CURRENT SCENARIO OF THERAPEUTICS FOR EBOLA VIRUS DISEASE

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ABSTRACT

Currently various countries in Africa, including Liberia, Sierra Leone, Guinea, Nigeria, are facing disaster due to Ebola Virus Disease (EVD), which is primarily caused by Ebola virus. 2014 outbreak of Ebola associated viral haemorrhagic fever has 55-60% fatality rate. The incubation period of Ebola is below 21 days; once the appearance of symptoms starts the person will be infective. As there is no specific vaccine, antiviral or drugs for treating Ebola resulting in large number of deaths. Most of the recent outbreaks occurred in remote areas of West Africa. Poverty, lack of awareness, access to health centres, human habitats taking its toll in spreading the disease in large scale. Few nucleotide analogues, protease inhibitors, receptor binding, monoclonal antibodies and anticoagulant therapies are exhibiting promising role in inhibiting the Ebola virus in various (*in vitro* and *in vivo*) models.

Keywords: Ebola, Ebola Virus Disease, EVD, Filovirus, Therapeutics, EHF, Viral Haemorrhagic Fever1

1. INTRODUCTION

Currently various countries in Africa, including Liberia, Sierra Leone, Guinea, Nigeria, are facing disaster due to Ebola Virus Disease (EVD). First Ebola outbreak occurred in Sudan (Nzara) and Congo (Yambuku) in the year 1976, concluding in the villages situated near the Ebola River from which the viral haemorrhagic fever got its name Ebola/Ebola Virus Disease (EVD). EVD belongs to *Filoviridae* which causes fatal Ebola haemorrhagic fever in humans with fatality rate nearly 90%. Several out breaks of Ebola have been reported from East Africa (Sudan: 1976, 1979, 2004) Central Africa (Democratic Republic of Congo, Uganda & Gabon: 1976, 1977, 1994, 1997, 2000, 2001, 2004, 2007) and in West Africa (Ivory coast: 1995) since its discovery in 1976. The most recent outbreak started in December 2013 and 2014 in eastern sector of the Republic of Guinea resulted in more than 337 deaths and spreading to republic of Liberia (Gatherer, 2014; Muyembe-Tamfum *et al*., 2012; Dixon and Schafer, 2014) and other countries.

Ebola belongs to family *Filoviridae* and other members in this group are Marburgvirus and Cuevavirus. Under Ebola virus genus consists of five diverse species Bundibugyo Ebolavirus (BDBV), Zaire Ebolavirus (EBOV), Reston Ebolavirus (RESTV), Sudan Ebolavirus (SUDV) and Taï Forest Ebolavirus (TAFV). BDBV, EBOV and SUDV have been associated with large EVD outbreaks near the Tropical rain forests of Central and West African distant villages, among these three EBOV causes high mortality rates in humans. RESTV and TAFV were not acquainted to cause illness or fatality in human. RESTV is mostly found in Philippines and China (Leroy *et al*., 2004; 2005).

2. TRANSMISSION

Transmission of virus from the wild animals like primates (Chimpanzees, Gorillas and African green monkeys) and fruit bats (*Hypsignathus monstrosus, Epomops franqueti*, *Myonycteris torquata* and *Pteropodidae*) (Groseth *et al*., 2007) are the natural hosts for the EVD (**Fig. 1**).

