Categorization and prioritization of drugs for consideration for testing or use in patients infected with Ebola

This table, which is updated on a continuous basis, summarizes the data on drugs that are either being tested or considered for testing in patients with Ebola virus disease (EVD) or have already been used in patients with EVD, as well as those which had been considered but which have been deemed to not be appropriate for further investigation.

Note: Drugs marked with an asterisk (*) indicate that these are proposed to work through a host-directed mechanism rather than a direct antiviral mechanism (e.g. through preventing endothelial integrity loss, preventing inflammation, enhancing the immune response). For these drugs, measurement of in vitro antiviral activity may be irrelevant.

CATEGORY A: DRUGS ALREADY UNDER EVALUATION IN FORMAL CLINICAL TRIALS IN WEST AFRICA

<table>
<thead>
<tr>
<th>DRUG / COMPANY</th>
<th>DRUG TYPE</th>
<th>EBOLA PRECLINICAL DATA</th>
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<tr>
<td>FAVIPIRAVIR (Fuji/Toyama Japan)</td>
<td>Small molecule antiviral with activity against many RNA viruses. Functions through inhibiting viral RNA-dependent RNA polymerase. Approved in Japan for treating novel/pandemic influenza.</td>
<td>In-vitro inhibition IC50 64 µM; higher than that needed for influenza. Mice: protected at 300mg/kg. Nonhuman primate (NHP): antiviral effect seen; 2 log reduction in viraemia. Model limitation due to frequent need to anesthetize NHP to administer drug orally.</td>
<td>Clinical use in healthy volunteers up to 3.6g on first day followed by 800mg twice daily (BID). No safety issues identified. Increased drug exposure in setting of hepatic dysfunction</td>
<td>200mg tablets; dosing at 6g/first day requires 30 tablets – potentially difficult to swallow. 1.6 million tablets available free (10,000 treatment courses). Thermostable.</td>
<td>4 patients received drug under compassionate use. No conclusions possible from these patients, but no obvious safety concerns identified. Clinical efficacy trial began in Guinea in December 2014. Target 6g dosing (day 1) followed by 2.4g per day (day 2-10). Preliminary data presented in early February by investigators does not permit a firm conclusion regarding efficacy and more data is required.</td>
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</table>
### CATEGORY B: DRUGS THAT HAVE BEEN PRIORITIZED FOR TESTING IN HUMAN EFFICACY TRIALS BUT FOR WHICH SUCH TRIALS ARE NOT YET UNDERWAY

