

Ebola Hemorrhagic Fever: Recent Update On Disease Status, Current Therapies And Advances In Treatment

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Abstract Swiftly growing viruses are a major intimidation to human health. Such viruses are extremely pathogenic like Ebola virus, influenza virus, HIV virus, Zika virus etc . Ebola virus, a type of Filovirus, is an extremely infectious, single-stranded ribonucleic acid virus that infects both humans and apes, prompting acute fever with hemorrhagic syndrome. The high infectivity, severity and mortality of Ebola has plagued the world for the past fifty years with its first outbreak in 1976 in Marburg, Germany, and Frankfurt along with Belgrade and Serbia. The world has perceived about 28,000 cases and over 11,000 losses. The high *lethality* of Ebola makes it a candidate for use in bioterrorism thereby arising more concern. New guidelines have been framed for providing best possible care to the patients suffering from Ebola virus i.e Grading of Recommendation Assessment, Development And Evaluation (GRADE) methodology to develop evidence-based strategy for the treatment in future outbreak of Ebola virus. No drugs have been approved, while many potent drugs like rVSV-EBOV, Favipiravir, ZMapp are on clinical test for human safety. In this review we will discover and discuss perspective aspects that lead to the evolution of different Ebola variants as well as advances in various drugs and vaccines for treatment of the disease.

Keywords: Filovirus; Ebola; Single-stranded ribonucleic acid; GRADE; vaccines; rVSV-EBOV; Favipiravir; ZMapp.

1. INTRODUCTION

The Ebola viruses (EBOV) belonging to family Filoviridae are non-segmented, negative-sense and single-stranded RNA viruses, with a size approximately

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19kbp. Firstly discovered in 1976, near to the Ebola River and prevalent regions of central, eastern and western Africa. Ebola is the cause for more than twenty *lethal* outbreaks of EVD (Ebola Virus Disease) having been investigated in Africa since 1976. A new strain known as Makona was responsible for outbreak in 2014. Ebola virus has been responsible for more than ten thousand deaths.

Ebola haemorrhagic fever (Ebola HF) is known globally as a fatal disease in humans and non-human primates (monkeys, chimpanzees and gorillas). Infection with the genus of Ebola causes severe and life threatening fever. Genus Ebola virus comprises 5 distinct species- Bundibugyo Ebola virus (BDBV), Zaire Ebola virus (ZEBOV), Reston Ebola virus (RESTV), Sudan Ebola virus (SUDV), Tai Forest Ebola virus (TAFV). BDBV, ZEBOV, and SUDV have been related with huge EVD outbursts in Africa (Barrette *et al.*, 2011)(Table.1).

Table 1: Various species of Ebola (Passi *et al.*, 2015)

Zaire Ebola virus (ZEBOV), now known as Ebola (EBOV) virus	Zaire species of Ebola virus was responsible for its first outbreak in Yambuku, Zaire in the year 1976. It is the most dangerous species of Ebola virus resulting to highest number of Ebola virus related deaths. Death rate is 80-90%. Symptoms comprise of chills feeling along with high fever similar to the symptoms of malaria.
Sudan Ebola virus (SEBOV)	This Ebola virus species originated in Nzara, Sudan in 1976. Firstly traced in cotton factory workers of Sudan, it simultaneously outbreak along with Zaire Ebola virus. It was also responsible for outbreaks in 1979, 2000 and 2004. The mediator of transmission for Sudan Ebola virus is still undiscovered and it has an average death rate of 41- 65%.
Bundibugyo Ebola virus (BDBV)	In 2007 and 2008 the outbreak of Ebola virus disease took place in the Bundibugyo district of Uganda that led to the discovery of a species of Ebola virus that were previously unknown. There were at least 100 or more Ebola virus sufferers with death rate of 30%.
Ivory coast Ebola virus (CIEBOV) /Tai Forest Ebola virus (TAFV)	Ivory Coast Ebola virus was first mapped out in Tai forests of the Côte d'Ivoire in Africa, where a female ethnologist got herself accidentally infected while carrying out necropsy on a dead infected chimpanzee. Initially in 1994, outbreak was amongst the wild African chimpanzees. Next outbreak of this virus took place in 1995, south of DRC. Its infection had stated only one non devastating case.
Reston Ebola virus (REBOV)	This species originated in 1989 in Reston, Virginia when diseased monkeys were traded into Reston from Philippines. It has been revealed to cause disease in non-human primates such as monkeys, but its non pathogenic to humans. No deaths have been specified with this virus. Recently, Ebola Reston virus has been recognized very freshly in pigs in Philippines.