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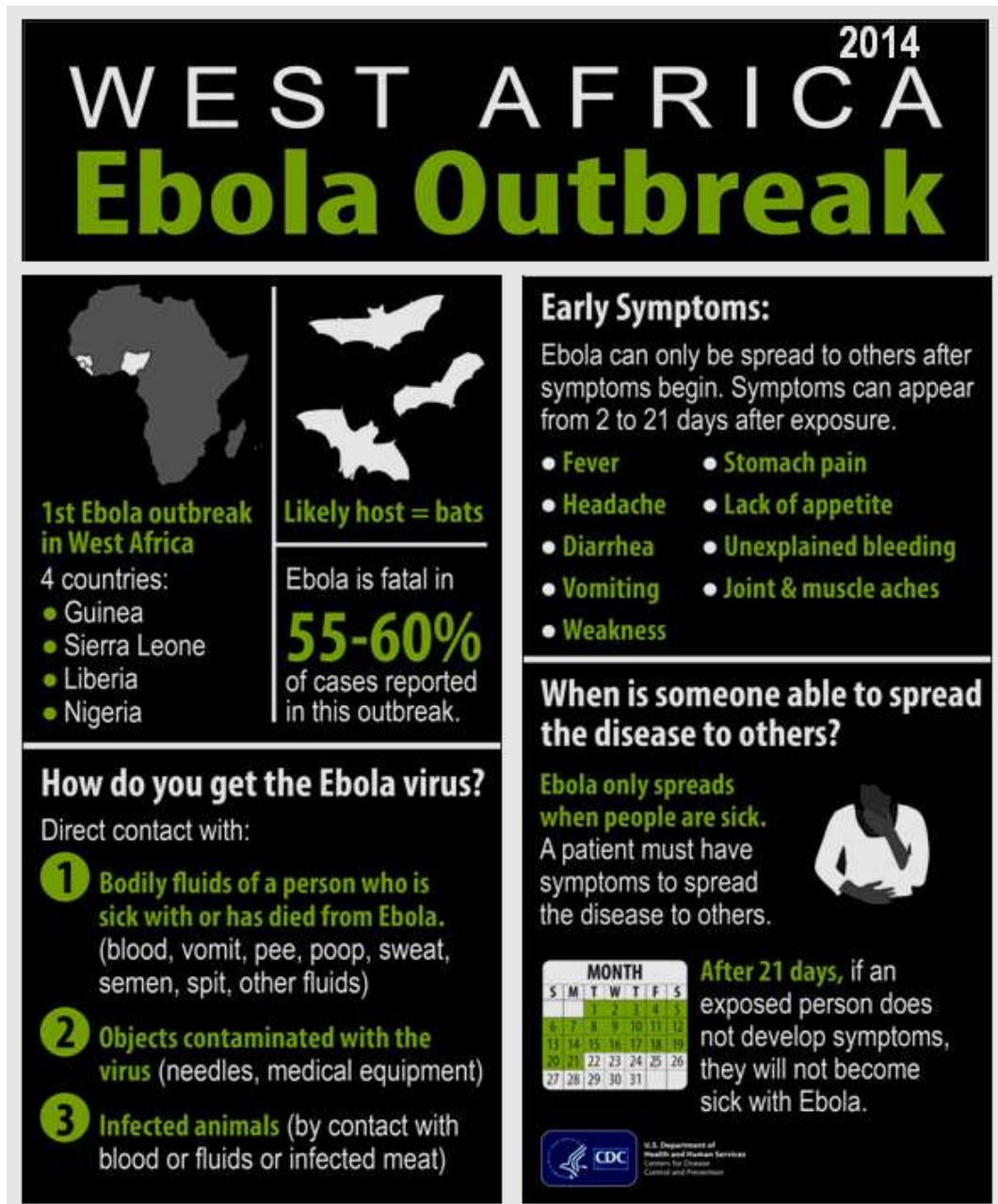
Fig. 1. Infographic exhibiting a basic understanding of the facts behind the Ebola virus including its geographic distribution, (which includes the African countries of Guinea, northern Liberia, Sierra Leone and Nigeria), the virus's likely host, (which seems to be bats), the mortality rate of Ebola Hemorrhagic Fever (EHF), how one becomes infected by the virus, the early symptoms of EHF and when it is possible for a patient ill with EHF to spread the virus to another human being. EHF is one of numerous viral hemorrhagic fevers. It is a severe, often fatal disease in humans and nonhuman primates (such as monkeys, gorillas and chimpanzees). EHF is caused by infection with a virus of the family *Filoviridae*, genus *Ebolavirus*. When infection occurs, symptoms usually begin abruptly. The first *Ebolavirus* species was discovered in 1976 in what is now the Democratic Republic of the Congo near the Ebola River. Since then, outbreaks have appeared sporadically. (Courtesy of Centers for Disease Control and Prevention (CDC), USA, ID#17677)

Transmission from primates to humans occurs through the activities like handling ill/infected, butchering, eating, contact through blood from these animals and subsequently viral infection spreads from humans via human to human transmission (Leroy *et al.*, 2004; Groseth *et al.*, 2007).

3. GENOME OF EBOLA

Ebola virus is 970 nm long and filamentous in nature, its diameter is around 80 nm with (-) ve stranded RNA. Genome of EVD is nearly 19kb in size which encodes for seven proteins NP (Nucleoprotien) vp35, vp40, GP (Glycoprotein), vp30, vp24 and L (Polymerase).

How Ebola virus attacks the human system is not completely elucidated. Ebola virus attaches to the host receptors through the GP (glycoprotein) mediated endocytosis into the host vesicles, fusion with the membrane leads to the release of Ribonucleo-capsid into the cytoplasm. Viral RNA dependent RNA polymerase binds to the leader region of the genome to start the sequential transcription of genes. The gene products (mRNA) are protected from the host proteins by capping and polyadenylation by the L protein during the synthesis (Stahelin, 2014; Watt *et al.*, 2014). Replication starts only when enough nucleoprotein to encapsidated the newly synthesized genomes budding of the virus occurs with, interaction of matrix protein and nucleocapsid under plasma membrane with the help of host ESCRT complexes (McDonald and Martin-Serrano, 2009; Grove and Marsh, 2011).

3.1. Signs and Symptoms

EVD is a severe acute viral illness often characterized by the sudden onset of fever, intense weakness, muscle and joint pain, headache and sore throat. This is followed by vomiting, diarrhoea, rash, impaired kidney and liver function and in some cases, both internal and external bleeding. Laboratory findings include low white blood cell and platelet counts and elevated liver enzymes. Few patients may experience rash, red eyes, hiccups, chest pain, cough, sore throat, difficulty in swallowing, difficulty in breathing un explained internal and external bleeding. Incubation period ranges from 2 to 21 days, people are only infective once the symptomatic phase starts and viral transmission can occur through blood and secretions from the patients (Roddy *et al.*, 2012; Dixon and Schafer, 2014).