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<tr>
<td><strong>Zmapp</strong></td>
<td>Cocktail of three monoclonal antibodies produced in tobacco plants.</td>
<td>NHP: 100% survival when administered 5 days after virus challenge.</td>
<td>No formal safety studies in humans yet. Phase I safety study initiated in January 2015.</td>
<td>Supply reported to be 15 treatment courses every 6 weeks.</td>
<td>8 patients treated on compassionate grounds to date. No conclusion regarding safety or efficacy possible. Some adverse reactions noted – possibly due to immune complex formation with virus. <strong>Phase I safety/PK study started in January 2015. Efficacy study due to start in early 2015.</strong></td>
</tr>
<tr>
<td><strong>TKM-100802</strong></td>
<td>Small inhibitory RNA which catalytically cleaves Ebola RNA once inside the cell. Sequence-specific to this strain of Ebola.</td>
<td>NHP: 67-100% efficacy among NHP given 4 to 7 doses with treatment initiated 30 minutes post-challenge.</td>
<td>A Phase I safety study found dose-related side effects including dizziness, chest tightness, raised heart rate. A lower dose was better tolerated. A study in healthy volunteers is on partial clinical hold.</td>
<td>Several hundred doses currently available. Several thousand doses could be available in short time period. IV infusion. Requires refrigeration.</td>
<td>Used on a compassionate basis in 6 patients. No conclusion regarding efficacy possible. Hypotension observed in some of the patients possibly related to drug administration. <strong>Clinical efficacy trial due to start in early 2015.</strong></td>
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<tr>
<td><strong>AVI-7537</strong></td>
<td>Antisense polymorpholino oligonucleotide. Inhibits Ebola virus replication by binding to RNA in sequence-specific manner to VP24 gene. Specific to this strain of Ebola.</td>
<td>NHP: 100% survival for Marburg virus (using Marburg sequence) and 50–60% survival for Ebola using Ebola sequence.</td>
<td>Phase I safety study completed. Tolerability demonstrated.</td>
<td>Limited no. of doses available.</td>
<td>No clinical trials planned at this time.</td>
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</table>
| **BCX-4430**  
* (Biocryst, USA) | Novel broad-spectrum direct-acting nucleoside analogue.  
NHP: Marburg virus—treatment at 15mg/kg starting 1, 24, or 48 hours after infection: 80–100% protection.  
NHP: Ebola — efficacy when administered 30-120 minutes post infection. Not efficacious at 48–72 hours.  
Mice: Ebola — 100% protection.  
Phase I safety trial initiated. Results expected early 2015  
Intramuscular (IM) or IV administration.  
Current drug supply limited to clinical studies. Supply for >1 000 patients available by May 2015.  
**Phase I safety trial underway.**  
No efficacy trial planned at this moment. Waiting for safety data from Phase I. |
| **INTERFERONS **  
* (with or without ribavirin) | Immune modulator with antiviral activity. Approved for hepatitis B and C therapy and multiple sclerosis.  
NHP: Trends toward delay to death (IFN-beta) but no survival benefit.  
Mice: interferon with or without ribavirin — no effect on survival.  
Used widely in chronic viral infection. Common side effects include fevers and myalgia.  
Available. Multiple sources and types (e.g. pegylated) Administered IV or SC.  
Requires refrigeration.  
**Considered to be problematic:** Safety/reactogenicity profile considered problematic in an Ebola treatment unit (ETU) clinical setting. Ensuring absence of comorbidities such as malaria may be required to minimize risk in using these drugs.  
**Clinical trial being considered in Guinea.** |
| **rNAPc2**  
* (Arca Biopharma, USA) | Anti-coagulant / anti-inflammatory (Tissue factor inhibitor).  
Recombinant protein cloned from saliva of hookworm  
33% survival of NHPs challenged with ZEBOV (treatment at 24 hours).  
Significant increase in survival time for all animals.  
100-150 treatment courses available.  
Recently retested and released.  
No trials planned at this moment. |
**CATEGORY C. DRUGS THAT HAVE ALREADY BEEN GIVEN TO PATIENTS FOR COMPASSIONATE REASONS OR IN AD HOC TRIALS**

In this category are drugs that have been used on a few patients, but not in formal clinical trials. Additional information on the safety and efficacy from the human use or additional preclinical data will be required before these products can be prioritized for formal clinical trials. This group also includes products that have been used, but are not yet available at GMP grade and hence cannot be prioritized.

These do not meet the WHO criteria for moving to formal clinical trials since preclinical data or human safety/PK data are insufficient.

