New therapeutic and preventive medicines to fight the Ebola epidemic: November 2014

World Health Organization

5 November 2014

In parallel…

Development

Testing

Licensure

Use

of Ebola experimental interventions is a HIGH PRIORITY

Whole blood and convalescent plasma

There is consensus that the use of whole blood and convalescent blood serums needs to be considered as a matter of priority.

Use of convalescent whole blood or plasma collected from patients who have recovered from Ebola virus disease for transfusion as an empirical treatment during outbreaks

The guideline covers:

- Identification of patients recovered from EVD as potential blood donors
- Informed consent and selection of donors
- Donor's blood grouping and screening for transfusion-transmissible infections
- Blood collection and donor care
- Labelling, storage, and transportation of blood and plasma products to sites where transfusion is given
- Selection of EVD patients for this intervention
- Clinical transfusion process
- Data collection at the transfusion site
- Assessment of effectiveness of this empirical treatment

http://apps.who.int/iris/bitstream/10665/135591/1/WHO_HIS_SDS_2014.8_eng.pdf

Experimental therapies used to treat Ebola

Prioritized for consideration based on the availability of NHP efficacy data with a filovirus challenge and justification for a human dose based on clinical data

Source: Adapted from the Washington Post, Oct 7, 2014

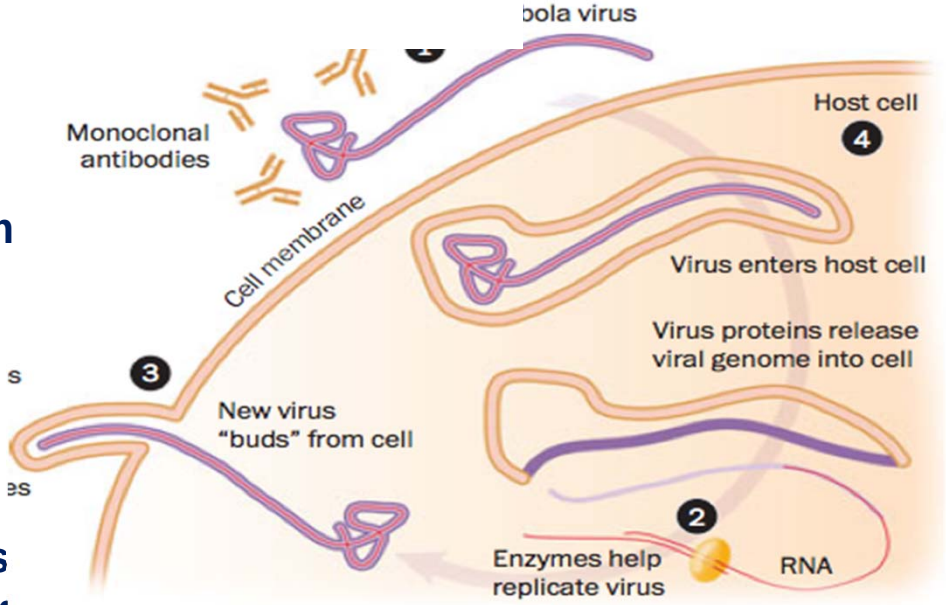
1- Targets the virus before it enters the cell

Zmapp A cocktail of three monoclonal antibodies, which block or neutralises the virus by binding to or coating a different site on the covering or “envelope” of the virus

Hyperimune globulin Antibodies that can neutralize the different EVD strains.

4- Bolsters human cells

Interferons - Induce an antiviral state in exposed cells and regulates the immune system



3- Prevents virus from exiting host cells

5- Testing existing drugs approved for other purposes

All drugs Screening all licensed drugs.

6- Whole blood transfus and convalescent plasma

2- Interferes with viral production

TKM 100802Ebola Target two essential viral genes to stop the Ebola from replicating.

AVI 7537 Sarepta Molecules that bind viral RNA, blocking gene function.

Favipiravir T705 Disrupts enzymes that the virus uses to make copies of himself.

