Filovirus Hemorrhagic Fever Outbreak Case Management: A Review of Current and Future Treatment Options

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Testing an innovative therapy for filovirus hemorrhagic fever (FHF) in an outbreak setting may be years away. Moreover, beyond anecdotal evidence, little is known about best practice for outbreak case management. Currently, Médecins Sans Frontières and others provide FHF patients with basic supportive treatment. We describe and discuss treatment possibilities, challenges, and potential next steps for FHF outbreak case management. More comprehensive supportive treatment, including vital sign monitoring, intensive care components, and goal-directed interventions may contribute to improved clinical outcome; the feasibility and effectiveness of this more comprehensive supportive treatment should be assessed. Our outlined summary may assist future FHF outbreak case management teams to create collaborative platforms and develop relevant treatment protocols aimed at improving clinical outcome.

Filovirus virions are filamentous, enveloped particles with a negative-sense, single-stranded RNA genome [1]. Filoviruses are taxonomically separated into 2 genera, *Ebolavirus* and *Marburgvirus*, and comprise the family Filoviridae. Respectively, they cause Ebola hemorrhagic fever (EHF) and Marburg hemorrhagic fever (MHF) in human and nonhuman primates, and are characterized by person-to-person transmission and high case fatality [2]. To date, 34 filovirus hemorrhagic fever (FHF) outbreaks and laboratory-acquired infections are known to have occurred in humans (23 EHF and 11 MHF), all in or originating from sub–Saharan Africa and yielding approximately 2800 laboratory-confirmed, suspect, or putative cases [3–7].

Herein, we review treatment possibilities, challenges, and potential next steps for improving FHF outbreak case management during outbreaks. Topics include: (1) innovative treatment, (2) standard supportive treatment, (3) past and current challenges for outbreak case management, and (4) recommendations for improved case management. This review may assist future FHF outbreak case management teams to deliver improved treatment for patients.

INNOVATIVE TREATMENT

Efforts by researchers working in high-containment laboratories to address the absence of an effective, approved, and available filovirus treatment in humans are ongoing. Evaluated in nonhuman primates (NHPs) and other animals, some postexposure prophylaxes have achieved promising results [8–10] and have the potential to be innovative components of human treatment [8–12]. Innovative treatment can be divided into 2 categories: (1) disease-modifying agents, and (2) inhibitors of viral replication [3].

Disease-Modifying Agents

The pathophysiology of FHF resembles sepsis and septic shock, with strong inflammatory responses and disseminated intravascular coagulation (DIC) [13]. This similarity served as the impetus for animal-model

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testing of recombinant human activated protein C (rhAPC; Xigris, Eli Lilly), a licensed therapy for severe sepsis in humans [14], which has been used with some success as postexposure prophylaxis for EHF in NHPs [15]. Coagulation abnormalities may occur earlier in the disease course than previously thought. Therefore, chemotherapeutic strategies controlling overexpression of tissue factor may also mitigate EHF in NHPs, as tissue factor can initiate DIC [16]. Recombinant nematode anticoagulant protein c2 (rNAPc2), a clotting inhibitor that blocks the action of the tissue factor-factor VIIa complex, has also been demonstrated to attenuate DIC and postinflammatory responses in NHPs [17].

Inhibitors of Viral Replication

Antisense phosphorodiamidate morpholino oligomers (PMOs) [9, 18–20] and short-interfering RNA (siRNA) [10, 21] molecules have been shown to interfere with filovirus replication. Building upon past PMO laboratory success [18–20], Warren et al [9] demonstrated that positively charged PMOs, when initiated 30–60 minutes after lethal challenge, protect >60% of rhesus macaques against Zaire ebolavirus (ZEBOV) infection and 100% of cynomolgus monkeys against Lake Victoria Marburgvirus (MARV) infection. Likewise, Geisbert et al [10] showed complete postexposure protection in rhesus macaques against hemorrhagic fever induced by ZEBOV by administering anti-ZEBOV siRNAs 30 minutes after lethal challenge and on 6 subsequent days; these findings compare favorably with earlier successful postexposure prophylaxes [10, 15, 22, 23]. Positively charged PMOs and siRNAs, as well as the relative success of a recombinant vesicular stomatitis virus-based vaccine administered to rhesus macaques 24 and 48 hours postexposure [8], bring the provision of effective filoviral treatment to human patients closer. It is hoped that refined targeting of specific viral genes and improvements in medication delivery to the host will improve the effectiveness of antiviral approaches to filovirus treatment.

