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| Candidate | Class | Available evidence | considerations |
|---|---|---|---|
| **Favipiravir (OS)** | Antiviral – RdRp Inhibitor | **In vitro activity** DOBV, **ANDV**, SNV, Maporal virus<br>**Protective against** non-fatal and lethal **ANDV**, SNV infection in hamster model<br>**Not protective**, after viraemia occurred (D5 animal model) | **Potential use** in **PEP** or **pre-emptive** treatment?<br>**Check** for **activity** and **EC90/50**<br>**Likely not useful** in **later stages** of disease |
| **Ribavirin (OS or IV)** | Antiviral – Nucleoside Analogue | **In vitro activity** HTNV, **ANDV**, SNV<br>**Protective** against lethal **ANDV** infection in hamster model<br>**HCPS** clinical data **not supportive** | **Potential** OS for **prevention?** |
| **Baloxavir** | Antiviral – CAP endonuclease inhibitor | **No published** classical **in vitro data**<br>Enzyme-Linked Focus Formation Assay showed **in vitro inhibition** against **HTNV** | **Preclinical stage**, check for in **vitro activity** and **EC90/50**<br>**Likely high IC50** needed for activity |
| **Molnupiravir** | Antiviral – RdRp Inhibitor | **No published** in **vitro activity data**<br>Mechanistic rationale | **Preclinical stage**,<br>check for in **vitro activity** and **EC90/50** |
| **Griffithsin/3mGFRT** | Entry inhibitor homodimeric lectin | **In vitro activity ANDV**, SNV, Entry inhibition,<br>**No animal data ANDV** but partial protection in suckling mice HTNV model | **Preclinical stage**,<br>**lack** of **ANDV** animal efficacy **data** |
| **Coumarin derivates** | Aromatic organic compound with antiviral activity | **In vitro activity ANDV**, HTNV,<br>**No animal data ANDV**, prolonged survival rate of HTNV-infected mice | **Preclinical stage**,<br>**Lack** of **ANDV animal** efficacy **data** |
| **Neutralising Antibodies** (ADI-65533, JL16+MIB22, SAB-163) | Monoclonal/polyclonal antibodies | **In vitro activity ANDV**, PUUV, SNV, HTNV<br>**Increased survival** in **ANDV hamster** models and other HTNVs | **Preclinical stage**, no safety data |
| **Icatibant** | Immunomodulator Bradykinin B2 receptor antagonist | **Antagonizes vascular leakage**<br>Two **clinical PUUV cases** showed **improved outcome** | Being considered **for severe cases** |
| **Vandetanib** | Immunomodulator Inhibitor of vascular endothelial growth factor receptor-2 (VEGFR-2) | **Reduction** of **ANDV** induced increased **endovascular permeability**<br>**Increased survival** in **ANDV hamster model** if given 5 days **prior to infection**<br>**Failure** to **protect** when **viraemia started** | **Preclinical stage**, |
| **Methylprednisolone** | Immunomodulators steroids | **High dose methyleprednisolone tested in a clinical trial with high dose for HPS hantavirus severe infections in Chile – no effect** | Should low dose be considered?<br>Other immunomodulators? Vilobelimab? Tocilizumab? FX-06? |

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# Timing of antiviral administration– Hamster model

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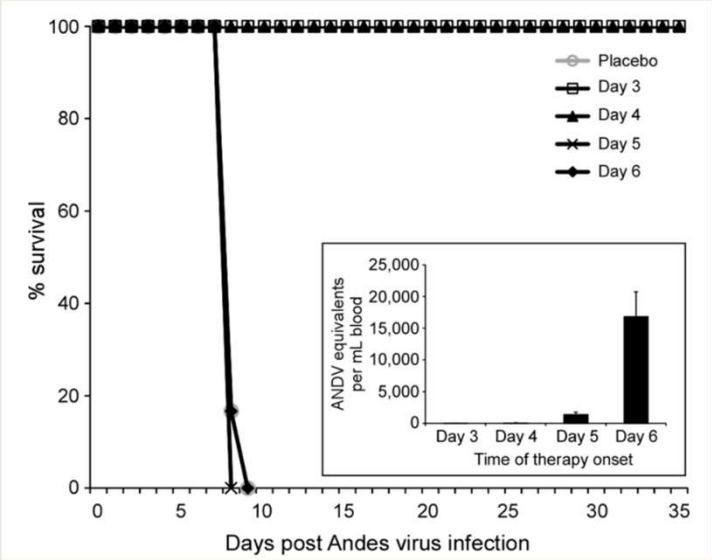


https://pmc.ncbi.nlm.nih.gov/articles/PMC3811478/



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# Viral sanctuaries and role of antivirals

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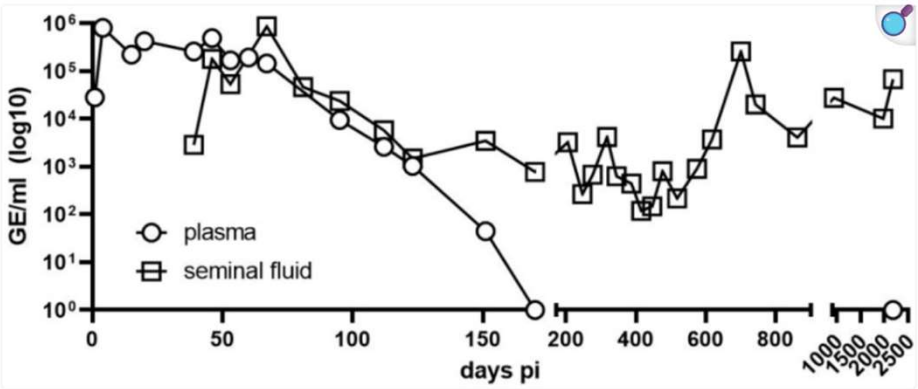


Detection of Andes virus RNA in plasma and semen. RNA levels from plasma (circles) and semen (squares) were assessed on the indicated days post infection using in-house quantitative real-time polymerase chain reaction; viral load on day 1 was from a serum sample, and from day 4 onward was from EDTA blood.

https://pmc.ncbi.nlm.nih.gov/articles/PMC10675069/men - PMC



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# Therapeutic Prioritisation TAG review

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Repurposed antivirals and immunomodulatory are classes of agents that should be considered for rapid clinical research evaluation.

Antivirals should be primarily considered in the context of post exposure prophylaxis or early treatment in the prodromic phase

Among repurposed antivirals, favipiravir is the candidate to be prioritized based on the available data, i.e. preclinical data vs hantaviruses and clinical experience for safety/PK and dose selection

Ribavirin has not been effective in the treatment of HPS viruses disease and while preclinical data and anecdotal clinical experience might support its for PEP, the safety profile and uncertain benefit risk reduce its suitability as a priority antiviral

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# Therapeutic Prioritisation TAG review

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Other repurposed antivirals, such as molnupiravir, need rapid in vitro testing to check for their potential utility, followed by animal model testing

Baloxavir should be tested as well for proper EC50/90 determination, but current data would not support its use at currently approved doses for influenza PEP and treatment

Very promising monoclonal antibodies with broad hantavirus antiviral activity are in the pipeline but still in preclinical stage. They need to be progressed swiftly to clinical testing including the option of combination therapy and long half life features to support PEP

Once the disease progresses to cardiopulmonary phase, immunomodulators as best option: proper characterization of pathophysiology, endothelial disfunction and vascular leakage needed to target interventions and patients phenotypes

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Thank you
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