

## Marburg and Ebola — Arming Ourselves against the Deadly Filoviruses

C.J. Peters, M.D.

An interview with Dr. Peters can be heard at [www.nejm.org](http://www.nejm.org).

As of May 26, 2005, the Angolan Ministry of Health had reported 399 cases of Marburg hemorrhagic fever, 335 of which were fatal. Even as this unprecedented spread of filovirus infection continued, Marburg's sister virus, Ebola, had killed nine people in the Republic of Congo. Although Ebola may now be the better-known sibling, Marburg virus was identified first, in 1967, after an infectious-disease clinician at the university hospital in Marburg, Germany, saw patients with a severe febrile syndrome associated with bleeding from multiple sites on the skin and the mucous membranes and shock. The patients all worked for a pharmaceutical manufacturer, and it later became evident that they had acquired their infection from African green monkeys that were used in the preparation of cell cultures for vaccines. The virus that was isolated in these cases was totally unrelated to any known virus family and turned out to have such a large, bizarre, branching morphology (see diagram) that initially many were even uncertain that it was a virus.

Nine years later, high-fatality outbreaks of unknown origin in Zaire (now known as the Democratic Republic of Congo) and Sudan alarmed the public health community. The viruses that were isolated from the epidemic in Zaire resembled Marburg morphologically and were christened Ebola virus; together with the Marburg virus, they formed the family Filoviridae. In fact, the 1976 outbreaks were caused by two different viruses that were, for unknown reasons, active in separate, remote areas. We now recognize two genera, Marburg virus and Ebola virus, the latter of which has four known species.

These viruses have continued to cause uncommon but alarming epidemics in Africa, which have

generally followed a recognizable pattern. One person becomes ill, and the disease begins to percolate through the community at a slow rate. It takes weeks or months to recognize that a filovirus is the cause, because there are no locally available diagnostic tests for these viruses. A clinical diagnosis of dysentery or typhoid commonly results in a delay in efforts to seek the correct diagnosis.

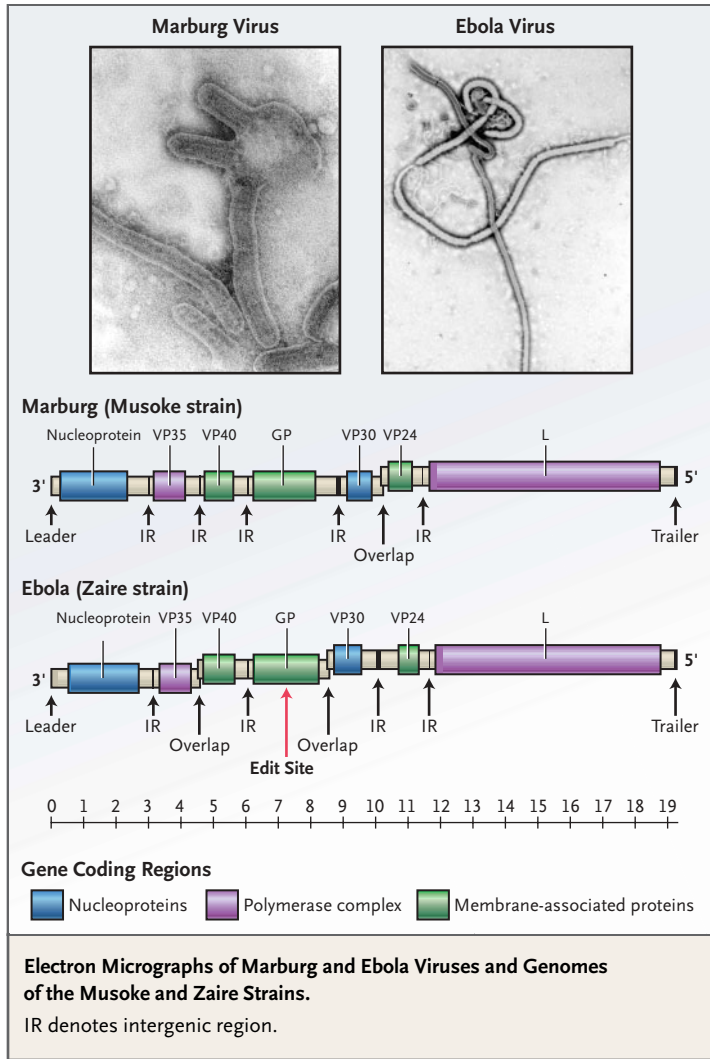
Then, the virus enters the medical care system. The most lethal route of spread is through parenteral infections. Many patients, including those infected with filoviruses, receive injections of various medications at health centers or from pharmacists or healers, and then unsterilized needles and syringes are reused, sometimes to administer medicines drawn from multidose vials. The single-use injection equipment that has been such a boon to the developed world has spelled disaster for the poorest nations. Plastic syringes cannot be heat sterilized and are usually simply rinsed. Needles are usually not sterilized, either. Even when syringes and needles designed for reuse are available, it is common for hospitals to own only a handful of injection sets, which tend to be reused without sterilization simply for logistic reasons. Indeed, it is a poorly kept secret that such reuse is common practice in African countries, where it has been implicated in the spread of hepatitis C and, almost certainly, human immunodeficiency virus (HIV).

Usually, filovirus hemorrhagic fevers predominantly affect adults — especially medical personnel and patients infected in the hospital. Even when an adult patient is cared for at home, children in the household rarely become infected. In the current Angolan epidemic, however, early cases occurred predominantly in children, who were infected in a pediatric ward or clinic through improperly sterilized injection equipment.

Equally important in spreading filoviruses in hospitals is the inadequate use of barriers by nurses.

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Micrographs courtesy of Frederick A. Murphy, Centers for Disease Control and Prevention.