The Availability of Innovative Treatment

Notwithstanding these experimental achievements [8–10], the availability of an effective and approved treatment for human testing in an outbreak setting may be years away. Reasons for this are 2-fold: (1) the development of an innovative treatment has been slow [8, 12, 24], and (2) researchers have yet to evaluate treatment success in NHPs later in the disease's clinical course [8–10].

Given the current time constraints in the NHP model (commencement of treatment 30 minutes [10], 30–60 minutes [9], or 24–48 hours postexposure [8]), the presently envisaged innovative treatment for humans would primarily benefit those who know their time of exposure and seek and have access to immediate care, such as biosafety level 4 laboratory technicians and health care workers (HCWs). However, short of experiencing an accidental needlestick, HCWs may not know when their exposure occurred and therefore may not seek early treatment. Furthermore, local populations in outbreak-prone regions of sub–Saharan Africa who are most 'at risk' for filovirus infection are typically unaware of the timing of their exposure and seek medical care only after experiencing severe symptoms. The 6 laboratory accidents since the 1967 discovery of filovirus constitute a diminutive percentage of all recorded infections (0.21%) [7, 12, 24–26] in comparison with the approximately 2800 known filovirus infections acquired in sub–Saharan African outbreak settings [3–7].

Recent achievements in postexposure prophylaxes [8–10] represent a major breakthrough in filovirus research. We commend the investigators' germane questioning [8–10] of how long treatment can be delayed in NHPs and still have a beneficial effect. Nonetheless, we remain far from administering an effective, approved, and available therapy during a human FHF outbreak in a sub–Saharan African setting. In the meantime, early case identification and contact tracing, with isolation and provision of supportive treatment in filovirus wards for individuals with suspected or laboratory-confirmed infections, remain the primary strategies for outbreak control and case management [2, 27–31].

AN OVERVIEW OF STANDARD SUPPORTIVE TREATMENT

Médecins Sans Frontières (MSF), the relevant Ministry of Health (MoH), and other responding partners and organizations provide suspect and laboratory-confirmed patients with supportive care when human filovirus outbreaks occur in their natural sub–Saharan African setting [28, 29, 32]. Supportive care, the current standard for FHF treatment, consists of oral medication, oral fluid rehydration, nutritional supplementation, and psychosocial support. Oral medication includes drugs that alleviate FHF-related symptoms such as nausea and vomiting (eg, metoclopramide and promethazine), dyspepsia (eg, aluminium hydroxide, cimetidine, ranitidine, and omeprazole), anxiety, agitation, or confusion (eg, diazepam, chlorpromazine), and pain (eg, paracetamol, tramadol, and morphine) when indicated. Due to the usual absence of an onsite laboratory capable of safely processing biological samples for alternative diagnoses, empiric oral artemisinin combination therapies for malaria and empiric oral antibiotics (amoxicillin, cotrimoxazole, cefixime, or ciprofloxacin) are uniformly administered. In the sub–Saharan African outbreak setting, supportive care has also recently been expanded to include prevention and treatment of dehydration via intravenous (IV) fluids, nasogastric delivery of nutritional and vitamin supplementation, and IV administration of medication [30]. Administration routes for optimum drug delivery are determined clinically.