2. EPIDEMIOLOGY

Since Ebola virus evoked on 1976 in Zaire and Sudan, five different subtypes of Ebola virus have been identified in several areas of Africa. Primarily affected countries within Africa – Sierra Leone, Liberia and Guinea witnessed overall 28616 cases causing 11310 deaths. The most recent widespread infection started in 2013 in West African nation of Guinea as established by the World Health Organization in March 2014 (Gatherer, 2014). In March 2015, Liberia reported with 1 case over 192 contacts with a suspicion of sexual transmission also on June 2015 it came up with 7 cases, over 126 identified contacts. Ultimately, March 2016 both Liberia and Guinea were again affected with 13 new cases over 1200 contacts with a possibility of sexual transmission. On 13th of April 2016, 7 other countries (Nigeria, Mali, the United States, Senegal, Spain, the United Kingdom and Italy) were also reported with the disease and met with 36 cases, out of which 8 deaths in Nigeria, 6 in Mali and 1 in the United States were stated. Also eight hundred and eighty one healthcare workers were infected throughout this disaster and 513 died as a result of the disease (Shiwani *et al.*, 2014).

3. EBOLA VIRUS DISEASE

EBOV leads to severe hemorrhagic fever resulting in *lethal* outcome in humans, and several species of non-human primates. Human Ebola outbreaks usually occur suddenly from a indefinite source, that spreads rapidly from person to person. EBOV were earlier categorized as “hemorrhagic fever viruses”, based on the clinical appearances, that includes coagulation defects, bleeding, and shock. But it’s no longer categorized as such because not all patients affected by Ebola developed substantial hemorrhagic symptoms, that frequently arises at terminal phase of fatal illness (Leroy *et al.*, 2011).

4. RISK FACTORS AND MODE OF TRANSMISSION

Ebola Virus is transmitted to humans via close contact with the blood, secretions, organs or other bodily fluids of diseased animals. In Africa, infection spread through handling of ill or dead infected chimpanzees, gorillas, fruit bats, monkeys, forest antelope and porcupines. There is no possibility of infection with asymptomatic persons as well as there is very low risk of infection during the incubation period and also during the first week of symptomatic illness. Higher risk of transmission arises in funerals due to contact with infected corpse (Brainard *et al.*, 2015). Threats of infection are also high among health care workers who take care of the infected, via unprotected contact with bodily fluids. (Francesconi *et al.*, 2003).

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5. CLINICAL MANIFESTATIONS

Initial symptoms are the rapid onset of fever, weakness, muscle pain, fatigue, intense headache and sore throat along with vomiting, diarrhea, rash, symptoms of impaired kidney and liver function, abdominal pain and unresolved haemorrhage. Incubation period is 2 to 21 days. Other related signs and symptoms include conjunctival injection, chest pain, arthralgias, myalgias, asthenia, and hiccoughs (West & von saint, 2014; Fischer *et al.*, 2015). Initial disease symptoms may be mistaken with other tropical disease such as malaria, dengue, or cholera. EVD causes upto 5 liters or more of watery diarrhea per day, continuing up to 7 days and often longer. Profuse vomiting and diarrhea can quickly lead to intravascular volume depletion, electrolyte disorders, hypoperfusion, and shock (Fowler *et al.*, 2014). Hemorrhagic manifestations of Ebola are late stage complications with symptoms like petechiae, ecchymosis, exuding from venipuncture sites, mucosal hemorrhage, haematemesis, or melena (Fischer *et al.*, 2015). Pregnant women will have impulsive abortions along with significant bleeding (Khan *et al.*, 1999).

