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How to treat Ebola virus infections? A lesson from the field

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The reported case fatality ratios (CFR) of Ebola virus disease (EVD) have been as high as 90% in previous outbreaks. While the cumulative CFR among patients medically evacuated and treated in Western countries was inferior to 20%, it peaked to approximately 75% between September and December 2014 in West Africa, thereafter decreasing to less than 40% (May 2015) without current evidence of major virus mutations capable to alter virus pathogenicity over the course of the epidemic. Therefore, the observed diminution of CFR is likely to reflect improvement of EVD patient care. Here, we summarize major lessons learned, that is, progresses and knowledge gaps, about the clinical management of patients in West African settings during the 2014–2016 outbreak.

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Introduction

As of 10 November 2016, the 2014–2016 West Africa Ebola epidemic has led to 28 616 confirmed, probable and suspected cases and 11 310 deaths in Guinea, Liberia and Sierra-Leone (World Health Organization; URL: http://apps.who.int/gho/data/node.ebola-sitrep). The magnitude of the outbreak has been unique regarding its size, geographic location, and duration. A total of 36 imported or sporadic cases have also occurred in Senegal, Nigeria, and Mali, as well as in the United States, and Europe (Centers for Disease Control and Prevention; URL: https://www.cdc.gov/vhf/ebola/outbreaks/2014-west-africa/case-counts.html).

Severe Ebola virus disease (EVD) may be described as a serious gastrointestinal illness leading to massive fluid (up to 10 L per day) and electrolyte losses [1,2], together with severe sepsis resulting in sequential multiorgan failures (kidneys, liver, respiratory and coagulation systems) [3–6,7••,8] and shock [9,10]. Clinical management of EVD remains more than challenging particularly in remote and austere West African settings. Ebola treatment units (ETUs) have been often stretched out to deal with the flow of patients, skilled personnel were lacking and staffing was low. Treating EVD patients also requires rigorous understanding of risk exposure, thorough training in infection prevention and control measures, and ability to work in hardship field conditions, under extreme heat and humidity, while wearing complete personal protective equipment [9,11••,12•]. Health care workers accounted for 3.9% (815/20 955) of all confirmed and probable cases in West Africa between January 2014 and March 2015. Despite these very challenging and risky conditions, the improvement of patient management over the course of the epidemic is striking. In fact, while fixed Ebolavirus (EBOV) mutations resulting in increased infectivity for human cells (*e.g.*, A82V in the glycoprotein and D759G in the polymerase) have been noted at the onset of the epidemic in almost 90% of 1000 sequenced patient isolates, there is currently no evidence of further fixed changes occurrence along the epidemic [13,14]. It is therefore likely that the dramatic fall of CFR from around 75% in September–December 2014 to less than 40% at the end of the outbreak reflects care enhancement [4,6,7••,15–17]. The latter CFR is far lower than figures as high as 90% reported during previous EBOV outbreaks [18,19].

Herein, we present major lessons learned about the clinical management of patients in West Africa during the 2014–2016 outbreak.

Supportive care

As the predominant manifestations of EVD are serious gastrointestinal symptoms (diarrhea and vomiting) leading to massive fluid and electrolyte losses [1,2], the primary goal of treating EVD patients is to aggressively restore and maintain volume and electrolyte balance and correct acid-base disturbances through supportive care. As suggested by Lamontagne *et al.* in 2014 [11••], supportive care is also a specific care of EVD. This concept has progressively gained authority leading to the development of consensus regarding clinical standards of care for a better management of EVD patients [4,20–22].

Table 1

Overview of most clinical trials with anti-EBOV specific interventions

Product name (other names)	Company (location)	Description	Formulation	*In vivo* anti-EBOV activity	Clinical trial(s)
Favipiravir (T-705; Avigan)	Toyama Chemical, Fujifilm group (Tokyo, Japan)	6-Fluoro-3-hydroxy-2-pyrazinecarboxamide Licensed anti-influenza drug (Avigan) in Japan in March 2014 Viral RNA polymerase (L) inhibitor	Orally available	Evaluated in immunodeficient EBOV mouse models [39,40]	Phase II (status: completed) – named JIKI – started in December 2014 in Guinea—Multicenter proof-of-concept non-comparative trial in Guinea. Efficacy of favipiravir in reducing mortality in Individuals with EBOV disease in Guinea (NCT02329054) [7••] Phase II (status: recruiting) – named FORCE – started in April 2016 in Guinea. Tolerance and activity assessment of high doses of favipiravir in male survivors with EBOV in semen (NCT02739477)
Convalescent plasma	Not applicable	ABO-compatible plasma from convalescent donors (unverified levels of neutralizing antibodies) [41]	Intravenous injections	Convalescent whole blood has been evaluated in EBOV non-human primate model [42]	Phase II/III (status: completed) – named Ebola-Tx – started in February 2015 in Guinea—non-randomized, comparative study. Assess the safety and efficacy of convalescent plasma for the treatment of EVD, Conakry, Guinea (NCT02342171) [41]
ZMapp	MappBio (San Diego, CA, USA)	Cocktail of three humanized chimeric neutralizing antibodies c13C6, 2G4 and 4G7 selected from MB-003 and ZMab antibody cocktails [45] Targets the viral glycoprotein	Intravenous injections	Evaluated in EBOV non-human primate model [45]	Phase I/II (status: ongoing but not recruiting) – named PREVAIL II – started in February 2015 in Guinea, Liberia, and Sierra Leone—Multicenter randomized safety and efficacy study. Putative investigational therapeutics in the treatment of patients with known Ebola infection (NCT02363322) [41]
TKM-130803 (TKM)	Arbutus Biopharma (formerly Tekmira Pharmaceuticals), Burnaby, Canada	Small interfering RNA-lipid nanoparticle product Target the messenger RNAs of the viral RNA polymerase (L) and the viral protein 35 (VP35)	Intravenous injections	Evaluated in EBOV non-human primate model [46]	Phase II (status: completed) – named RAPIDE-TKM – started in February 2015 in Sierra Leone. Open-label, single arm to investigate the efficacy of TKM-130803 with a concurrent observational study of Ebolavirus Disease in Sierra Leone (PACTR201501000997429) [47]
Brincidofovir (CMX001)	Chimerix (Durham, NC, USA)	3-Hexadecyloxy-1-propanol (HDP) lipid conjugate of the acyclic nucleoside phosphonate cidofovir EBOV mode of action unknown; antiviral activity requires the lipid (HDP) moiety but not phosphorylation [49]	Orally available	Not reported [48]	Phase II (status: withdrawn) – Open label, multicenter study – started in October 2014. Safety and tolerability of Brincidofovir (BCV) for EBOV disease (NCT02271347) [48]
GS-5734	Gilead (Foster City, CA, USA)	Monophosphoramidate prodrug of an adenosine analogue [57] Viral RNA polymerase (L) inhibitor	Intravenous injections	Evaluated in EBOV non-human primate model [57]	Phase II (status: recruiting) – named PREVAIL 4 – started in June 2016 in Liberia—double blind, randomized, two-phase, two-arms. Antiviral activity, longer-term clearance of EBOV, and safety in male Ebola survivors with evidence of EBOV persistence in semen (NCT02818582)