Gloves are used only rarely — often not even during surgical procedures — and gowns are not commonly available. Thus, hospital personnel often bear the brunt of these epidemics and participate in the dissemination of disease. In many places, a lack of health care facilities hobbles attempts at control: patients are cared for at home and infect their care providers. In places where appropriate facilities exist, patients with a filovirus disease have little motivation to seek hospitalization, knowing that their neighbors will ostracize their family, that they will probably die in the hospital, and that when they do, they will be whisked away in a body bag — so that their family will be denied the final preparation of the body and the culturally appropriate mourning and burial. And indeed, although hospitalization is important in controlling epidemics, medical institutions have very little to offer individual patients:

even supportive care is limited by costs and the fear of infecting staff members.

Most of these epidemics eventually dissipate owing to some combination of the closure of some hospitals because of the attrition of the staff, the institution of good infection-control practices with externally supplied materials in other hospitals, quarantine, and the relatively low transmissibility of filoviruses. Studies have consistently implicated close contact with body fluids or injections as the primary route of interhuman transmission. In addition, extensive viral involvement of the subcutaneous tissues brings the viruses very close to anyone who cares for patients or prepares their bodies for burial. In well-equipped modern hospitals, the incidence of transmission of filoviruses is very low, primarily because unprotected contact with the patients and their blood rarely occurs — thanks in large part to the discipline that has grown up around HIV infection.

We still have no idea how filoviruses are maintained in nature. At first, nonhuman primates were suspected to be the reservoirs, but it is now evident that they, too, are simply targets. They may serve as links to humans, as they did in the original outbreak in Marburg and as they apparently have in the ongoing chain of Ebola virus transmission in the Republic of Congo. To satisfy the increasing appetite for exotic meats, professional hunters now enter forests to kill nonhuman primates and other “bush meat,” and others scavenge dead chimpanzees; any of these animals may be infected with a filovirus. Most recent speculation about the source of these viruses has centered around bats — a hypothesis that is supported by a recent Marburg virus epidemic in the Democratic Republic of Congo, in which infection was generally acquired in subterranean gold mines.

Our progress in understanding the filoviruses has been slow because of their rare appearance in nature, the danger they pose to those who study them, and a lack of financial support. Until we began to see them as prime candidates for use in bioterrorism, it was only the occasional epidemic and the remarkable grip of movies and books on the imagination of scientists and the public that motivated research on these viruses. Recently, modern virology and the development of reverse genetic systems have allowed us to understand some of the functions of the different viral proteins (see diagram). The viruses are approximately 80 nm in diameter and 800 to 1100 nm in length, although

they often assume longer and even branching forms. They contain a single negative-sense RNA strand comprising 19 kb. Because they are RNA viruses, they are regarded as having high mutation potential and should be capable of evolving under the appropriate selection pressures.

The high virulence of these viruses seems to be explained in part by the ability of their proteins to defeat the human immune response in several different ways. The most important limb of the innate immune response of the host, which consists of type I interferons, is evaded through the suppression of induction by the VP35 protein and the blocking of interferon action by the VP24 protein. Thus, a crucial host response is not available to resist viral growth, and if interferon is synthesized, it is not able to perform such critical functions as the inhibition of viral growth; the activation of natural killer cells, macrophages, and dendritic cells; and the enhancement of the adaptive immune response. Infected macrophages are induced to secrete cytokines that result in bystander apoptosis of lymphocytes in the tissues that are responsible for the acquired immune response. Circulating infected monocytes express large amounts of tissue factor and initiate disseminated intravascular coagulation, with its attendant tissue damage. Viral infection of endothelial and parenchymal cells of many organs results in further tissue damage, which seems to be mediated directly by the expression of the glycoprotein.

The large amounts of virus and viral antigen in all organs of fatally infected humans and nonhuman primate models of disease suggest that recovery will not readily occur in most cases, even with effective supportive care. In addition, the extreme

histologic damage to the immune system and the lack of a detectable humoral immune response in fatal cases suggest that no help from the adaptive immune system is on the way. It has been difficult to detect neutralizing or protective antibodies even in convalescent patients, and if such antibodies as can be detected are administered passively to infected macaques (the best model of human disease), they have generally failed to offer robust protection.

It is likely that any substantial reduction in mortality will require an effective antiviral drug, one of the most important needs in this field. Several prototype vaccines to protect nonhuman primates against Marburg virus infections have shown promise, although numerous attempts to develop vaccines against Ebola virus have failed. Recently, however, two vaccines that solidly protect monkeys have been developed, one involving a vesicular stomatitis virus base and the other using an adenovirus vector. A single injection of the adenovirus construct can protect monkeys, and phase 1 trials of this vaccine have begun. The current filovirus epidemics are in large part a consequence of transmission from the use of unsterilized needles. If such spread were halted, the filoviruses would not present a major problem; and because of hygienic medical practices, they represent little or no natural threat to the developed world. Still, a highly mutable RNA virus that may be transmitted among humans and can be shown in the laboratory to be infectious as an aerosol might conceivably evolve in dangerous directions. We should therefore stop these epidemics promptly whenever they occur and should remain aware that these viruses may someday be harnessed as bioterrorist weapons.

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## Torcetrapib and Atorvastatin — Should Marketing Drive the Research Agenda?

Jerry Avorn, M.D.

In light of the success of the statin drugs, interest in preventive cardiology has shifted to new frontiers of pharmacologic intervention: defining optimal

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levels of low-density lipoprotein (LDL) cholesterol, inhibiting cholesterol absorption, addressing the inflammatory component of atherosclerosis, and increasing the levels of protective high-density lipoprotein (HDL) cholesterol. This last approach attracted attention last year when it was reported that a new drug, torcetrapib, could substantially increase levels of HDL cholesterol by inhibiting cholesteryl