6. ACUTE NEUROLOGICAL MANIFESTATIONS

Throughout acute phase, EVD patients have number of neurological signs and symptoms, while serious neurological manifestations are proportionately unusual. Most commonly, patients will have nonspecific headache, which often presents as an early symptom. Altered mental status, which may range from mild confusion to delirium with hallucinations, may also occur, but may be secondary to a host of variables, including electrolyte abnormalities and shock. Severe cases may lead to coma (West & von saint, 2014). Meningitis and encephalitis associated to EVD have been recognised in recent outbreak, also in prior outbreaks, while the prevalence is not well noted (Sagui *et al.*, 2015; Howlett *et al.*, 2016).

7. DIAGNOSIS

Diagnosis through laboratory testing show low levels of white blood cell and platelet along with elevated liver enzyme levels (Dallatomasina *et al.*, 2015). Ebola Virus Disease is distinguished from other transmittable diseases like malaria, typhoid fever and meningitis by using various diagnostic methods recommended by WHO for eg. antibody capture Enzyme-Linked Immunosorbent Assay (ELISA), antigen capture detection tests, serum neutralization test, electron microscopy, reverse transcriptase Polymerase Chain Reaction (PCR) assay (Drosten *et al.*, 2003).

8. PATHOPHYSIOLOGY OF THE DISEASE

Ebola virus invades the tissue via infected fluid that associates with mucosal or skin breaks, where they effectively reproduce in the monocytes, macrophages, and dendritic cells (Beeching *et al.*, 2014). In vitro studies revealed that virus envelope made of glycoprotein is liable for both receptor binding and fusion with host cell membrane. The host immune attack fails to defend as heavily glycosylated viral envelope includes both N- and O-linked glycan providing protection to the virus (Ansari, 2014). The white blood cells carry the virus within the entire body to tissues and organs such as liver, lymph nodes, lungs and spleen. Presence of viral particles within the body and cell injuries caused by viruses promotes release of chemical signals (TNF- α , IL-6 and IL-8) responsible for fever and inflammation. Ebola infection damages human cells by causing infection to the endothelial cells that reduces reliability of the blood vessels and cell adhesion molecules leading to liver damage and improper clotting (Hensley *et al.*, 2005).

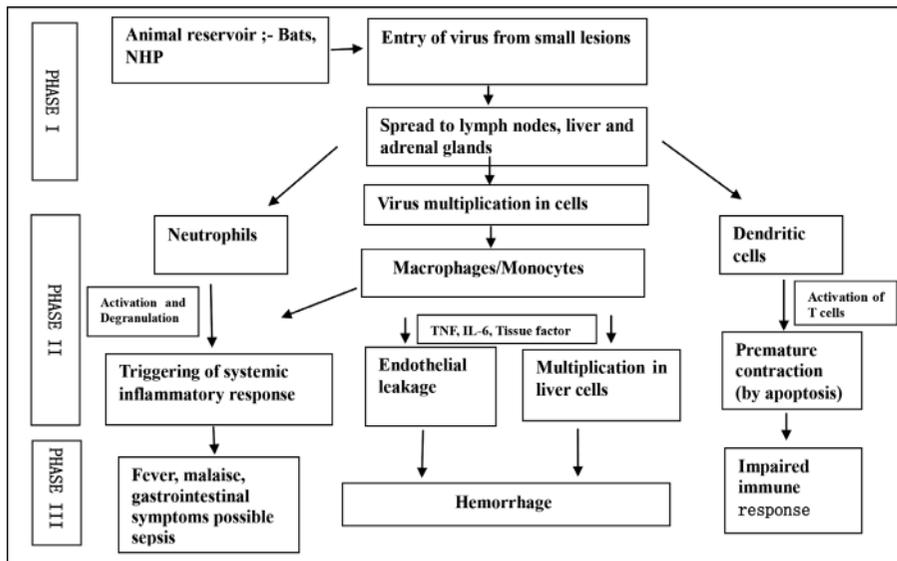


Figure 1: Phases of Ebola Virus Infection (Gebretadik *et al.*, 2015).

