***Review Article***

# MARBUG VIRUS DISEASE: AN OVERVIEW


## Abstract

Marburg virus disease (MVD) is a highly fatal, but uncommon viral disease which causes viral infection accompanied by hemorrhage and fever. It is caused by Marburg virus (MARV), a zoonotic virus belonging to the family of viruses known as *Filoviridae*, a single stranded RNA negative-sense virus, of the *Marburg marburgvirus* species. Marburg virus was established to have up to 88% fatality rate. Fruit bat is thought to be the natural host for Marburg virus as well as other non-human primate such as the grivet monkeys(*Chlorocebus aethiops*), however noted that fruit bats could be the actual host for the MVD. Marburg virus has two recognized variants, *Lake Victoria marburgvirus* and *Ravn Marburgvirus* with up to 20% overall divergence. The zoonotic transmission of Marburg virus occurs through prolonged exposureto an infected host animal through bites, or contact with fluid, faeces, droplets, or blood from an infected animal host, whereas the human-to-human transmission is as result of prolonged contact with an infected person, or contact with surfaces contaminated with MARV. MVD has the incubation period of 2 – 21day period after initial exposure to the virus and is marked with abrupt and rapid manifestation of symptoms such as high fever, chills, severe headaches, malaise and myalgia, possibility of nausea, vomiting, chest pain, and sore throat, jaundice, pancreatic inflammation, extreme weight loss, disorientation, shock, liver failure, extensive bleeding, and multi-organ malfunction. MVD can be diagnosed using a variety of methods, including culture, reverse transcription polymerase chain reaction (RT-PCR), serology, and immunohistochemistry for confirmation. Since no vaccine has been approved so far for MVD, it can be prevented by avoiding contact with the suspected fruit bat (*Rousettus aegyptiacus)* host as well as their habitats and by avoiding handling of, and contact with sick animals, and contact with persons suspected to be infected with MVD. MVD treatment can be done with supportive therapy which includes electrolyte and fluid balancing, oxygen status and blood pressure maintenance, lost blood and clotting factors' replacement in instances of excessive bleeding, and complicated or secondary infection treatment. This study focuses on creating more awareness on Marburg virus disease following the recent outbreak in some regions of the world.




## Introduction

Marburg virus disease (MVD) is a highly fatal, but uncommon viral disease which causes viral infection accompanied by hemorrhage and fever [1,2,3]. According to Benisek and Ratini[4],and a report compiled by Mayo Clinic[5], MVD is similar to Ebola and used to be referred to as Marburg hemorrhagic fever (MHF) [4,5]. Marburg virus (MARV), a zoonotic virus belonging to the family of viruses known as *Filoviridae*, a single stranded RNA negative-sense virus, of the *Marburg marburgvirus* species, is responsible for causing MVD [3], with about 88% fatality rate based on WHO's report [2].Some studies have also reported case fatality rate of 23-90% [6].

Marburg virus (MARV) was detected first in two German cities of Marburg and Frankfurt, and in Belgrade, Serbiain 1967 [7,2,3,4], during a laboratory studies with infected grivet monkeys also known as *Chlorocebus aethiops*, imported from Uganda, Africa [4].Slenczka and Klenk [8], in their work reported that thirty-one persons were infected Min the outbreak of which seven mortalities was recorded [8]. Further cases of the spread were recorded in African region in countries such as Angola, Kenya, South Africa, lityUganda, and Democratic Republic of Congo

**Comment [RK1]:** ?what does it imply?

**Comment [RK2]:** ?

[2]. According to Towner *et al.* report in 2009 [9], an infectious MARV was isolated from Egyptian fruit bats (*Rousettus aegyptiacus* alongside its *B* strain and close relative RAVN virus (RAVV) [9]. This study suggested that the fruit bat is involved in the natural maintenance of MVDs [9], although further research is required to certifyfruit bat as the natural host for the virus. As reported by Paweska *at al.* [10], the first ever experimental study conducted on the Egyptian fruit bat in 2012revealed the possibility of their involvement in MARV ecosystem [10]. The experimental bat~~h~~s were reported to develop minimal viremia for at least five days, but showed no sign of illness physically. Viral replication in major organs such as the liver and spleen, and other organs with the possibility of involvement in viral transmission like the kidney, salivary gland, lungs, mammary gland, organs of reproduction, the bladder, and the intestine was shown to be high [10]. The CDC however noted that fruit bat~~h~~ could be the actual host for the MVD, although further study is needed to establish the thoughts [3].

