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Letter to the Editor

Remdesivir triphosphate as a potential repurposed drug against the emerging Bundibugyo Ebolavirus 2026

Dear Editor,

Bundibugyo virus disease (BVD) is a rare and often fatal form of Ebola disease caused by the contagious Bundibugyo virus (BDBV), a member of the *Orthoebolavirus* (formerly *Ebolavirus*) genus within the family *Filoviridae* family.[1] This zoonotic disease is a deadly illness with a reported morality rate range from 30 to 50%.[2] Currently, two East-central African countries, namely, the Democratic Republic of Congo (DRC) and Uganda have had outbreaks of the rare BDBV. On 17 May 2026, World Health Organization (WHO) declared multiple Ebola outbreaks as a Public Health Emergency of International Concern (PHEIC) due to a surge in the number of confirmed deaths and cases. As of 23 May 2026, a total of the 83 confirmed cases, 9 confirmed deaths with 746 suspected cases and 176 suspected deaths, have been reported from the Ituri, Nord-Kivu, South-Kivu provinces of DRC with a Case Fatality Rate (CFR) of **11%**. Uganda has reported 5 confirmed cases and 1 confirmed death.[3] These confirmed cases reported from Uganda are linked to the people who have recent history of travel from the DRC or contact with confirmed travel cases of BDBV.

Currently, there are no FDA approved drugs for the treatment of BVD, however, nmazeb (REGN-EB3) and Ebanga (mAb114) have been approved for *Zaire ebolavirus*.[4,5] Therefore, there is a pressing demand for counter measures for the treatment of BDBV. One expedited approach is to screen repurposed drugs that could serve as potential inhibitors of the key drug targets of the BDBV proteins and aid in controlling viral replication.

Remdesivir triphosphate (RTP) is a substrate for RNA synthesis and been reported to be easily incorporated by viral RNA-dependent RNA polymerases (RdRp).[6] The analog monophosphoramidate prodrug was found to inhibit the replication of human and animal coronaviruses based on the in vitro and preclinical studies.[7,8] Remdesivir marketed as Veklury is currently approved by the U.S. Food and Drug Administration (FDA) and other global health agencies for the treatment of coronavirus disease 2019 (COVID-19). Preliminary studies also reported the potential effectiveness of this antiviral candidate against the Ebolavirus species, Ebola Zaire (EBOV) and BDBV, however, its performance was found to differ between laboratory models and clinical trials.[9,10] Due to the absence of effective antivirals and remdesivir role as an inhibitor of viral RdRp in clinical COVID-19, it's now in consideration for the treatment of the patients infected with BDBV in the ongoing outbreaks in DRC and Uganda.

In the present study, we performed molecular and mutational annotation of RNA-dependent RNA polymerase from BDBV and molecular docking of Remdesivir triphosphate (RTP) to RNA-dependent RNA polymerase in BDBV to evaluate inhibition potential inhibition of RTP against the RdRp encoded by the Large (L) protein of the BDBV. Recently, we sequenced a clinical isolate (CL023114) of a 59-year-old BDBV infected patient which was identified as travel case. Genome sequencing was performed using the Illumina NextSeq and the sequence was submitted to the Pathoplexus platform with accession number of PP_006XCJJ.1. Based on the sequence alignment with reference genome (NC_014373.1), we noted that the encoded L protein was found to possess a total of 14 amino acid substitutions (Fig. 1a). Of the 14, six amino acid substitutions (L1011F, N1342H, K1738N, Q1770R, N1771D, and R1954G) were found to be unique to CL023114 (BDBV 2026). To predict an accurate three dimensional (3D) structural model of the L protein (RdRp), the Google DeepMind-based AlphaFold3 algorithm was employed. The predicted template modeling (pTM), score of 0.85 was obtained, this score indicates a high global confidence of the modeled structure of the L protein.

The modeled structure was truncated to avoid the non-binding artifacts during the molecular docking and optimize the computational efficiency. Based on the UniProt (Accession: B8XCN5_9MONO) annotation, the primary core catalytic engine of the RdRp is annotated for residues 625 to 809 (Fig. 1b-c). This range excludes the important structural elements for the nucleotide-binding pocket (F motif loop). We therefore addressed this issue by constructing a broader model containing residues 500 to 850 using command based PyMOL(https://www.pymol.org/) to preserve the 3D model architecture of palm and fingers subdomains of the binding pocket of RdRp (Fig. 1d). Before docking, this truncated structure model was further utilized for energy minimization using the AMBER forcefield embedded in the ChimeraX package (https://www.rbvi.ucsf.edu/chimerax/).