When a cell is infected with EBOV, receptors located in the cytosol recognizes the infectious molecule associated with virus that leads to activation of protein together with interferon regulatory factor 3 and factor 7 that ultimately triggers signaling cascade and releases type 1 interferon. Type 1 interferon then binds to the receptors IFNAR1 and IFNAR2 of the neighboring

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cell that further activates STAT1 and STAT2 signaling proteins that moves into the nucleus and triggers gene expression coding antiviral proteins (Leung *et al.*, 2006). EBOV's VP24 proteins interferes with the production of antiviral proteins by constraining STAT1 signaling protein entry into neighboring cell nucleus, thus with the inhibition of these immune responses EBOV quickly spreads throughout the body (Volchkov *et al.*, 2006) (Fig.1).

10. MANAGEMENT

No specific treatment for Ebola hemorrhagic fever has been approved by FDA yet though prospective candidates are present, being in phase 3 or waiting approval. Patients identified to be at risk of infection are immediately isolated and attended by health care personnel that have been trained in bio-safety and outfitted with protective equipment. All equipment utilized must be disinfected due the high risk of contamination from infected bodily fluids and bio-waste should be disposed properly. Disinfection can be carried using bleach, detergents etc. Boiling equipment in water for 5 minutes or providing heat of 60°C for about 1 Hour can also eliminate the virus (Cook *et al.*, 2015). Primarily, supportive treatment is provided to increase survival chance of patient involving fluid balance maintenance, treatment of any other infections that may occur and symptomatic treatment (Clark *et al.*, 2012). Supportive care guidelines for care of Ebola patients have been developed utilizing Grading of Recommendations Assessment, Development And Evaluation (GRADE) methods.

Due to gastrointestinal fluid losses, fluid balance must be maintained by utilizing oral re-hydration solutions or intravenous fluids depending on the status of the patient (Hunt *et al.*, 2015; MacDermott & Herberg, 2017). Loperamide may be utilized to decrease the fluid losses in the patient (Chertow *et al.*, 2015). Electrolyte balance must be maintained by replacement and regular monitoring (Hunt *et al.*, 2015). Symptomatic treatment is provided for various complications. Paracetamol is utilized for management of fever and pain, although opioid analgesics may be utilized for severe pain. Ondansetron, metoclopramide are utilized for nausea and vomiting. Antacids are given in case of dysphagia/acid reflux. Anticonvulsants (e.g., phenobarbital) used for management of seizures which may rarely occur. In case of agitation, sedatives are recommended. Hemorrhage usually occurs, thereby clotting factors and blood products are regularly administered. Broad spectrum antibiotics are utilized in case of sepsis (Clark *et al.*, 2012).

Also, contact tracing is performed to control the outbreak by observing all persons that have been in contact with the afflicted person for 21 days for development of signs and symptoms of Ebola Virus (EBOV) infection. In case,

the contact falls ill, the contact tracing is repeated for their contacts (Saurabh & Prateek, 2017).

11. DRUGS ON CLINICAL TESTING

Many therapies recently developed have not been fully tested until now for safety and efficacy (Bishop, 2015). The biggest challenge being that the virus needs bio-safety level 4 facilities for handling (Kortepeter *et al.*, 2008).

