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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.

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

DRUG / COMPANY	DRUG TYPE	EBOLA PRECLINICAL DATA	KNOWN SAFETY ISSUES	AVAILABILITY AND LOGISTICAL CONSIDERATIONS	COMMENTS
FAVIPIRAVIR (Fuji/Toyama Japan)	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.	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.	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	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.	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).**
BRINCIDOFOVIR (Chimerix, USA)	Small molecule antiviral with activity against dsDNA viruses. Developed and used for treatment of CMV.	In-vitro EC50 varies by assay from 120nM to 1.3 µM. Thought to be a concentration readily achieved in clinic. Selectivity index 290.	Testing in >1 000 patients: main symptom GI tolerability,and AST/ALT elevations	PO drug. Twice weekly dosing after initial load. 22 000 x 100mg tablets (>3 500 treatment	5 patients received under compassionate use. No major side effects noted – some laboratory changes in white blood count, bilirubin, and Alkaline Phosphatase. No

	In theory, should not work on Ebola (RNA virus), mode of action may be different to that for DNA viruses.	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.		courses) available. Thermostable.	conclusions possible since combined with other drug therapies. **Clinical efficacy trial began in Liberia in January 2015.** Monitoring of supplementary preclinical data ongoing.

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CATEGORY B: DRUGS THAT HAVE BEEN PRIORITIZED FOR TESTING IN HUMAN EFFICACY TRIALS BUT FOR WHICH SUCH TRIALS ARE NOT YET UNDERWAY

DRUG / COMPANY	DRUG TYPE	EBOLA PRECLINICAL DATA	KNOWN SAFETY ISSUES	AVAILABILITY AND LOGISTICAL CONSIDERATIONS	COMMENTS
Zmapp (MappBio, USA)	Cocktail of three monoclonal antibodies produced in tobacco plants.	NHP: 100% survival when administered 5 days after virus challenge.	No formal safety studies in humans yet. Phase I safety study initiated in January 2015.	Supply reported to be 15 treatment courses every 6 weeks.	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. **Phase I safety/PK study started in January 2015. Efficacy study due to start in early 2015.**
TKM-100802 (Tekmira, Canada)	Small inhibitory RNA which catalytically cleaves Ebola RNA once inside the cell. Sequence-specific to this strain of Ebola.	NHP: 67-100% efficacy among NHP given 4 to 7 doses with treatment initiated 30 minutes post- challenge.	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.	Several hundred doses currently available. Several thousand doses could be available in short time period. IV infusion. Requires refrigeration.	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. **Clinical efficacy trial due to start in early 2015.**
AVI-7537 (Sarepta, USA)	Antisense polymorpholino oligonucleotide. Inhibits Ebola virus replication by binding to RNA in	NHP: 100% survival for Marburg virus (using Marburg sequence) and 50–60% survival for	Phase I safety study completed. Tolerability demonstrated.	Limited no. of doses available.	No clinical trials planned at this time.

	sequence-specific manner to VP24 gene. Specific to this strain of Ebola.	Ebola using Ebola sequence.			
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. Humans with EVD with high IFN-gamma levels are those who are most likely to progress to death. **Clinical trial being considered in Guinea.**

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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.

DRUG / COMPANY	DRUG TYPE	EBOLA PRECLINICAL DATA	KNOWN SAFETY ISSUES	AVAILABILITY AND LOGISTICAL CONSIDERATIONS	COMMENTS
Zmab (Defyrus [Canada] and Public Health Agency of Canada)	Cocktail of three monoclonal antibodies produced in mammalian cells. Two of the monoclonals are also used in Zmapp.	NHP: 100% efficacy.	No safety studies in humans.	GLP product (not GMP); only for research use.	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.
AMIODARONE (Generic)	Antiarrhythmic agent approved for cardiac dysrhythmia.	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.	Used widely in cardiological practice. Known pulmonary and thyroid toxicity. Use in hypokalemic patients may result in QT prolongations.	Available, thermostable. PO and IV routes. Once daily dosing.	Has been used on compassionate basis in 65 patients at up to 20mg/kg/day (Freetown, Sierra Leone). Reported case fatality rate (CFR) of 50% compared with 57.4% CFR for entire patient population at the ETU. **Statistical significance of this result not known at this stage.** At this dose, blood levels would be predicted to transiently exceed EC50 and higher doses may be needed to be effective, which could present risks.

