible hypothesis regarding the virus's second immune evasion protein: VP24.

Ebola VP24 blocks the nuclear STAT1 transport by selectively competing with phosphorylated STAT1 for binding to karyopherin/importin-α (Reid et al., 2006; Xu et al., 2014; Zhao et al., 2025). Since IVM has been shown to bind to the ARM-repeat domains of importin-α (Wagstaff et al., 2012; Yang et al., 2020) and VP24 utilizes exactly these interfaces, IVM represents a plausible candidate.

Hypothesis: We postulate that IVM could interact with the VP24-karyopherin axis by modulating the availability of the ARM domains; however, this requires direct validation in BDBV models.

3.3 Pharmacokinetic and Translational Safeguards

Although NTZ has direct Ebola-relevant preclinical data, a pharmacokinetic (PK) translation cannot be automatically assumed and must be specifically evaluated in BDBV-relevant models and under the physiological conditions of severe illness (Driouich et al., 2022).

For Ivermectin, the main limitation lies in pharmacokinetic translation: Concentrations required for nuclear transport effects in vitro may not be achievable in vivo with approved dosing regimens (Momekov & Momekova, 2020; Bray et al., 2020). Therefore, IVM should be viewed strictly as an exploratory adjunct and not as a primary intervention.

4. Ethical Implementation via the WHO MEURI Framework

The use of unproven interventions in outbreak situations requires the highest level of ethical and operational rigor (Krech et al., 2014; Calain, 2018). The protocol aligns with the WHO MEURI framework (WHO, 2014) and includes:

1. 1. Absence of approved specific therapies for BDBV.
2. 2. A scientific rationale based on in vitro data.
3. 3. Ethical review by national bodies.
4. 4. Informed consent.
5. 5. Prospective data collection and monitoring.

Under this framework, NTZ is positioned as the primary candidate, while IVM functions as an optional exploratory arm.

5. Conclusion

Given the high lethality, lack of specific therapy, and a favorable safety profile of the drugs, a monitored emergency evaluation is ethically and scientifically justifiable. NTZ offers a direct preclinical rationale for enhancing innate immunity, while IVM remains mechanistically plausible as an adjunctive hypothesis. Strict embedding in the MEURI

protocol with clear stopping rules and ethical approvals ensures a risk-minimized approach to evaluation while respecting standard of care.

References

Basler, C. F. (2009). Evasion of Interferon Responses by Ebola and Marburg Viruses. Journal of Interferon & Cytokine Research, 29(9), 511-520. https://doi.org/10.1089/jir.2009.0066

Basler, C. F., et al. (2000). The Ebola virus VP35 protein inhibits activation of interferon regulatory factor 3 and interferon-beta production. Journal of Virology, 74(18), 8410-8419. https://doi.org/10.1128/jvi.74.18.8410-8419.2000

Bray, M., et al. (2020). Ivermectin and COVID-19: A report in Antiviral Research, widespread endorsement on social media, pastoral care, and psychiatry. Antiviral Research, 178, 104805. https://doi.org/10.1016/j.antiviral.2020.104805

Calain, P. (2018). The Ebola clinical trials: a precedent for research ethics in disasters. Journal of Medical Ethics, 44(1), 11-12. https://doi.org/10.1136/medethics-2016-104120

Cárdenas, W. B., et al. (2006). Ebola virus VP35 protein binds double-stranded RNA and inhibits alpha/beta interferon production induced by RIG-I signaling. Journal of Virology, 80(11), 5168-5178. https://doi.org/10.1128/JVI.02199-05

Driouich, J. S., et al. (2022). Pre-clinical evaluation of antiviral activity of nitazoxanide against Ebola virus. Antiviral Research, 203, 105315. https://doi.org/10.1016/j.antiviral.2022.105315

Jasenosky, L. D., et al. (2019). The FDA-Approved Oral Drug Nitazoxanide Amplifies Host Antiviral Responses and Inhibits Ebola Virus. iScience, 19, 1279-1290. https://doi.org/10.1016/j.isci.2019.07.003

Krech, R., et al. (2014). The 2014 Ebola outbreak: ethical use of unregistered interventions. Bulletin of the World Health Organization, 92(9), 622. https://doi.org/10.2471/BLT.14.145318

Lamontagne, F., et al. (2018). Evidence-based guidelines for supportive care of patients with Ebola virus disease. The Lancet, 391(10121), 700-712. https://doi.org/10.1016/S0140-6736(17)31795-6

Luthra, P., et al. (2013). Mutual antagonism between the Ebola virus VP35 protein and the RIG-I activator PACT determines infection outcome. Journal of Virology, 87(19), 10427-10441. https://doi.org/10.1128/JVI.01374-13

MacNeil, A., et al. (2010). Proportion of Deaths and Clinical Features in Bundibugyo Ebola Virus Infection, Uganda. Emerging Infectious Diseases, 16(12), 1969-1972. https://doi.org/10.3201/eid1612.100627

Momekov, G., & Momekova, D. (2020). Ivermectin as a potential COVID-19 treatment from the pharmacokinetic point of view: antiviral levels are not likely attainable with known dosing regimens. International Journal of Antimicrobial Agents, 56(6), 106006. https://doi.org/10.1016/j.ijantimicag.2020.106006

Reid, S. P., et al. (2006). Ebola virus VP24 binds karyopherin alpha1 and blocks STAT1 nuclear accumulation. Journal of Virology, 80(11), 5468-5479. https://doi.org/10.1128/JVI.02349-05

Rijal, P., et al. (2023). Therapeutic monoclonal antibodies for Ebola virus infection. Current Opinion in Virology, 58, 101284. https://doi.org/10.1016/j.coviro.2022.101284

Rossignol, J. F. (2014). Nitazoxanide: a first-in-class broad-spectrum antiviral agent. Antiviral Research, 110, 94-103. https://doi.org/10.1016/j.antiviral.2014.09.008

Wagstaff, K. M., et al. (2012). Ivermectin is a specific inhibitor of importin α/β-mediated nuclear import able to inhibit replication of HIV-1 and dengue virus. Biochemical Journal, 443(3), 851-856. https://doi.org/10.1042/BJ20112116

WHO. (2014). Ethical considerations for use of unregistered interventions for Ebola virus disease (EVD). WHO Technical Report Series, 982. URL: https://apps.who.int/iris/handle/10665/130997

WHO. (2019). Optimized Supportive Care for Ebola Virus Disease. WHO Clinical Management Guidelines. URL: https://apps.who.int/iris/handle/10665/324844

WHO. (2026). Disease Outbreak News: Bundibugyo ebolavirus. URL: https://www.who.int/emergencies/disease-outbreak-news/

Xu, W., et al. (2014). Ebola virus VP24 targets a unique NLS binding site on karyopherin alpha 5 to selectively compete with nuclear import of phosphorylated STAT1. Cell Host & Microbe, 16(2), 187-200. https://doi.org/10.1016/j.chom.2014.07.008

Yang, S. N. Y., et al. (2020). The broad spectrum antiviral ivermectin targets the host nuclear transport importin α/β1 heterodimer. Antiviral Research, 177, 104760. https://doi.org/10.1016/j.antiviral.2020.104760

Zhao, Y., et al. (2025). Biophysical Basis for Karyopherin-Dependent Ebola VP24 Nuclear Transport. PMC12390655. URL: https://pmc.ncbi.nlm.nih.gov/articles/PMC12390655/