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Review Article

EBOLA VIRUS: AN OVERVIEW DISEASE AND TREATMENT

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ABSTRACT

Objective: *Ebola virus* disease (EVD) is a life-threatening viral disease. Death rate ranges between 30% and 90%, the first EVD outbreak was reported in the 1970s in Zaire. The global danger of this virus requires the need for producing effective vaccines and drugs is facing its outbreak threat. Even though there is no available commercial vaccine so far against EBOV, a few vaccine candidates are under evaluation to examine their therapeutic efficacy.

Methods: Based on many types of research, we present in our review the properties of the *E. virus* and EVD, the ongoing efforts to develop diagnostics, vaccines, and drugs for the cure of EVD.

Results: Despite the efforts of health organizations to study, reduce and treat Ebola infection, there are still many challenges including the early diagnosis and control of infection among people in addition to finding a suitable treatment and vaccine in addition to many social and medical reasons.

Conclusion: The good clinical knowledge about the disease and infection control is very important to fight against the outbreaks. Therefore, it is necessary to develop training programs to increase awareness about the diseases in affected areas.

Keywords: *Ebola virus*, Outbreak, Treatment, Hemorrhagic fever.

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INTRODUCTION

EBOV infects primarily humans, monkeys, and bats; but other species such as mice and fawns may also contact infection. There are five identified species of EBOV, four species (*Zaire ebolavirus, Sudan ebolavirus, Tai Forest ebolavirus,* and *Bundibugyo ebolavirus*) are known to infect humans and cause disease, whereas *Reston ebolavirus* is non-human primate pathogen [1-3].

Ebola virus is the causative agent of Ebola hemorrhagic fever (EHF). The first infection was recognized in 1976 in the Northern Democratic Republic of Congo, in Zaire as well. Since then, *E. virus* disease (EVD) became endemic in Africa. Among these epidemic areas, 318 cases were recorded in DRC, and 284 cases were recorded in Sudan and two different species of EBOV were confirmed: EBOV-Zaire and EBOV-Sudan. In 1977, one fatal case due to EBOV was reported in Zaire, and EBOV subsequently reemerged with 34 cases, 22 of which were fatal in Sudan in 1979. No further cases were recorded until 1994. In 1995, EVD due to EBOV reemerged in the DRC [3-7].

The chronology of previous EVD outbreaks according to the WHO is shown in Table 1.

Structure of *E. virus*

E. virus is a filamentous shape virus with dimensions of 800 nm long and 80 nm in diameter and has an encapsulated single-stranded negative RNA [9]. There are seven expressed proteins by Ebola: Nucleoprotein (NP), glycoprotein (GP), RNA-dependent RNA polymerase (L), and four structural viral proteins: (VP24), (VP30), (VP35), and (VP40) (Fig. 1) [10-13].

The role of these proteins is summarized as follows:

- NP: Essential for RNA encapsulation
- GP: Essential for the attachment of the virus to the host cell membrane and entering the nucleocapsid of the virus into the host cytoplasm
- VP24: Essential for virus assembling and in transcription by being a part of the nucleocapsid structure [14]
- VP30: Suppression of viral RNA silencing
- VP35: Binds to NP to remove the nucleocapsid to facilitate the transcriptional expression
- VP40: Required for virus localization out of the host cell membrane and gives filamentous shape to virus together with GP and helps maintain the structural integrity of the virion [15-17].

LIFE CYCLE

The natural reservoir host of *E. virus* is fruit bats and accidental hosts are humans and non-human primates. *E. virus* can be directly transferred by blood or body fluids such as urine, saliva, sweat, feces, breast milk, and semen. *E. virus* also can be transferred by sexual contact [19-23].

After entering the body through small wounds on the skin or mucous membranes, the virus targets monocyte/macrophages and dendritic cells. The infection then spreads through the lymphatic vessels to regional lymph nodes and from there causes secondary viremia infecting the spleen, liver, and adrenal glands (Fig. 2) [13].