The AutoDock Vina (version 1.1.2) embedded in the CB-dock2[11] package was employed to identify cavities and molecular docking. For docking, RTP was docked with RdRp (PDB ID: 7BV2) of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) as a positive control, while acyclovir was docked with the 3D BDBV 500–850 binding pocket substructure of RdRp as a negative control (Supplimentry Figures 1–2). Docked RDT with the BDBV RdRp 500–850 substructure exhibited a favorable binding affinity of −7.0 kcal/mol. This was comparable to the positive control value of −7.3 kcal/mol for RdRp of SARS-CoV-2 which was FDA approved for COVID-19. RDT binding to BDBV 500–850 substructure was substantially higher than the weak interaction observed for acyclovir binding (negative control), which showed a binding affinity of only −4.8 kcal/mol. Different functional groups of RTP were found to strongly interact to the BDBV RdRp with a number of molecular bonds including conventional hydrogen bonds, carbon hydrogen bonds, Pi-cation, Pi-anion, Pi-alkyl and van der Waals (vdW). As evident from Fig. 2a-d, the amine group (-NH_2) manifests two strong conventional hydrogen bonds with Glu554. The aromatic

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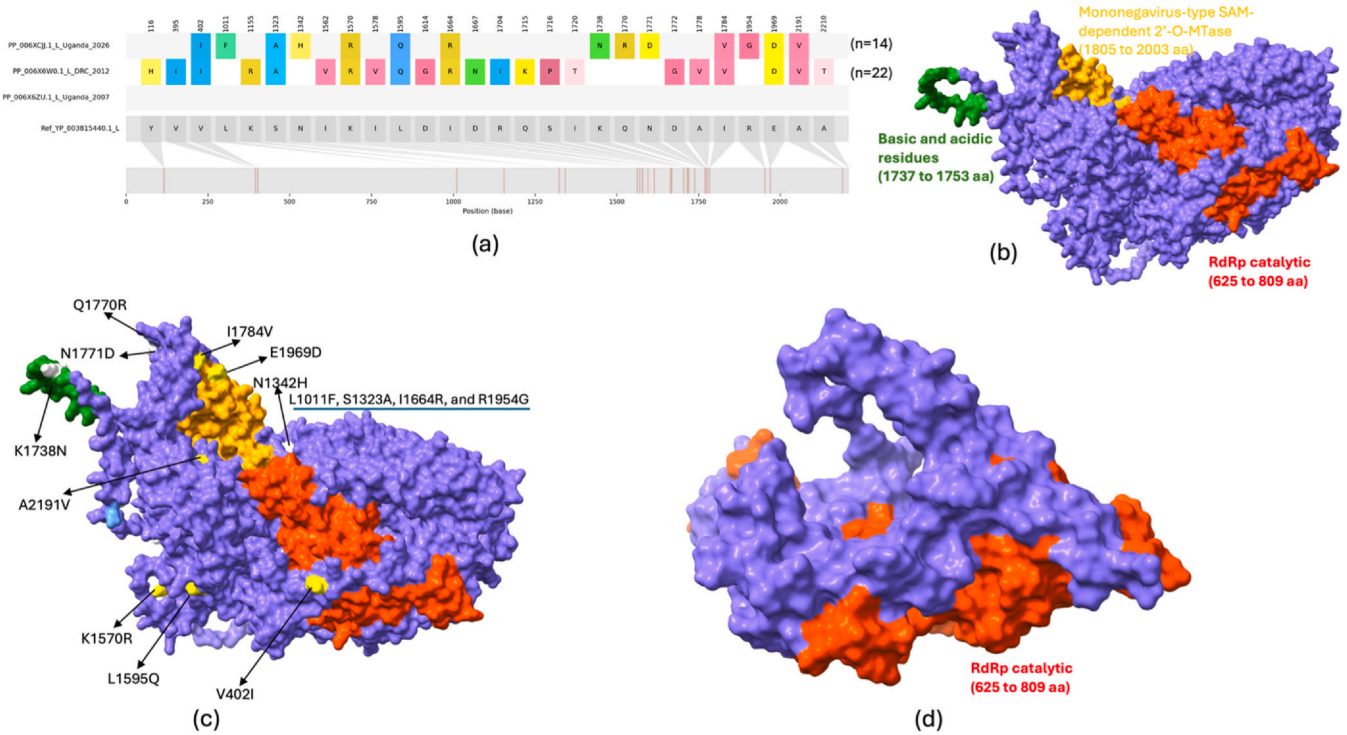