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<td><strong>Zmab</strong> (Defyrus [Canada] and Public Health Agency of Canada)</td>
<td>Cocktail of three monoclonal antibodies (mAb) produced in mammalian cells. Two of the monoclonals are also used in Zmapp.</td>
<td>NHP: 100% efficacy.</td>
<td>No safety studies in humans.</td>
<td>GLP product (not GMP); only for research use.</td>
<td>Used on a compassionate basis in 4 patients. Research quality material. Not GMP at this stage so no trial planned. No plans at moment for taking to GMP production.</td>
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<tr>
<td><strong>Zmapp from CHO cells</strong> (several manufacturers)</td>
<td>MAb cocktail. Same cocktail and same sequences as Zmapp but produced in CHO cells. In theory should be similar to Zmapp but different glycosylation may affect efficacy.</td>
<td>In vitro comparability to Zmapp. Animal studies underway.</td>
<td>No safety data in humans yet.</td>
<td>GMP products.</td>
<td>Used on a compassionate basis in at least 1 patient. 10s-100s of treatment courses potentially available.</td>
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<tr>
<td><strong>AMIODARONE</strong> (Generic)</td>
<td>Antiarrhythmic agent approved for cardiac dysrhythmia.</td>
<td>EC50: 1.4-7.6 µM, SI 6-12. Mice: 0-40% at 90mg/kg. Higher doses may be more appropriate for mice. NHP: no data.</td>
<td>Used widely in cardiological practice. Known pulmonary and thyroid toxicity. Use in hypokalemic patients may result in QT prolongations.</td>
<td>Available, thermostable. PO and IV routes. Once daily dosing.</td>
<td>Has been used on compassionate basis in 65 patients at up to 20mg/kg/day (Freetown, Sierra Leone). Reported case fatality rate (CFR) of 40% compared with 50% CFR for entire patient population at the ETU.</td>
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<tr>
<td><strong>IRBESARTAN</strong> * + <strong>ATORVASTATIN</strong> * +/- <strong>CLOMIPHENE</strong> (generics)</td>
<td><strong>Clomiphene</strong>: EC50 in vitro 2.2 µM. Efficacy in mouse challenge: 90% survival. NHP: caused severe adverse events (SAEs) (ocular); trials stopped. Atorvastatin: EC50 22µM. Irbesartan: no antiviral activity.</td>
<td>All three drugs widely used in routine clinical practice.</td>
<td>Supply unlimited.</td>
<td>Up to 300 patients may have received combinations of these drugs in Sierra Leone. Anecdotal reporting of treatment of 15 of these patients at the Maforki Ebola holding and treatment centre in Port Loko indicated a positive effect on outcome. However, no detailed clinical reporting available hence no conclusion possible.</td>
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<tr>
<td><strong>FX06</strong> * (F4 Pharma, Germany)</td>
<td>Synthetic peptide derived from sequence of human fibrin, claimed to prevent vascular leaking. Developed for and used in cardiac treatment.</td>
<td>NHP studies underway.</td>
<td>100 volunteers have received drug in human Phase I and IIA studies. Well tolerated.</td>
<td>Administration by IV infusion or bolus. 2 000 treatment courses available. Stable at 25°C for 4 weeks.</td>
<td>2 EVD patients have received this drug under compassionate use. No conclusions regarding efficacy can be drawn yet.</td>
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CATEGORY D: DRUGS THAT DEMONSTRATE PROMISING ANTI-EBOLA ACTIVITY IN-VITRO OR IN MOUSE MODELS, BUT FOR WHICH ADDITIONAL DATA SHOULD BE GENERATED PRIOR TO PROCEEDING TO CLINICAL TRIALS. However, in the absence of other interventions, these compounds could be considered. These drugs do not meet the WHO criteria for moving to formal clinical trials since preclinical data insufficient.

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<td>AZITHROMICIN (Generic)</td>
<td>Antibiotic. Approved for treatment of numerous bacterial infections.</td>
<td>EC50 2.79, SI 20.4 Mouse: 10–60% survival (IP); 0% survival (PO). Guinea pig: 0–6% survival. NHP: no data.</td>
<td>Well tolerated; used in critically ill patients.</td>
<td>Available, thermostable. PO or IV. Daily dosing.</td>
<td>Dose used in mice may be too low and animal studies should be repeated with doses expected to correlate with human PK. Dose in mice could be increased 10-fold.</td>
</tr>
<tr>
<td>CHLOROQUINE (Generic)</td>
<td>Anti-malarial</td>
<td>EC50 16µM; Very high SI Mice: 8/10 (IP route). Guinea pigs: no protection up to 100mg/kg. NHP: no data.</td>
<td>Well tolerated and commonly used, although presumably at doses sub-therapeutic for EVD</td>
<td>PO drug. Once daily</td>
<td>Significantly higher dose likely necessary to obtain relevant levels versus EC50 in mice, which may explain failure. Likely higher clinical doses required to be effective but combination therapy to be considered to lower dose.</td>
</tr>
<tr>
<td>ERLOTINIB / SUNITINIB (Roche, USA)</td>
<td>Anti-neoplastic agents</td>
<td>EC50 2.2-2.5uM; SI 8.8-10 Mice: 10/10 (IP route) in combination only. Repeat with PO route pending. NHP: no data.</td>
<td>Generally well tolerated with short-term use.</td>
<td>High cost.</td>
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### SERTRALINE
(Zoloft®)
(Pfizer, USA)