Steps of the virus life cycle: Viruses attach to the host receptors by GP which is endocytosed into vesicles in the host cell. Then, the viral membrane fuses with the vesicle membrane, and the nucleocapsid is released into the cytoplasm. The transcription of RNA process begins with the binding of the polymerase complex to a single binding site located within the leader region of the genome. The complex then slides along the RNA template and sequentially transcribes the individual genes in their 3'–5' order. Encapsidated, negative-sense genomic ssRNA is used as a template for the synthesis (3'–5') of polyadenylated, monocistronic mRNAs and, using the host cell's ribosomes, tRNA molecules, etc., the mRNA is translated into individual viral proteins, with an increase of viral protein levels, a switch occurs from translation to replication. Assembly starts by the nucleocapsids which accumulate in the perinuclear region; then it is

Table 1: The chronology of previous EVD outbreaks

Year	Country	EVD	Cases	Deaths
2018–2019	The Democratic Republic of the Congo	Zaire	Ongoing	
2018	The Democratic Republic of the Congo	Zaire	54	33
2017	The Democratic Republic of the Congo	Zaire	8	4
2015	Italy	Zaire	1	0
2014	Spain	Zaire	1	0
2014	UK	Zaire	1	0
2014	USA	Zaire	4	1
2014	Senegal	Zaire	1	0
2014	Mali	Zaire	8	6
2014	Nigeria	Zaire	20	8
2014–2016	Sierra Leone	Zaire	14124*	3956*
2014–2016	Liberia	Zaire	10675*	4809*
2014–2016	Guinea	Zaire	3811*	2543*
2014	The Democratic Republic of the Congo			
2012	Democratic Republic of Congo	Bundibugyo	57	29
2012	Uganda	Sudan	7	4
2012	Uganda	Sudan	24	17
2011	Uganda	Sudan	1	1
2008	Democratic Republic of Congo	Zaire	32	14
2007	Uganda	Bundibugyo	149	37
2007	Democratic Republic of Congo	Zaire	264	187
2005	Congo	Zaire	12	10
2004	Sudan	Sudan	17	7
2003	Congo	Zaire	35	29
2003	Congo	Zaire	143	128
2001–2002	Congo	Zaire	59	44
2001–2002	Gabon	Zaire	65	53
2000	Uganda	Sudan	425	224
1996	South Africa	Zaire	1	1
1996	Gabon	Zaire	60	45
1996	Gabon	Zaire	31	21
1995	Democratic Republic of Congo	Zaire	315	254
1994	Côte d'Ivoire	Taï Forest	1	0
1994	Gabon	Zaire	52	31
1979	Sudan	Sudan	34	22
1977	Democratic Republic of Congo	Zaire	1	1
1976	Sudan	Sudan	284	151
1976	Democratic Republic of Congo	Zaire	318	280

*Including Suspect, Probable and Confirmed EVD cases. Source: World Health Organization [8]. EVD: *Ebola virus* disease

transported to the budding sites at the plasma membrane. Budding occurs at the plasma membrane where VP40 and GP play important roles in the budding process. Finally, the virion is released [25-28] Fig. 3.

Symptoms of the disease

The incubation period usually extends 5–7 days, although it can be as minimum as 2 days and as maximum as 21 days.

Approximately 95% of the patients show signs within 21 days after the infection which is the recommended period for the follow-up of the disease.

Typical symptoms include fever, profound weakness, diarrhea, abdominal pain, cramping, nausea, and vomiting for 3–5 days and

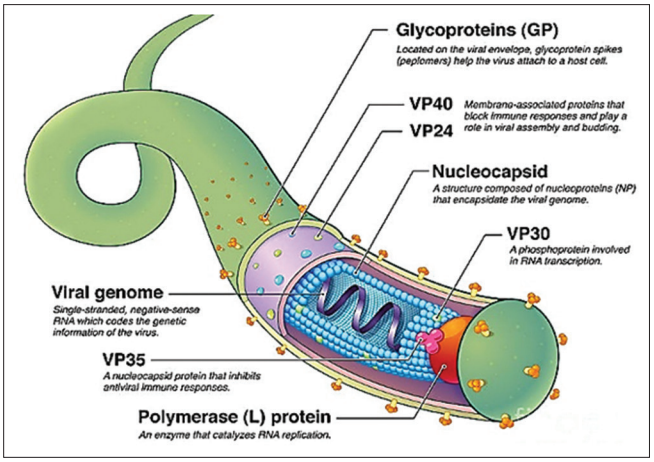

Fig. 1: Structure of *Ebola virus* [18]

may persist for up to a week. Laboratory complications including elevated aminotransferase levels marked lymphocytopenia, and thrombocytopenia may occur.

Clinical EHF is featured by sudden onset of fever, fatigue, chills, general malaise, headaches, myalgia, anorexia, and gastrointestinal distress within 3–13 days following exposure to the virus [23,30-32].