PAST AND CURRENT CHALLENGES FOR OUTBREAK CASE MANAGEMENT

Adverse Reaction to Disease Control and Case Management Strategies

Filovirus outbreak response is a formidable undertaking, particularly as locations are typically remote and fear of the disease is considerable among patients, communities, and outbreak response teams. Because of these and other inherent challenges, numerous errors have been made when implementing control and case management strategies during outbreaks [30, 33–38]. Community resistance has resulted from dissatisfaction over the response teams' poor communication with patients, families, and community leaders regarding response activities [33, 37, 38], and, at times, refusal by HCWs to offer supportive treatment to infected patients for whom death was assumed to be certain [30]. Community members have been distressed by unidentifiable HCWs wearing personal protective equipment (PPE) and anguished by not being allowed to observe the area surrounding the filovirus ward, to visit their hospitalized relatives on the FHF ward, or to confirm the deceased's identity prior to interment [33, 38, 39].

The resulting fear and anger has led some communities to refuse collaboration with outbreak response teams, thereby making case identification, contact tracing, and case management difficult or impossible. Events in Uganda, Gabon, Republic of the Congo, and Angola demonstrated that community resistance can become so severe and violent that outbreak response teams are prevented from accomplishing their mission [30, 33–38]. For example, during the 2005 Uige, Angola, MHF outbreak, verbal and physical aggression toward the team resulted in a temporary suspension of community-based activities [38], so that only a fraction of the reported cases was isolated and treated [30, 31]. Patient refusal of isolation and treatment on a filovirus ward not only defeated a crucial component of outbreak control [38], it impeded the establishment and improvement of outbreak case management [30, 31].

During nearly every filovirus outbreak, the response team acknowledged errors and underwent a learning process that improved the effectiveness of that particular intervention. However, largely due to filovirus outbreaks being unpredictable in both timing and location within sub–Saharan Africa, the majority of individuals who undergo a learning process are not present at subsequent outbreaks. As a result, nearly every outbreak response team has experienced a similar cycle of error and correction when implementing control and case management strategies. Outbreak response teams have continuously focused on improving their relations with the affected community while concurrently implementing measures to reduce secondary disease transmission; less emphasis has been placed on the provision of optimum patient care, which may, for some patients, improve the chance of survival [29–31; personal communication by filovirus ward clinicians: Benjamin Jeffs, Esther Sterk, and Jonas Torp].

Figure 1. Filovirus ward clinicians extract a venipuncture-acquired blood sample for laboratory confirmation from a patient potentially infected with Ebola virus during the Bundibugyo, Uganda, 2007–08 Ebola hemorrhagic fever outbreak. When wearing full personal protective equipment, filovirus ward clinicians are increasingly confident to establish contact with patient body fluids and deliver a more expanded supportive treatment. Photo by Claude Mahoudeau.

Administration and Expansion of Supportive Treatment

Until recently, some filovirus clinicians were reluctant to provide components of supportive treatment that potentially exposed them to patient body fluids, arguing that the risk of occupational infection outweighed the possible benefit of increased chances of patient survival. For example, providers have been reluctant to give IV fluids due to the potential danger of needlestick injuries. It is now recognized that the majority of these injuries occur while recapping a used needle rather than through the process of injection [2, 40], suggesting that parenteral drug administration can be performed safely if clinicians and nurses adhere strictly to biosafety measures, which include staff training and supervision, safe venipuncture material, proper lighting, and adequate disposal of sharps [30, 41]. The provision of intravenous volume replenishment is a cornerstone of effective sepsis treatment; insofar as pathophysiological processes in FHF mirror those of other sepsis syndromes, parenteral fluids may improve clinical outcome for some patients.

Filovirus clinicians' recent willingness to expand supportive care reflects their increasing confidence in establishing contact with patient body fluids while wearing full PPE [30] (Figure 1). This behavioral change was also a response to anecdotal evidence suggesting that an expanded supportive treatment strategy favorably influences FHF patients' clinical outcome [30, 42]. Clinicians were also aware of the 3.8 times higher case fatality proportion observed during the 1998–2000 Durba and Watsa MHF (83%) outbreaks compared with the 1967 MHF outbreaks in Germany and former Yugoslavia (22%). A disparity in the provision of supportive treatment was

theorized to have been a contributing factor to the considerable difference in survival ratios [31].