11.1 Monoclonal Antibodies(mAbs) :

MB-003 is a mixture of three monoclonal antibodies c13C6, h13F6 and c6D8 (Qiu *et al.*, 2014). Treatment with MB-003 increased survival in animals infected with EBOV as it targets the surface glycoprotein of EBOV (Davidson *et al.*, 2015). Another mAB, ZMAb, a combination of m1H3, m2G4 and m4G7 monoclonal antibodies, has been used to produce protection from EBOV for more than 10 weeks in primates (Qiu *et al.*, 2014). After testing the six monoclonal antibodies, ZMapp was created which has m2G4 and m4G7 from ZMAb combined with c13C6 from MB-003 (Davidson *et al.*, 2015). It was found to be highly efficacious in primates but in a trial on patients in Liberia, Guinea, results were found to be lacking efficacy hence further research is required (Prevail *et al.*, 2016). Also, a cocktail of three monoclonal antibodies isolated from mammalian cells, MIL-77 has been sanctioned for use on compassionate basis with an IND for phase-1 trial having been filed (Qiu *et al.*, 2016).

11.2 Blood and blood products:

Convalescent Blood and plasma have been shown to have high efficacy due to the fact that patients surviving Ebola disease have been known to produce antibodies against it. Trials done on guinea pig regarding convalescent plasma have shown no outstanding results but no adverse effects were noted deeming the treatment safe (Van Griensven *et al.*, 2016).

11.3 Vaccines:

No vaccines have been approved by FDA for treatment of humans till date. But various promising candidates exist and are being tested in clinical trials.

rVSV-EBOV, the first proven vaccine to be highly effective against EBOV established by Public Health Agency of Canada and Merck Inc., is a vesicular stomatitis virus with decreased virulence, in which an Ebola virus gene has been added. The modification induces ZEBOV surface glycoprotein which causes production of antibodies while binding with host cells. It has shown

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high potential in preventing development of disease post exposure and except for joint pain, no severe adverse effects were noted. Multiple studies have proven its effectiveness against Ebola (Regules *et al.*, 2017; Henao-Restrepo *et al.*, 2017). The vaccine can propagate both humoral and cellular immune responses (Sameem & Dias, 2017).

ChAd3-ZEBOV, developed by National Institute of Allergy and Infectious Diseases and GlaxoSmithKline, has been derived from chimp adenovirus type 3 (ChAd3) and expresses glycoproteins of two Ebola virus species, Zaire and Sudan. This when administered produces antibodies against EBOV. Genetic modifications prevent the virus to replicate in humans. Single dose administration has been proven to be effective with only mild adverse effects (Ledgerwood *et al.*, 2017). MVA-Bn-Filo has been used a booster vaccine along with ChAd3-ZEBOV to elongate immunity (Tapia *et al.*, 2016).

Ad26.ZEBOV, a vaccine developed by Janssen Pharmaceutica, Johnson and Johnson, obtained from human adenovirus serotype 26, expresses the Mayinga Ebola variant glycoprotein. This is given along with a boost vaccine MVA-Bn-Filo. The combination causes elongated immunity up to 8 months (Milligan *et al.*, 2016).

MVA-Bn-Filo (multivalent modified vaccinia Ankara) is a vaccine developed by Bavarian Nordic. It encodes multiple filovirus glycoproteins, thereby, elucidating its use along with other vaccines as a booster vaccine (Sridhar, 2015; Milligan *et al.*, 2016)

Ad5.ZEBOV, developed in china, is a relatively newer vaccine utilizing the adenovirus type 5 vector of the more recent 2014 Zaire Guinea strain. Although at an early clinical stage, Phase I and II trials proved good safety although efficacy in humans is still not proven.

GamEvac-Combi, a combination of rVSV and Ad5, has been recently developed, the reason for development being the emergence of new strains of Ebola. It expresses the surface glycoprotein of the more recent 2014 Makona strain. Open phase I/II studies have proven safety and immunogenic potential in healthy individuals. The results justify commence of Phase III trials (Dolzhikova *et al.*, 2017).