In a study carried out by Kajihara *et al.* [11] on Marburg virus in Egyptian fruit bats in Zambia, a genome of MARV was discovered in a bat captured in September 2018 [11]. This research showed MARV to share very close traits with the viruses responsible for the MVD outbreak in DR Congo [11]. The study confirmed Zambia to be at risk of MVD.In another research conducted by Koundouno *et al*. [12], in August 2021, a case of Marburg virus disease was detected in Guinea, and additional two cases recently reported in Ghana this year (2022) [12]. The fruit bat is reported to be widely distributed across Africa, a situation which makes more areas highly susceptible for Marburg disease outbreak when compared to other regions [3]. The CDC also reported that MARV is not known to be home to MARV [3].

MVD has an ~~incubation has an~~ incubation period of 2 – 9 days during which no transmission occurs [6], and is primarily transmitted from animal to humans through the fruit bat. Also a record of over 2300 deaths is attributed to MARV since its discovery in 1967 according to Leroy *et al*. [13]. It was further reported that there is a rising interest in the study of the disease from both scientists and the general public owing to their unusually high fatality rate. This is due to a perceived potential to serve as a biological weapon [13].

**Causative Agent**

Marburg virus, a singled-stranded, non-segmented, enveloped, negative sensed RNA virus is a *Filovirus* [14]. Mark et al. [14] and Glaze *et al*. [15] reported that Marburg virus has two recognized variants, *Lake Victoria marburgvirus* and *Ravn Marburgvirus* with up to 20% overall divergence, with the Ravn variant being implicated in the 1987 single case in South Africa, and few other cases discovered in eastern DR Congo [15]. Bausch *et al.* [16] reported that the Lake Victoria variant has been responsible for all additional human cases, including the instance in Guinea that happened in 2021 [16].The only viral protein that can be found on a cell surface is the Marburg glycoprotein (GP), which has been the main focus of experimental viral vaccinations [14]. Marburg viruses are made up of structural protein, which is seven in number. They contain helical ribonucleocapsid at the center comprising of the genomic RNA enveloped around a polymer od nucleoprotein (NP). The RNA-dependent RNA polymerase (L), together with a transcription activator and the polymerase cofactor (VP35), is connected to the ribonucleoprotein (VP30). The major (VP40) and minor (VP24) matrix proteins work together to

build a matrix around the ribonucleoprotein. A fatty membrane generated from the host cell membrane encircles these particles [17].