Though laudable, the recent expansion of supportive care is limited. To date, standard patient monitoring of vital signs (respiratory rate, blood pressure, and pulse), pulmonary signs (rales), and fluid intake-output ratios are not systematically monitored and thus are not components of expanded supportive treatment. Furthermore, expanded supportive treatment lacks essential components of intensive care such as the correction of electrolyte and metabolic derangement, goal-directed management of hemodynamics, oxygen supplementation, and immune modulating and other mitigation strategies for hyperinflammatory responses and DIC [43]. A more comprehensive supportive treatment strategy, including vital sign monitoring and intensive care components, may contribute to improved clinical outcome; its feasibility and effectiveness should be assessed.

Generating Evidence for Improved Case Management

The collection and analysis of quality patient clinical data had low priority in the majority of past filovirus outbreaks. Little information has therefore been gathered about best practice for filovirus case management beyond anecdotal evidence [30, 31]. Systematic collection of relevant data has also been hindered, in part, by safety concerns regarding transferring patient clinical records from inside the filovirus ward to outside. Records were often nonexistent, haphazardly logged, or destroyed as being potentially infected fomites. The standardization of data collection templates [44] and the prioritization of transferring clinical data from inside the filovirus ward to the outside [45] have, to some extent, helped to overcome these obstacles in recent outbreaks.

RECOMMENDATIONS FOR IMPROVED CASE MANAGEMENT

With clinical data collection now prioritized and the need for more comprehensive care obvious, the feasibility and effectiveness of a comprehensive supportive treatment strategy should be defined, applied, and assessed. However, a study to assess treatment effectiveness has not been, to date, attempted in a filovirus outbreak setting.

Detecting an association between comprehensive supportive treatment and clinical outcome would require the application of an appropriate study design to the collection and analysis of quality data. An appropriate study design may include a randomized, controlled trial (with respect for clinical equipoise) or an observational study; quality data must subsume patient demographics, clinical manifestations over the course of the illness, treatment regimen(s) administered, and clinical outcome. In concordance with an already suggested framework [3], institutions responsible for supporting filovirus outbreak case management, such as MSF and the World Health Organization (WHO), must create a collaborative platform aimed at developing a comprehensive supportive treatment protocol approved by institutional and outbreak-prone-country MoH ethical review boards. The collaborative platform should be functional prior to the occurrence of FHF outbreaks and be sufficiently agile and resilient to be deployed upon outbreak recognition. The protocol should incorporate "best available" standards of care, and, if and when available for an outbreak setting, include innovative treatment under appropriate ethical and clinical supervision. Specifically, investigators (WHO, MSF, and others) must (1) develop a definition of a comprehensive supportive treatment that can be administered under field conditions, (2) establish an appropriate evaluation scheme, (3) develop the protocol, and (4) implement the study protocol at a future filovirus outbreak in collaboration with the relevant MoH. Of note, MSF can ensure logistics, such as cold chain and relevant medical supplies, for the administration of an innovative treatment under field conditions.

A comprehensive and supportive treatment assessment initiative, coupled with the recording and analysis of quality epidemiological and clinical data, would contribute to the evidence base for filovirus case management. Pending the development of an innovative therapy, this may be the only way for future sub–Saharan African filovirus outbreak patients to receive care that may favorably influence their chance of survival.