4. TARGETTING VIRAL PROTEINS

4.1. Protease Inhibitors

VP30 is essential for transcription of Ebola and it is phosphorylated at N-terminal serine clusters and threonine residues at positions 143 and 146. Host cellular Protein Phosphatase 1 (PP1) controls VP30 dephosphorylation as expression of a PP1-binding peptide cdNIPP1 increased VP30 phosphorylation. 1E7-03 compound targeted at non-catalytic site of PP1 inhibited the transcription and replication in cell culture model (Ilinykh *et al.*, 2014). Phosphorodiamidate Morpholino Oligomers (PMOs) are short nucleotides binds to the RNA which can alter the RNA-RNA interactions and RNA- Protein interactions which effects viral transcription and translation. The AVI-7537 PMO has been effective in targeting the VP24 gene of Ebola virus (Iversen *et al.*, 2012).

4.2. Nucleotide Inhibitors

BCX4430 a nucleoside analogue act as broad spectrum antiviral compound which can be a potential candidate in treatment of patient in delayed/later stages of infection (Warren *et al.*, 2014).

4.3. Biologically Active Compounds/Antivirals

Fullerene sugar balls (anti adhesive agents) are the new class of biologically active compounds derived from C60 core they bind to the lectins through glycoside cluster effect which are effective against bacteria. Mannosylated fullerene sugar balls can be used as antivirals as they have shown effect on Ebola pseudotyped infection model. (Nierengarten and Nierengarten, 2014). Griffithsin (lectin) derived from red alga binds to the N-linked Glycans found on the surface of viruses like HIV, HCV, SARS and Ebola virus can be used as antiviral after proper validation (Barton *et al.*, 2014). Favipiravir (T-705) a pyrazinecarboxamide derivateive inhibited the replication of Ebola in later stages of infection thereby decreasing the pathogenesis and disease severity and it has effective against E718 strain (Aerosol Ebola virus) in both cell culture and animal model. This is broad spectrum antiviral administered through oral route it is effective against influenza and it is under phase III clinical trials for the same (Smither *et al.*, 2014; Oestereich *et al.*, 2014). Kinase inhibitors (Genistein and Tryphostin) AG1478 pre-treated host cells with this inhibited the infection of Ebola virus which can be used as broad spectrum antiviral (Kolokoltsov *et al.*, 2012).

4.4. Targetting Host Cellular Proteins

Endoplasmic reticulum α-glucosidases I and II are essential for viral maturation and release of virion. The glycolysated viral envelope proteins uses calnexin mediated folding pathway and the compound CM-10-18 (imino sugar) and its derivatives are α-glucosidase inhibitors which have shown effect against various hemorrhagic fevers can be used as potent antiviral (Chang *et al.*, 2013). Clomiphene and cationic amphiphiles (Ro 48-8071, Terconazole, Triparanol, AY 9944, Amorolfine and U18666A) induces defects in Niemann-Pick C1 Protein (NPC1) required for viral entry but they have to use in higher concentrations and various combinations of cationic amphiplhies to block the viral entry (Shoemaker *et al.*, 2013). Nedd4 E3 ubiquitin ligase of host protien was utilized by viral PPxY late (L) domain of filoviruses and other RNA viruses like arena virus and rhabdo viruses in budding. L domain of PPxY can be of ideal choice for blocking the budding and filoviruses infections (Han *et al.*, 2014). Studies on macrophages and dendritic cells with pre-treatment of pyridinyl imidazole p38 MAPK inhibitors can block the entry and infection of EBOV (Johnson *et al.*, 2014).

4.5. Antibody/Monoclonal Antibodies Against Ebola

Recombinant adenovirus expressing the Glycoprotein (GP) of Ebola virus has elicited good humoral/antibody response against Ebola virus in wild type and interferon α/β receptor knock-out mouse (O'Brien *et al.*, 2014). ZMAb, combination of three EBOV-GP-specific monoclonal antibodies were administered 24-48 h post exposure to Ebola virus in primates were survived after re challenged them with virus at 10 weeks and 13 weeks are also survived (Qiu *et al.*, 2013).

5. FUTURE DIRECTIONS

Recent outbreak of Ebola was the outcome of complex human behavioral, environmental factors on the public. There are many drugs which are under clinical and at pre-clinical level can target both viral and human host proteins. Development of rapid diagnostic tools should be given priority. Establishment of a system for continuous surveillance of emerging and re-emerging diseases is a need of the hour. The cost effective drugs should have global acceptance, accessibility, affordability. The awareness programmers should be conducted in large scale to eradicate the disease and we need to proceed with sense of urgency.

6. ACKNOWLEDGMENT

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