DIAGNOSIS

Rapid and reliable diagnosis of EVD is essential for appropriate and effective patient management. Diagnosis of suspected cases is confirmed by EBOV-specific laboratory tests that detect the EBOV genome (e.g., reverse transcriptase polymerase chain reaction [RT-PCR]) [33]. During the period of Ebola infection, viral RNA can be detected by RT-PCR in saliva, tears, sweat, breast milk, urine, vaginal fluid, and seminal fluid regardless of the acute disease [9,12]. Infection can also be diagnosed by measurement of the EBOV antigen or specific antibodies [34], IgM antibodies can be detected starting from 2 days after the first symptoms appear and disappear after 30–168 days. IgG response is generally considered to start between 6 and 18 days post-onset of illness and remains detectable for years [3]. In the past 10 months, the West Africa EVD outbreak has stimulated the development of new diagnostic tests, including rapid antigen detection tests and nucleic acid detection tests such as loop-mediated isothermal amplification assays [34].

INFECTION CONTROL AND TREATMENT

Immediate isolation of infected cases is very important before proceeding in any action [32]. The risk of *E. virus* infection can be decreased by averting contact with blood or body fluids from infected people, addition to avoid visiting the patients in the hospital, and by careful hand washing and hygiene [12]. It is necessary to abstain from breastfeeding for the possibility of transmission of the virus through the milk, in addition to safe sex practices, especially after the appearance of infection after the recovery of infected people [19].

So far, there is no authorized safe and effective treatment for EVD. Current treatment is merely supportive, including the control of pain and secondary infections, as well as fluid therapy [35]. Symptoms and complications of EVD should be treated immediately after they occur. Hypovolemia due to massive fluid loss through vomiting and diarrhea is the most common symptom of EVD. Thus, it is necessary to maintain fluid volume by modulation. The electrolyte ratios regulate the daily fluid input and output. It was also observed that antiemetic and antidiarrheal drugs may limit the massive loss of fluids and should be approved [36] when disseminated intravascular coagulation develops. They must control the coagulation factors, the remedy of thrombocytopenia and anemia. In addition, respiratory failure is more often secondary to EVD complications, and therefore, oxygen therapy in severe cases should be used [17,37-39].

Table 2: Table of drug clinical trials

Product/company	Phase	Trial location	Description
Favipiravir Fujifilm/Toyama, Japan	Phase II	By INSERM in Guinea: Conakry, Guéckedou, Macenta, Nzérékoré	Used to treat influenza The drug has been administered to around 200 patients who received 9 days of oral treatment. There is no control group The EU has announced preliminary findings from these trials which show the antiviral may be effective in treating patients with early-stage EVD. In adults and adolescents with a low to moderate viral load, the case fatality rate was 15% (vs. 30%, historically). WHO is taking a cautious interpretation given the lack of concurrent controls in the study
TKM-100802 (siRNA) Tekmira, Canada	Phase II	By Oxford University in Kerry Town, Sierra Leone	siRNA – a short RNA sequence that cleaves Ebola RNA in cells and prevents virus multiplication. Treats 100% of infected monkeys A clinical trial started in early March 2015 in Port Loko, Sierra Leone, led by Oxford University with funding from the Wellcome Trust The trial was halted on June 19 on the grounds of having met one of the clinical endpoints. Continuing enrolment was not likely to demonstrate an overall therapeutic benefit
ZMapp Mapp USA	Phase II	By NIAID in Liberia, Sierra Leone and the United States of America	The product has been used on several patients under compassionate use A multi-country, the multisite randomized controlled trial opened to enrollment in Liberia and the United States in February 2015 and in Sierra Leone in March 2015. Enrollment is ongoing – currently, more than 35 patients have been enrolled No data on efficacy are available yet Preparations to extend this trial to Guinea (in collaboration with INSERM) are in progress
MIL-77 MathWorks, China	Phase I		Efficacy in monkeys comparable to Zmapp To date, used in two expatriated patients under compassionate use IND for Phase I filed in China Prioritized for use on Ebola patients in the condition of not interfering with the clinical assessment of the efficacy of Zmapp
BCX-4430 Biocryst, USA	Phase I	By Quotient Clinic in the UK	Broad-spectrum direct-acting nucleoside analog Phase I safety trial is underway. No efficacy trial is planned until safety data have been analyzed
Interferons	Phase II	By Guinea MOH in Coyah, Guinea	Approved for the treatment of Hep B and C and multiple sclerosis
Amiodarone	Observational	At the Lakka and Goderich ETU in Sierra Leone	Used to treat cardiac dysrhythmia Was used compassionately in approximately 80 patients in Sierra Leone and reportedly reduced case fatality ratio when compared with local historical norms. The statistical significance of this result is not known due to variations in case fatality rates across sites and overtime This treatment is no longer being used
Atorvostatin+Irbesartan ±Clomiphene		Sierra Leone	Approved for cholesterol control/hypertension/infertility, respectively Apparently used to treat some patients in Sierra Leone; however, there has been no confirmation from the treatment centers that such studies took place, and no clinical data on the patients are available. Therefore, no conclusion on utility, safety or efficacy is possible
Amodiaquine		Médecins Sans Frontiéres (MSF)	Antimalarial products were provided to all patients entering Ebola treatment centers. When MSF switched from an antimalarial containing lumefantrine to one containing amodiaquine, the case fatality rates dropped It is not known if this is due to the efficacy of amodiaquine against Ebola or the toxicity of lumefantrine in patients with EVD
Brincidofovir Chimerix, USA	Phase II	By Oxford University at the ELWA 3 Clinic, Monrovia, Liberia	An antiviral used to treat CMV Clinical trial halted and abandoned; the drug has been deprioritized for use in Ebola treatment