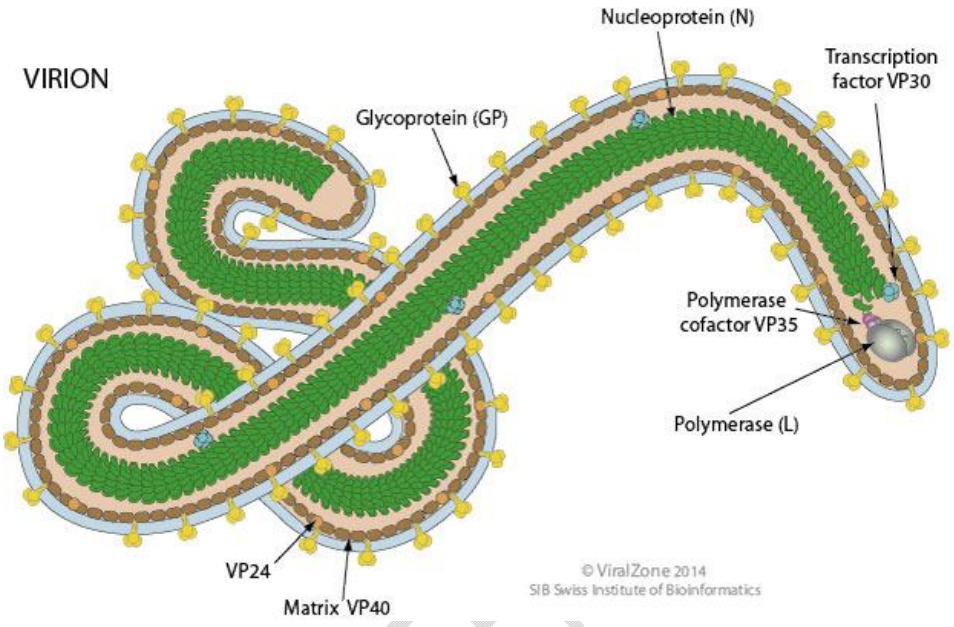


**Fig. 1.**A*Marburg virus filamentous structure [28]*

**Transmission Routes**

The zoonotic transmission of Marburg virus occurs through prolonged exposureto the infected host animal through bites, or contact with fluid, faeces, droplets, or blood from an infected animal host [2,3,4]. Human-to-human transmission occurs through direct contact with an infected person's body fluids such as the blood, or other body fluids such as urine, saliva, faeces, vomit, amniotic fluid, sweat, breast milk and semen [2,3,4]. Other routes of exposure include through caregiving to an infected person, contact with surfaces contaminated with fluids from an infected person, or exposure in the laboratory [3]. Sara and Mary ~~in their~~ reported in an article that Marburg have been found to be transmitted via tears [18].

**Fig. 2.** *Bats captured from the Kitaka mine, Uganda where two cases of Marburg virus infection were reported [2]*



**Signs and Symptoms**

The WHO, Benisek *et al.*, CDC, and several other reports ~~conducted~~ on MARV showed that the incubation period after exposure to the virus and initial infection is between 2 – 21day period [2,3,4], with abrupt and rapid manifestation of symptoms such as high fever, chills, severe headaches, malaise and myalgia [2,3]. Based on studies conducted byBrauburger et al.,Kortepeter et al., and Pavlin [19,20,21], it was observed that the incubation period varies from 5-10 days [19], to 3-13 days [20], and 2 – 26 days [21] respectively. Other symptoms which accompany these onset period are severe watery diarrhea, cramps and pain in the abdomen, nausea, and vomiting are all possible from day three [2]. WHO [2] reported that the diarrhea can persist for a week. The CDC also reported instances of maculopapular rash which appears particularly on the trunk (chest, back, stomach) within the onset period of three days [3]. According to the CDC [3] and several reports from studies, the possibility of nausea, vomiting, chest pain, and sore throat exists. Jaundice, pancreatic inflammation, extreme weight loss, disorientation, shock, liver failure, extensive bleeding, and multi-organ malfunction are some of the most severe symptoms that might develop [3]. Within a week, many patients experience severe hemorrhagic symptoms, and in lethal instances, bleeding is typically present, frequently in many locations. Bleeding from the nose, gums, and vagina frequently accompany fresh blood in vomitus and feces [2]. At the sites of venepuncture (where intravenous access is established to administer fluids or draw blood samples), spontaneous bleeding can be particularly difficult [2]. Persistent high fevers during the acute stage of the illness have been reported in patients [2]. Confusion, impatience, and violence might result from central nervous system involvement. There have been few reports of orchitis (testicular inflammation) in the late stage (15 days).Mark et al. [14] in their study revealed that autopsy report of Marburg virus victims showed focal necrosis without inflammation in the liver, spleen, testes, ovaries, and the pancreas, and signs of hemorrhagic diatheses in all organs [14]. The entire brain has been found to have glial nodule

encephalitis. Additionally, there is severe renal impairment and tubular insufficiency symptoms. Lymphatic tissue exhibits monocytoidal and plasmacellular change [14]. In severe cases, death typically occurs8 to 9 daysfrom onset, usuallyaccompanied by significant loss of blood and shock [2]. The WHO report suggested rehydration with oral or intravenous fluids as supportive care and specific symptoms treatment to facilitate the survival of the patient [2].

**Diagnosis**

Marburg viral disease (MVD) clinical diagnosis is often challenging [3]. Most of the symptoms of MVD are identical to those of other infectious diseases such as malaria, typhoid fever, or dengue or viral hemorrhagic fevers that may be prevalent in an area (for instance; Lassa fever or Ebola) [2,3].Depending on the progression of the infection, MVD can be diagnosed using a variety of methods, including culture, reverse transcription polymerase chain reaction (RT-PCR), serology, and immunohistochemistry for confirmation [14] within the early days the symptoms appear [3].Biological samples recommended for the testing according to Mark et al. [14] include blood, body fluids and tissue obtained from the infected person.The CDC noted in their report patients with early MARV symptoms should be isolated while notification is issued to public health personnel for sample collection and subsequent diagnosis [3]. The samples obtained are considered by the WHO to be extremely biohazard risk and strongly recommend their laboratory testing to be carried out under optimum containment environment [2]. The CDC *Biosafety in Microbiological and Biomedical Laboratories (BMBL)* rates Marburg virus as a Risk Group 4 Pathogen [22]. The NIH/National Institute of Allergy and Infectious Diseases in 2009,rated MARV as a Category 'A' Priority Pathogen alongside smallpox and other bacterial infections [23], and in 2014 was classified as a Category 'A' Bioterrorism Agent/Disease by the U.S CDC [24]. When transferred domestically and abroad, all biological specimens must be wrapped utilizing the triple packing system as recommended by the WHO [3].