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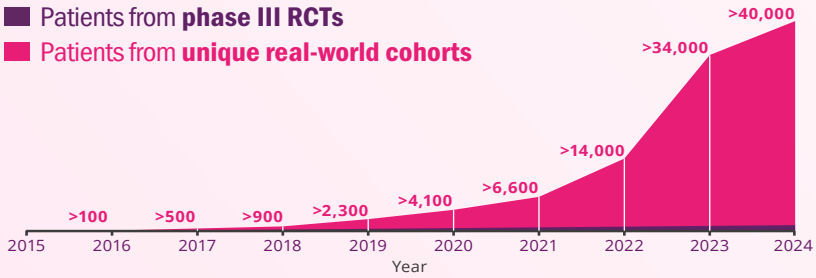

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ABBREVIATIONS

3TC, lamivudine; **CD4,** cluster of differentiation 4; **DTG,** dolutegravir; **FDA,** United States Food and Drug Administration; **FTC,** emtricitabine; **HIV,** human immunodeficiency virus; **ITT-E,** intention-to-treat exposed; **NRTI,** nucleoside/nucleotide reverse transcriptase inhibitor; **RCT,** randomised controlled trial; **RNA,** ribonucleic acid; **TAF,** tenofovir alafenamide fumarate; **TDF,** tenofovir disoproxil fumarate; **XTC,** emtricitabine.

FOOTNOTES

*Data extracted from a systematic literature review of DTG+3TC real-world evidence. Overlap between cohorts cannot be fully excluded.

**The reported rate reflects the sum-total of resistance cases calculated from GEMINI I and II (n=1/716, through 144 weeks), STAT (n=0/131, through 52 weeks), and D2ARLING (n=0/106, through 24 weeks).[5–7]

†GEMINI I and II are two identical 148-week, phase III, randomised, double-blind, multicentre, parallel-group, non-inferiority, controlled clinical trials testing the efficacy of DTG/3TC in treatment-naïve patients. Participants with screening HIV-1 RNA ≤500,000 copies/mL were randomised 1:1 to once-daily DTG/3TC (n=716, pooled) or DTG + TDF/FTC (n=717, pooled). The primary endpoint of each GEMINI study was the proportion of participants with plasma HIV-1 RNA <50 copies/mL at Week 48 (ITT-E population, snapshot algorithm).[13]

‡STAT is a phase IIIb, open-label, 48-week, single-arm pilot study evaluating the feasibility, efficacy, and safety of DTG/3TC in 131 newly diagnosed HIV-1 infected adults as a first line regimen. The primary endpoint was the proportion of participants with plasma HIV-1 RNA <50 copies/mL at Week 24.[6]

§D2ARLING is a randomised, open-label, phase IV study designed to assess the efficacy and safety of DTG/3TC in treatment-naïve people with HIV with no available baseline HIV-1 resistance testing. Participants were randomised in a 1:1 ratio to receive DTG/3TC (n=106) or DTG + TDF/XTC (n=108). The primary endpoint was the proportion of participants with plasma HIV-1 RNA <50 copies/mL at Week 48.[7] Results at week 24 of the study.

||The reported rate reflects the sum-total of resistance cases calculated from TANGO (n=0/369, through 196 weeks) and SALSA (n=0/246, through 48 weeks).[8,9]

¶TANGO is a randomised, open-label, trial testing the efficacy of DOVATO in virologically suppressed patients. Participants were randomised in a 1:1 ratio to receive DOVATO (n=369) or continue with TAF-containing regimens (n=372) for up to 200 weeks. At Week 148, 298 of those on TAF-based regimens switched to DOVATO. The primary efficacy endpoint was the proportion of subjects with plasma HIV-1 RNA ≥50 copies/mL (virologic non-response) as per the FDA Snapshot category at Week 48 (adjusted for randomisation stratification factor).[8,13]

#SALSA is a phase III, randomised, open-label, non-inferiority clinical trial evaluating the efficacy and safety of switching to DTG/3TC compared with continuing current antiretroviral regimens in virologically suppressed adults with HIV. Eligible participants were randomised 1:1 to switch to once-daily DTG/3TC (n=246) or continue current antiretroviral regimens (n=247). The primary endpoint was the proportion of subjects with plasma HIV-1 RNA ≥50 copies/mL at Week 48 (ITT-E population, snapshot algorithm).[9]

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