					Careful maintenance of K+/Mg++ levels and monitoring of ECG changes important.
IRBESARTAN + ATORVASTATIN +/- CLOMIPHENE (generics)	Irbesartan: angiotensin receptor blocker (anti-hypertensive) claimed to maintain endothelial integrity. Atorvastatin: statin approved for cholesterol control claimed to have anti-inflammatory effect. Clomiphene: selective estrogen receptor modulator approved for fertility treatment demonstrated to have antiviral activity.	Clomiphene: IC50 in vitro 2.2 µM. Efficacy in mouse challenge: 90% survival. NHP: caused severe adverse events (SAEs) (ocular); trials stopped.	All three drugs widely used in routine clinical practice.	Supply unlimited.	Up to 300 patients may have received these drug combinations 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. Investigations currently underway to gather efficacy and safety data from these patients.
FX06 (F4 Pharma, Germany)	Synthetic peptide derived from sequence of human fibrin, claimed to prevent vascular leaking. Developed for and used in cardiac treatment.	NHP studies underway.	100 volunteers have received drug in human Phase I and IIa studies. Well tolerated.	Administration by IV infusion or bolus. 2 000 treatment courses available. Stable at 25°C for 4 weeks.	2 EVD patients have received this drug under compassionate use. No conclusions regarding efficacy can be drawn yet.

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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.

DRUG / COMPANY	DRUG TYPE	EBOLA PRECLINICAL DATA	KNOWN SAFETY ISSUES	AVAILABILITY AND LOGISTICAL CONSIDERATIONS	COMMENTS
A**ZITHROMICIN** (Generic)	Antibiotic. Approved for treatment of numerous bacterial infections.	EC50 2.79, SI 20.4 Mouse: 10–60% survival (IP); 0% survival (PO). Guinea pig: 0–6% survival. NHP: no data.	Well tolerated; used in critically ill patients.	Available, thermostable. PO or IV. Daily dosing.	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.
CHLOROQUINE (Generic)	Anti-malarial	EC50 16µM; Very high SI Mice: 8/10 (IP route). Guinea pigs: no protection up to 100mg/kg. NHP: no data.	Well tolerated and commonly used, although presumably at doses sub-therapeutic for EVD	PO drug. Once daily	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.
ERLOTINIB / SUNITINIB (Roche, USA)	Anti-neoplastic agents	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.	Generally well tolerated with short-term use.	High cost.	
SERTRALINE (Zoloft®)	Anti-depressant (SSRI)	EC50 1.15µM	Well tolerated in healthy adults and	PO drug. Once daily.	

(Pfizer, USA)		Mice: 7/10 (IP route). NHP: no data.	children.		
CLOMIPHENE	Selective estrogen receptor modulator. Approved for treatment of ovulatory failure.	EC50: 2.2µM. Mice: 90% survival (IP). NHP: caused SAEs (ocular); trials stopped.	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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CATEGORY E: DRUGS THAT HAD BEEN PRIORITIZED OR CONSDIERED FOR PRIORITIZATION AND HAVE NOW BEEN DEPRIORITIZED BASED ON NEW DATA OR MORE DETAILED ANALYSIS OF OLD DATA.

TOREMIPHENE	Selective estrogen receptor modulator (SERM). Approved for treatment of metastatic breast cancer.	EC50 0.57 µM, SI 33 Mice: 50% survival (IP). NHP: no data.	Black box warning on use in patients with hypokalaemia. Risk of cardiac effect (QT prolongation). Hot flashes and fluid retention are side effects.	Available, thermostable. Oral tablet or liquid. Daily dosing.	Black box warning. Electrolyte concerns in EVD would require careful K+/Mg++ monitoring and EKG. Not readily feasible in most ETUs.