**ELISA TESTING**: ELISA or enzyme linked immunosorbent assay diagnosis targets the antigen or antibody of the virus in the patient's sample [25].

**Reverse transcription polymerase chain reaction (RT-PCR):** RT-PCR testing aims at detecting the genetic material of the virus in the test sample [25].

**Prevention**

Marburg virus zoonotic transmission can be prevented by avoiding contact with the suspected fruit bat (*Rousettus aegyptiacus)* host as well as their habitats and by avoiding handling of, and contact with sick animals [3]. MVD transmission can also be prevented by limiting visits to regions plagued with the disease [25]. Human-to-human transmission can be contained by isolating the suspected or confirmed infected patient in a specialized biocontainment unit [3,14], observation of safety measures such as putting on ofappropriate personal protective equipment (PPE), gloves, masks, gowns, and face shields or goggles to prevent contact with blood or other body fluids.; and sterilizing or disposing of needles, tools, and patient waste [3,14]. Healthcare personnel who employ sharp objects and other tools in the diagnosis of patients and management or investigation of samples must apply high level of safety protocol such as proper hygiene, sterilization of reusable equipment, and appropriate disposal or incineration of non-reusable tools

and wastes from the diagnosis of an infected person [25]. Correll and Lubelchek [25] suggested in their study that the number of persons who are allowed to visit a patient in isolation during treatment should also be limited, and if possible, a particular individual or family member should be assigned to giving care to the patient so as to limit contact with the patient, and consequently the spread of the virus [25]. In~~n~~ instances of death, the members of the family of the deceased should be educated to exercise strict caution in touching the body of the deceased [25]. The CDC [3] recommends educating the general population especially, caregivers and health personnel on the clinical signs and symptoms of MVD as a way of creating better awareness on MVD and encouraging stronger safety measures against the spread of MVD [3]. Disinfection of contaminated areas and tools used in sampling and /or treating an infected is highly advised to prevent the spread and transmission of MVD [25]. Improvement in the use of testing modern tools and procedures has been advised by the CDC as a means of containment of MVD [3]. The use of rapid means of sample collection, transportation, and widening access to remote areas is suggested to hasten diagnosis and prevention of MVD spread.

**Treatment**

As at the time of this study, no specific treatment has been discovered, or vaccine approved for MVD [2,3,4,14], however, supportive therapy which includes electrolyte and fluid balancing, oxygen status and blood pressure maintenance, lost blood and clotting factors' replacement in instances of excessive bleeding, and complicated or secondary infection treatment [2,3,4,14]. Mark et al. [14] and Benisek et al. [4] cited that some vaccines are under study for MVD treatment including immunotherapeutics, phosphorodiamidate morpholino oligomers (PMOs), lipid-encapsulated small interfering RNAs, small molecule inhibitors, interferons, and antiviral nucleoside analogs [14].

**Vaccines**

In the study conducted by Mark et al. [14], it was reported that several vaccine constructs have been tested in cynomolgus macaques ~~have~~ andshown to offer protection against both variants of MARV (Marburg and Ravn). According to Reynolds and Marzi [26], three potential Marburg vaccines—cAd3, MVA-BN-Filo, and MARV DNA—are now undergoing Phase I clinical trials; MVA-BN-Filo is slated to undergo Phase 2/3 clinical testing. Protection in NHPs has been shown by a number of Marburg candidate platforms (rVSV, VLP, Adenovirus, and DNA) [26].

**Complication**

A study conducted by Charles and Melissa [27] and Brauburger et al. [19] revealed some sequelae such as hair loss, testicular atrophy, liver inflammation, encephalitis,skin desquamation, hyperhidrosis, amnesia,and decreased libidowhich accompany MVD infection.

**Conclusion**

Marburg virus disease (MVD) caused by Marburg virus (MARV) is rare, but fatal viral disease which originates from fruit bat and is marked by hemorrhage and fever. It has symptoms similar to those malaria and other endemic diseases. So far, it has no cure but can be managed through

supportive therapies. Taking appropriate measure to limit the disease spread remains a crucial role to remedy the spread of MVD which has become a recent public health concern.

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