Source: World Health Organization [40]

Table 3: Table of vaccine clinical trials

Product/company	Phase	Trial location
ChAd3-ZEBOV GlaxoSmithKline and PHAC	Phase I	By VRC at NIH, USA By Oxford University in the UK By CVD in Mali At the University of Lausanne, Lausanne, Switzerland
rVSV-ZEBOV NewLink Genetics and Merck Vaccines USA	Phase I	By WRAIR in the US By NIAID in the US By CTC North GmbH in Hamburg, Germany At Albert Schweitzer Hospital in Lambarene, Gabon At the University of Geneva, Geneva, Switzerland At the IWK Health Center, Halifax, Canada By KEMRI Wellcome Trust in Kilifi, Kenya
Ad26-EBOV and MVA-EBOV Johnson and Johnson and Bavarian Nordic	Phase I	By the University of Oxford in the UK and NIAID, USA TBD, Kenya TBD, Uganda TBD, United Republic of Tanzania
Recombinant protein Ebola vaccine candidate Novavax	Phase I	Australia
ChAd3-ZEBOV GlaxoSmithKline and PHAC	Phase II	TBD, Cameroon TBD, Ghana TBD, Mali TBD, Nigeria TBD, Senegal
VSV-EBOV NewLink Genetics and Merck Vaccines USA	Phase III	By WHO, Médecins Sans Frontiéres and Government of Guinea in Conakry, Guinea
VSV-EBOV	Phase III	By Médecins Sans Frontiéres, WHO and Government of Guinea in Conakry, Guinea
ChAd3-ZEBOV GlaxoSmithKline and PHACand VSV-EBOV NewLink Genetics and Merck Vaccines USA	Phase II/III	By US NIH and MOH Liberia in Monrovia, Liberia
VSV-EBOV NewLink Genetics and Merck Vaccines USA	Phase III	By US CDC and MOH Sierra Leone in Freetown, Sierra Leone

Source: World Health Organization [41]