Fig. 1. Sequence to structure presentation of the RdRp encoded by the L protein of the BDBV strain representing the ongoing outbreak in the Democratic Republic of Congo and Uganda. (a) Sequence alignment between L protein of Bundibugyo virus (BDBV) new and old sequences. (b) Surface structure view of the modeled 3D structure of the BDBV L protein. Functional domains are highlighted with corresponding colors. (c) Superimposed surface three dimenstional representation of the mutative and wild L protein structures. Common mutations are highlighted with yellow color, while unique mutations are depicted in white color. Underline mutations belong to the other side of the protein. (d) Surface representation of the truncated L protein (500 to 850 aa). The RNA-dependent RNA polymerase catalytic domain is highlighted with red color (625 to 809 aa).

heterocycle of RTP form a Pi-alkyl interaction (hydrophobic) with Lys555 residue and an electrostatic Pi-charge with Lys553. In the triphosphate tail, the oxygen atoms of the phosphate groups manifest two conventional hydrogen bonds with the Arg561 and Gln713 residues. As shown in Fig. 2c-d, the tail of RTP is stabilized by strong multiple electrostatic forces (attractive charge, Pi-cation, and Pi-anion) and forms the interactions with the Glu556, Asp632, Asp742, and Glu709 residues. Other than these interactions, the complex of BDBV RdRp and RTP is further stabilized by a number of multiple vdW interactions with Met594, Asn637, Met740, Gly741, and Lys803 residues. Taken together, the combination of the multiple chemical interactions shows that RTP tightly binds to the pocket and is predicted to block viral replication (Fig. 2e-f).

Based on the 3D visualization of the complex, we observed that among the interacted residues, five residues namely (Lys553, Glu554, Lys555, Glu556, and Arg561) belong to the motif F (the finger domain ceiling). Motif F is important to form the “roof” over the incoming nucleotide substrate. The Glu554 and Lys555 tightly docked with the aromatic rings while the Arg562 tightly docked with the first phosphate group that showed that the RTP fits in the active site of the protein, adjacent to the F548 residue which has been defined as the resistance marker region in previous published reports.[12,13] Two interacting residues (Asp632 and Asn637) belong to motif A (the palm core) which is highly conserved and important for coordination with template RNA and substrate entry. In our analysis, we observed that interacted Gln713 belongs to the motif B forming a hydrogen bond with the terminal phosphate group. This motif plays a role in the conformational transition during the process of nucleotide selection. Three amino acid residues namely, Met740, Gly741, and Asp742 belong to the motif C neighboring regions and is also known as the catalytic floor background. These residues are adjacent to the catalytic engine (S759-D761).

The integrated molecular modeling and docking analysis presented here show that the RTP forms a stable complex with the RNA-dependent RNA polymerases of BDBV 2026 with the aid of dense interaction bonds. The binding value of RTP to RdRp was consistent with the binding value of RTP to SARS-CoV-2 RdRp. RTP has already been approved against the SARS-CoV-2 and other human and animal coronaviruses, we expect treatment of BVD with RTP will act in a similar fashion, providing inhibition of BDBV viral replication in humans. The evidence shown in this study, plus Remdesivir’s low side effect profile [9], in addition to emerging evidence of effectiveness against Sudan Ebolavirus in clinical settings supports the rationale for compassionate use *(in press NEJM)*. It should be noted, however, RTP is recommended at the earliest stages of COVID-19, with effectiveness diminishing when given only during later stages of disease. Treatment of BDBV with RTP may have a similar effective window and must be taken into consideration in clinical trial design or in compassionate use. This aligns with the early use of RTP that exhibited efficacy against Sudan Ebolavirus disease during the 2025 outbreak in Uganda (unpublished data, Bakamutumaho et al., one of the co-authors of this paper).

In summary, in the present study, we mapped the mutations in the L protein encoded by the newly sequenced genome of BDBV 2026 from the ongoing ebola outbreak in DRC and Uganda. Based on the mutation mapping profile, we observed no new mutations in the RdRp catalyst domain. Subsequently, we modeled the RdRp BDBV 2026 protein and docked RTP with the RdRp catalyst domain. RTP is an approved antiviral drug for SARS-CoV-2. The binding affinity of RTP to BDBV 2026 RdRp was found similar to the binding affinity of RTP to SARS-CoV-2 RdRp catalytic domain. RTP was found to tightly fit within the pocket site and the complex of the RTP and RdRp showed dense molecular interactions aiding in stabilizing the complex. Validation may be confirmed mechanistically with the aid of cell culture and preclinical challenge studies.