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<th><strong>Anti-depressant (SSRI)</strong></th>
<th><strong>EC50 1.15µM</strong></th>
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<tr>
<td>Mice: 7/10 (IP route).</td>
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<tr>
<td>NHP: no data.</td>
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Well tolerated in healthy adults and children.

PO drug. Once daily.

### CLOMIPHENE

Selective estrogen receptor modulator. Approved for treatment of ovulatory failure.

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<th><strong>EC50: 2.2µM.</strong></th>
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<tr>
<td>Mice: 90% survival (IP).</td>
</tr>
<tr>
<td>NHP: caused SAEs (ocular); trials stopped.</td>
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</table>

Generally well tolerated at prescribed doses. Hot flashes and ovarian enlargement are side effects.

Available, thermostable. Oral tablets. Daily dosing

Standard clinical dosing not in range of predicted protective concentration. For consideration in combination with other drugs.

Side effects (ocular) are a concern.
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<tr>
<th>CATEGORY E: DRUGS THAT HAD BEEN PRIORITIZED OR CONSIDERED FOR PRIORITIZATION AND HAVE NOW BEEN DEPRIORITIZED BASED ON NEW DATA OR MORE DETAILED ANALYSIS OF OLD DATA.</th>
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<tbody>
<tr>
<td><strong>TOREMIPHENE</strong> Selective estrogen receptor modulator (SERM). Approved for treatment of metastatic breast cancer.</td>
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<tr>
<td>EC50 0.57 µM, SI 33 Mice: 50% survival (IP). NHP: no data.</td>
</tr>
<tr>
<td>Black box warning on use in patients with hypokalaemia. Risk of cardiac effect (QT prolongation). Hot flashes and fluid retention are side effects.</td>
</tr>
<tr>
<td>Black box warning. Electrolyte concerns in EVD would require careful K+/Mg++ monitoring and EKG. Not readily feasible in most ETUs.</td>
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<tr>
<th><strong>BRINCIDOFOVIR</strong> (Chimerix, USA) Small molecule antiviral with activity against dsDNA viruses. Developed and used for treatment of CMV.</th>
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<tr>
<td>In theory, should not work on Ebola (RNA virus), mode of action may be different to that for DNA viruses.</td>
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<tr>
<td>In-vitro EC50 varies by assay from 120nM to 1.3 µM. Thought to be a concentration readily achieved in clinic. Selectivity index variable depending on assay. Mice: no therapeutic benefit seen in two separate studies, but no pharmacokinetics (PK); therefore, not known if effective concentration reached. NHP: Rhesus macaque – not feasible due to PK profile. Guinea pig: study planned to determine PK and efficacy.</td>
</tr>
<tr>
<td>Testing in &gt;1 000 patients: main symptom GI tolerability, and AST/ALT elevations</td>
</tr>
<tr>
<td>PO drug. Twice weekly dosing after initial load. 22 000 x 100mg tablets (&gt;3 500 treatment courses) available.</td>
</tr>
<tr>
<td>5 patients received under compassionate use. No major side effects noted – some laboratory changes in white blood count, bilirubin, and Alkaline Phosphatase. No conclusions possible since combined with other drug therapies.</td>
</tr>
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</table>

Clinical efficacy trial began in Liberia in January 2015.

Clinical trial halted in late January 2015 due to lack of patients being enrolled, and withdrawal of the drug for investigational use in Ebola patients by the company.