GreEMTri (Ebola-Marburg vaccine), developed in 2014 by Greffex, Inc., is a trivalent vaccine containing Zaire Ebola virus (ZEBOV), Sudan Ebola (SEBOV) and Marburg Virus (MV) genes with deleted Ad (Adenovirus) genes. It produces glycoprotein genes of all three Viruses, thereby, can be used against all three. It can target the recent variants of ZEBOV, SEBOV and MV. It can trigger better immune responses at lower dose and can be given through multiple routes (Sameem & Dias, 2017).

rGP Nanoparticle, developed by Novavax, Inc. in 2014, is a vaccine containing nanoparticles of Ebola glycoprotein (EBOV GP) of Makona strain in a saponin based matrix adjuvant. Studies have found it highly immunogenic (Sharma & Ketki, 2017).

INO-4212, a DNA-based vaccine made by Inovio Pharmaceuticals and US Defence Advanced Research Projects Agency (DARPA) is a interleukin-12 immune activator. It codes for both Mayinga and Makona glycoproteins. Phase 1 studies are currently underway (Keshwara *et al.*, 2017).

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11.3 Interferons:

Interferons have a major role in immune response against viruses. Infected cells release interferons which then activate immune cells and halt viral replication by inhibiting viral gene expression. Use of modified Interferon alpha prolonged survival in Non Human Primates (NHP) (Bradfute, 2017). Conducted studies proved that interferons are moderately effective and treatment is beneficial only in early stages (Dyall *et al.*, 2017).

11.4 Antivirals:

Favipiravir, formerly T-705, is a broad spectrum antiviral drug that acts by forming an active metabolite which prevents viral RNA replication by inhibiting RNA dependent RNA polymerase. Oral doses have proven effective against EBOV in animals even after a week post infection. In humans, however, highest effect was noticed in patients with moderate viral spread, but it was ineffective against higher level of viremia. Oral use, good tolerability and availability make it a viable candidate for further studies (Haque *et al.*, 2015; Sissoko *et al.*, 2016).

Brincidofovir, an experimental drug, inhibits viral DNA polymerase, thereby, halting viral replication. Brincidofovir showed anti EBOV activity but the Phase 2 clinical trials were halted due to lack of new cases thereby withdrawn from investigational use (Florescu & Keck, 2014).

Galidesivir (BCX4430) is a broad spectrum antiviral drug developed by BioCryst Pharmaceuticals. This adenosine analogue, prevents viral RNA replication by inhibiting RNA Polymerase. It has shown efficacy against EBOV and Marburg Virus in animals while not effecting human RNA or DNA, thereby, Phase I study were initiated and are still ongoing. The drug is administered intramuscularly, but administration through oral route is also possible. (Warren *et al.*, 2014; Kilgore *et al.*, 2015).

TKM-Ebola was developed by Arbutus Biopharma as an experimental antiviral which was a combination of siRNAs that targeted EBOV proteins,

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thereby, inhibiting replication. Effect was proven in non-human primates (NHP) but the drug was not able to prove efficacy in humans. After Phase II studies were halted due to no proof of efficacy, the company suspended production (Haque *et al.*, 2015; Thi *et al.*, 2015; Dunning *et al.*, 2016).

AVI-7537, an antiviral developed by Sarepta Therapeutics, consists of phosphorodiamidate morpholino oligomers, which targets EBOV gene. The drug improved survival chance in NHPs that were infected. Phase 1 studies offered evidence of safety and pharmacokinetics but later Phase 1 studies were stopped due to funding issues (Heald *et al.*, 2014; Haque *et al.*, 2015).

JK-05, an antiviral compound developed in china, is reportedly similar to Favipiravir and acts by inhibiting RNA polymerase, thereby, halting replication. The compound has been sanctioned for emergency use and preclinical studies have been reportedly performed. Although no clinical data is available, China has been reported to have sent the drug to west Africa during the outbreak in 2014 (Kilgore *et al.*, 2015).