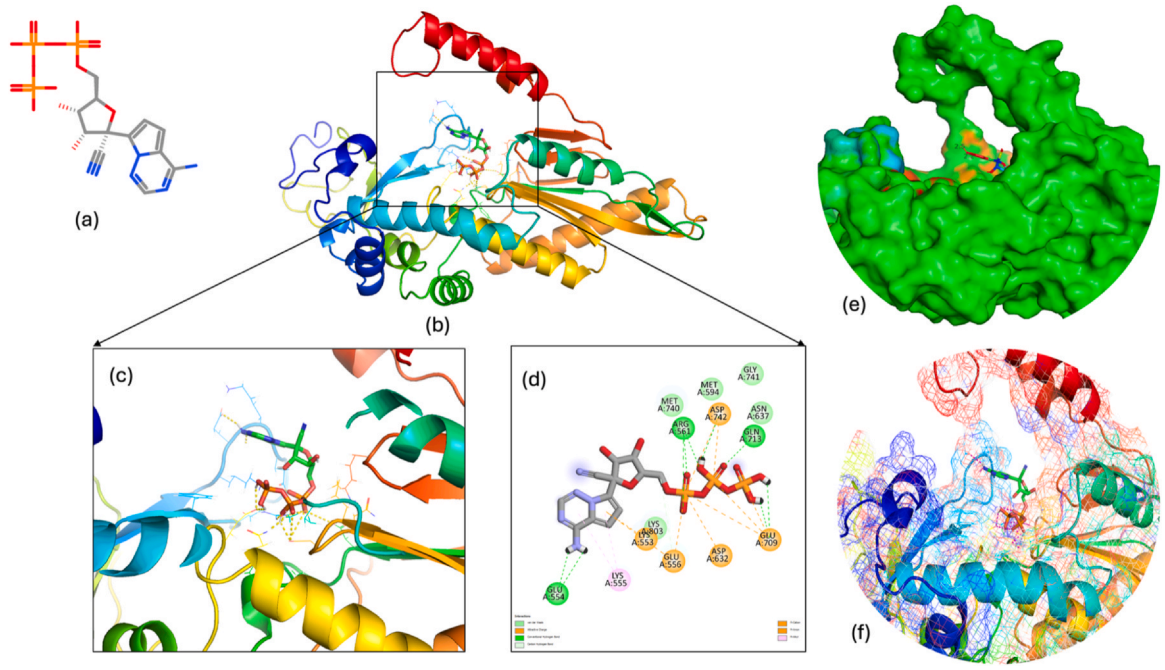

Fig. 2. Three dimenstional (3D) and two dimesntional (2D) representation of the docking complex of Remdesivir triphosphate (RTP) and RNA-dependent RNA polymerase (RdRp) catalytic domain of Bundibugyo virus (BDBV). (a) 2D structure of the RTP. (b) Cartoon representation of the of truncated RdRp domain in complex with RTP. RTP is shown with rainbow color. (c) Expended view of the complex. Interactions are highlighted with yellow dot lines. (d) 2D plot of interactions between RTP and RdRp domain. (e) Surface representation of the complex interacted residue's location is highlighted with orange color. (f) Mesh representation of the complex, RTP is shown in the rainbow color.

Author contributions

Genome Sequencing of BDVB clinical isolate: AN, IS, SN, MW, HKB; Providing laboratory resources and policy instruments for outbreak response: CO, J-ROA, DA, HKB; Annotations: AK; Conceptualization: MD, MW, AK, BB, BK, WM, PB, HKB, DK, WS; Drafting the manuscript: MD, AK, DK; Reviewing and editing the manuscript: All authors.

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Declaration of Competing Interest

GSM, AK, MD, and DJK are shareholders of the company BioForge Canada Limited. BioForge Canada Limited is a company that uses bioinformatics in immunological approaches in the monitoring, prevention, and treatment of infectious diseases. The authors disclose that the interests of BioForge Canada Limited had no impact in this study. DJK is a scientific advisory board member for Emergent BioSolutions. All other authors declare no competing interests.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jinf.2026.106788.

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