BCX4430 Biocryst Disrupts enzymes that the virus uses to make copies of himself.

Brincidofovir Disrupts enzymes that the virus uses to make copies of himself.

Type of intervention	Admin. route	No. doses / time	Storage
Convalescent plasma	IM, IV equipment & supplies for sterile injection and/or infusion, & HCW who can administer	1st batches could be available by end 2014	Commercial IVIGs may be stored at room temperature; however these contain stabilizers and are pH-controlled. May require refrigeration and rewarming before transfusion.
ZMapp	IV equipment & supplies for sterile infusion & HCW who can administer	Few hundred doses by end 2014 (tentative)	Shipping & storage -20°C. MappBio currently gathering stability data to determine stability at 4°C. Antibody preparations should be stored in small aliquots, and thawed once; repeated freezing and thawing may negatively impact antibody – hence frost-free freezers are not appropriate, as they alternate between freezing and thawing.
Hyperimmune globulin from animal plasma	IM or IV depending on volume needed (?) - equipment & supplies for sterile injection and/or infusion & HCW who can administer	Large-scale GMP-compliant equine or transgenic animal batches for human use not before mid-2015	Other hyperimmune globulins (e.g., TIG & RIG) should be stored at 2-8°C and should not be frozen
TKM-100802: **(Lipid nanoparticle siRNAs)**	IV equipment & supplies for sterile infusion & HCW who can administer	Up to 100% survival in rhesus macaques. Survival better with 7 vs 4 PI treatment doses	Lyophilized LNP stable at 40°C
AVI 7537 (phosphorodiamidate siRNA) antisense RNA)	IV equipment & supplies for sterile infusion & HCW who can administer	75% survival in rhesus macaques (40 mg/kg) Mfr. estimates 16 mg/kg, but says this may be an overestimation.	Product is stored in bulk at 2-8°C, for stability, but after fill/finish and lyophylized, stable at room temp for months; vials have been retested for stability at 12-18 months with good results.
Interferons (Type 1 [α,β])	SQ/IM equipment & supplies for sterile infusion & HCW who can administer	Not known – probably 1 injection/day.	Store at 2-8°C. Do not leave out of refrigerator for >24h. Do not freeze or shake. Protect from light (instructions for PEGASYS peginterferon α-2a for subcutaneous use).
Favipiravir/T-705	Oral	14 days bid in mice (Smither). No data in humans against Ebola.	Stable at room temperature
BCX4430	IM equipment & supplies for sterile injection & HCW who can administer	Unknown – studies in macaques showed protection against MARV when given 15 mg/kg IM bid x 14 d beginning 1-48 hours post infection.	Probably stable at room temperature

Two candidate vaccines

A- rVSV-ZEBOV – recombinant vesicular stomatitis virus

The rVSV vaccine aims to induce EVD-specific immune responses.