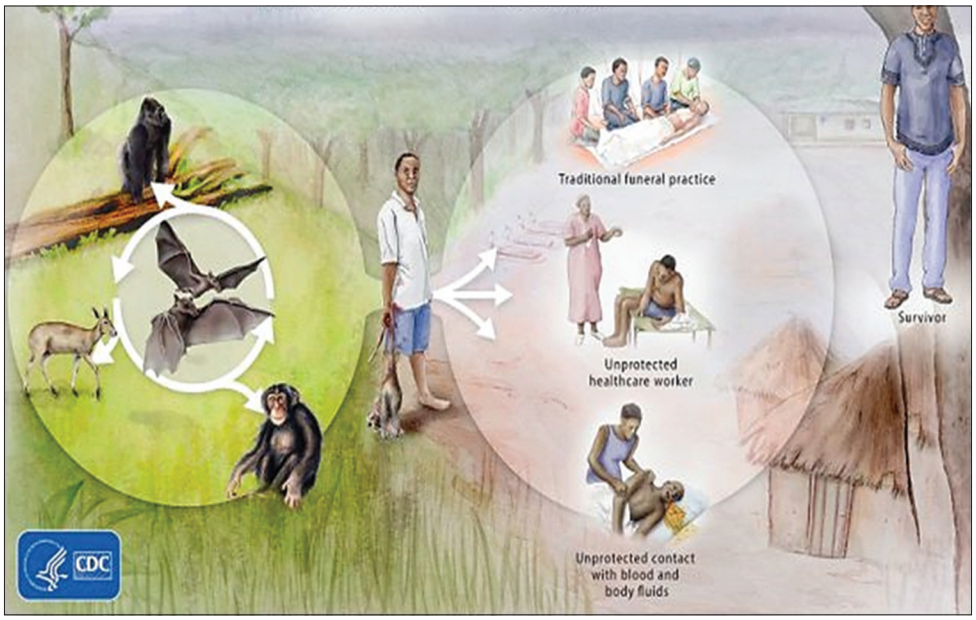

Fig. 2: *Ebola virus* transmission. Source: Centre for Disease Control [24]

WHO has issued a document for the classification, testing, and use of drugs in patients who are infected with the *E. virus*, as shown in Table 2 [11].

With the global effect of the West Africa outbreak EVD, research and development for new Ebola vaccine candidates have been stimulated, though no authorized vaccine is currently available. Previously, the development of vaccine candidates has led to the initiation of Phase I, II, and III human clinical trials, Table 3 [29,41].

CONCLUSION

The current EVD outbreak urges the health care and public health systems to respond to infectious disease emergencies and develop the healthcare infrastructure in developing countries and to increase awareness in countries at risk for EVD imported cases [3,7]. Human Ebola outbreaks usually occur unexpectedly with a subsequent rapid spread from person to person. *E. viruses* are highly contagious infectious. Understanding the clinical aspects, immediate diagnosis and suitable treatment are major steps toward the prevention of death and transmission of the virus to other people [9].

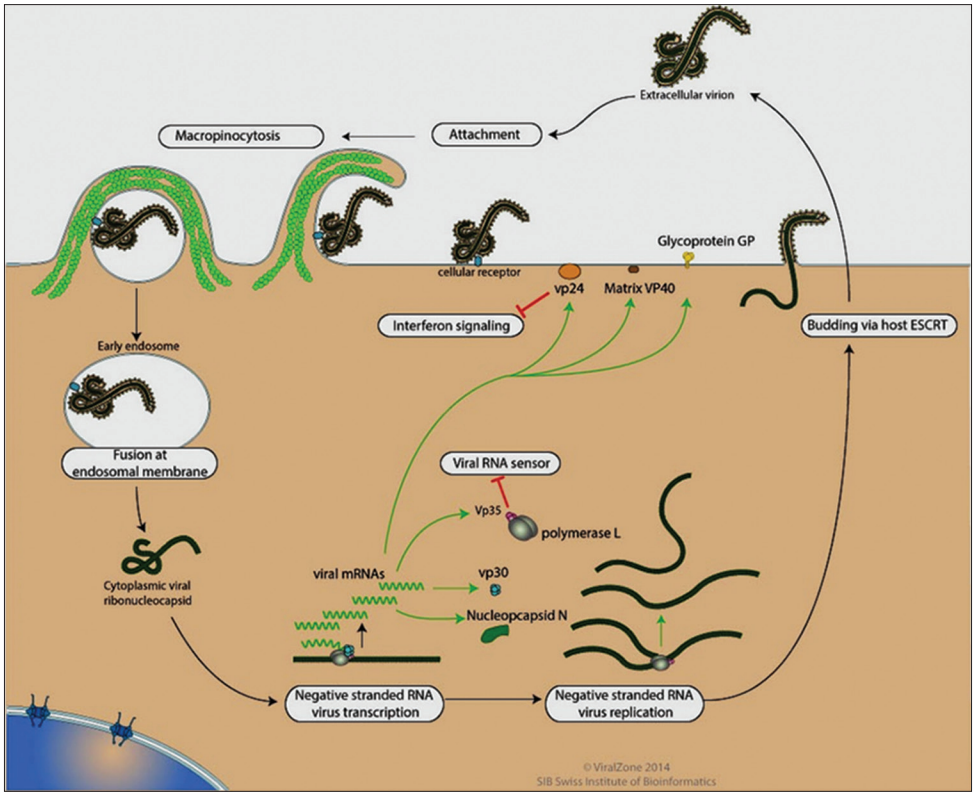

Fig. 3: The life cycle of Ebola, Source: ViralZone, Swiss Institute of Bioinformatics [29]

AUTHORS' CONTRIBUTIONS

Both authors have contributed for review article preparation and editing of the manuscript.

CONFLICTS OF INTEREST

We declare that there are no conflicts of interest.

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