GS-5734, a novel antiviral drug developed by Gilead Sciences is a nucleoside pro drug that is highly potent against Filo viruses. It metabolizes into an active component which then constrains viral RNA replication. Treatment in NHP produced high efficacy and also presence of active metabolite in various organs suggests its potential in decreasing virion presence in bodily fluids. Its been used in some cases of EBOV infections in humans though the most notable would be its effectiveness in a newborn where GS-5734, along with ZMapp and coalescent blood transfusion decreased viral presence without producing any developmental defects (Warren *et al.*, 2016; Dörnemann *et al.*, 2017).

11.5 Other Drugs:

FX06, developed by MChE-F4Pharma is a human fibrin derived synthetic peptide currently being tested for vascular leak syndrome. The drug has been administered to two patients, during late stages of EBOV infection. One patient reportedly recovered. However no concrete data regarding efficacy is available (Wolf *et al.*, 2015).

rNAPc2 (Recombinant nematode anticoagulant protein c2), an anticoagulant that inhibits tissue factor developed from saliva of hookworm by Arca Biopharma, USA has been evaluated for prevention of thrombosis. The drug has been used to increase survival in EBOV infected NHP but still no data on tolerance or efficacy in humans is available (Geisbert *et al.*, 2003).

During screening of green fluorescent protein of EBOV, various compounds with activity were identified out of which FGI-103, FGI-104 and FGI-106 produced protection through prophylactic treatment in Ebola mouse model (de Wit *et al.*, 2011).

Azithromycin, an antibiotic was tested for efficacy against EBOV. Increased survival was noted in mouse models however the drug was ineffective when given to guinea pigs (Madrid *et al.*, 2015; Sweiti *et al.*, 2017).

Various FDA approved drugs have been utilized in treatment of Ebola. Amiodarone, an antiarrhythmic drug was used in one study involving Ebola patients in Sierra Leone which reported decreased mortality although effectiveness was not established. The use was justified due to inhibition of filo virus cell entry in preclinical studies (Turone, 2014; Sweiti *et al.*, 2017).

Clomiphene and Toremiphene which are FDA approved Selective estrogen receptor modulators (SERM) used for infertility and breast cancer respectively, have been studied for anti-Ebola activity in mouse. These SERMs inhibited EBOV entry, thereby, increasing survival in mouse models (Johansen *et al.*, 2013).

A combination therapy utilizing Atorvastatin, Irbesartan and in some cases Clomiphene, was reportedly given to 100 Ebola patients in Sierra Leone out of which only 2 deaths were reported rest survived (Fedson & Rordam, 2015).

Chloroquine, an antimalarial drug, has been indicated to have some anti-Ebola activity by barring EBOV entry into host cells. Tests in animals produced increased survival (Madrid *et al.*, 2015; Sweiti *et al.*, 2017). Another antimalarial drug, Amodiaquine was used in a comparative study against lumefantrine in Ebola patients. The study found that patients treated with Amodiaquine had a better survival rate than those treated with lumefantrine, although no data on effectiveness of Amodiaquine was given (Gignoux *et al.*, 2016).

12. CONCLUSION

Although the recent outbreak in Africa (2014) has been declared as an emergency no more by WHO, the fear of future outbreaks prompt researchers throughout the world to take action. Also high *lethality* and infectivity of Ebola Virus put it as a candidate for use in Bio-terrorism. This along with the emergence of new strains like Makona (west Africa 2014 outbreak) forced development of new therapeutics against the virus, through which many promising drugs like ZMapp, rVSV vaccine etc, have emerged. Though many new therapeutics have been developed or are in development, performing clinical trials to measure their safety and efficacy remains a huge hurdle due to the bio-safety level 4 status of the disease and unavailability of subjects. Even if future outbreaks may occur, it is needless to say that the world is much better equipped to handle Ebola then it was back in 2014. With Better diagnostics, better management and therapeutics future outbreaks will be much better contained and have better survival rates.

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