NewLink Pharmaceuticals/Public Health Agency of Canada

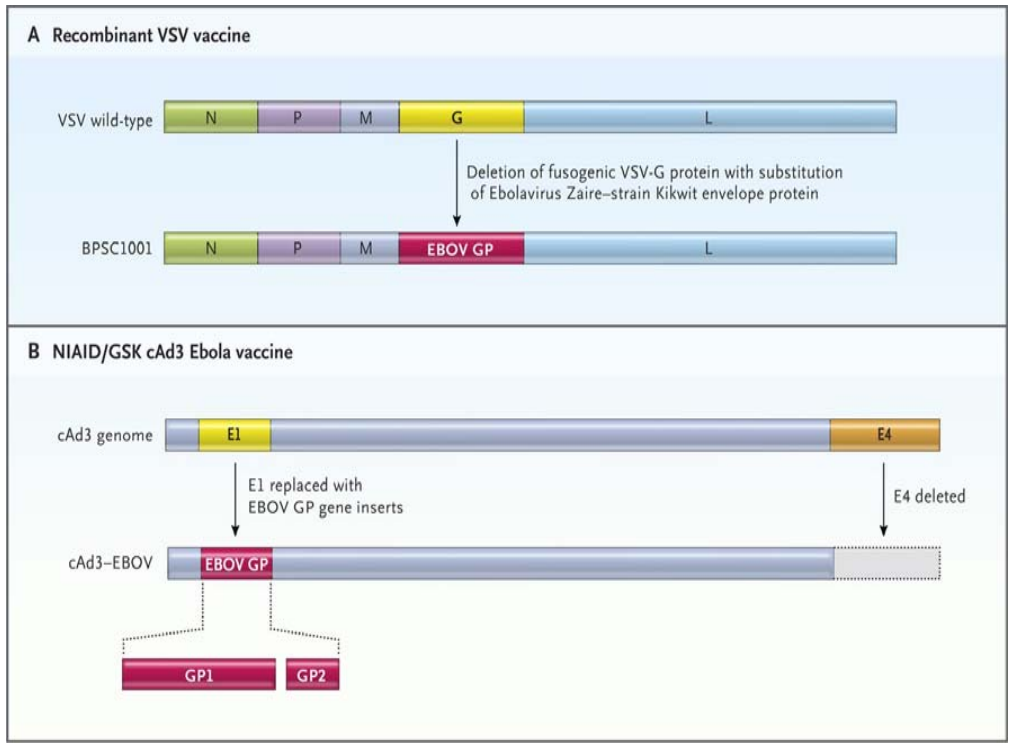
800 vials donated to WHO by the Government of Canada

B - ChAd3-ZEBOV – chimpanzee adenovirus 3

Uses a chimpanzee adenovirus that does not grow, containing the gene for EVD surface protein.

GSK/NIAID

25 000 doses by December 2014



Kanapathipillai R et al. N Engl J Med 2014. DOI: 10.1056/NEJMp1412166

Candidate vaccines selected based on protection in nonhuman primates post-lethal challenge (100%) and availability of GMP-grade vaccine.

Additional vaccines in the pipeline, but at a less advanced stage of development.

World Health Organization

ChAd3 : Overview of Phase 1 trials

Site	*Number vaccinated*	*Trial start (planned dates)*	*Characteristics*
VRC – USA	20	September 2014	Bivalent, healthy adults, dose-escalation, safety
Oxford – UK	60	September 2014	Monovalent, healthy adults, dose-escalation, safety
CVD – Mali	40	October 2014	Monovalent, healthy adults, dose-escalation, safety
Gambia	40	Pending	Monovalent, healthy adults, dose-selection, safety
Lausanne, Switzerland	100	October 2014	Monovalent, healthy adults, dose-selectio0n, safety
Total vaccinated Phase I = 260			

rVSV : Overview of Phase 1 trials

Site	Number vaccinated	Trial start (planned dates)	Characteristics
WRAIR – USA	30	October 2014	Healthy adults, dose-escalation, safety
NIAID – USA	30	October 2014	Healthy adults, safety, two-dose schedule
Hamburg, Germany	20	Nov 2014	Healthy adults, dose-selection, safety
Lambarene, Gabon	60	Nov 2014	Healthy adults, dose-selection, safety
Kilifi, Kenya	40	Nov 2014	Healthy adults, dose-selection, safety
Geneva, Switzerland	100	Nov 2014	Healthy adults, dose-selection, safety
Total vaccinated Phase I = ≥250			

Key milestones - Vaccines

Target date	Milestone
September - October 2014	Initiation of Phase 1 trials for the two most advanced vaccines
November 2014	Agreed protocols (including for Phase 3 trials) across different sites
	Preparation started of sites in affected countries for Phase 3 studies
November – December 2014	Initial safety and immunogenicity data from Phase 1 trials available
December 2014	Start of Phase 3 trial in Liberia
April 2015	Early results on vaccine efficacy

In parallel with acquisition of efficacy data – Planning for large-scale use, including systems for vaccine financing, allocation, and use