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Improving the Clinical Care of Patients with Ebola in Resource Limited Settings-Antivirals are not enough

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Abstract

The West African Ebola outbreak presented unprecedented political, epidemiological, logistical, social and clinical challenges. Environmental conditions, personal protective equipment, limited clinical equipment and therapeutics, and staff shortages made caring for critically ill Ebola virus disease (EVD) patients difficult. We reflect on our clinical experiences in caring for EVD patients, as well as the strategies employed to try and optimize clinical care in a resource-limited setting. Novel technologies and systems are required for the delivery of patient care.

Keywords: Ebola virus disease; Diarrhoea; Haemorrhage; Cannulation; Intravenous fluids (IV); Intramuscular antibiotics (IM)

Introduction

The West African Ebola outbreak was the largest, most complex Ebola virus disease (EVD) outbreak to date [1]. The affected countries suffer from poor healthcare infrastructures and a chronic shortage of healthcare workers [2], compounded by healthcare worker (HCW) EVD deaths during the outbreak [3,4]. Resultantly, these countries were overwhelmed, hampering their responses and resilience [5]. EVD is a challenging disease to manage, further magnified manifold within a resource-limited setting (Tables 1 and 2).

We reflect on some of the major challenges in caring for EVD patients in West Africa, and some of the solutions implemented to try to improve clinical care (Table 3). Given the death toll [6], failure of local health infrastructures [7,8], and the economic impact [9], it is essential that lessons be learnt in anticipation of future outbreaks in resource-limited settings, and novel technologies and systems of care developed. Unfortunately, without significant improvements in methods of monitoring and care deliverance, it seems unlikely that antivirals will dramatically impact mortality.

The Setting

The situation in West Africa

Though EVD care in Europe and the United States was challenging [10,11] isolation units benefited from high staffing ratios, clinical expertise, advanced monitoring and environmental controls. These units cared for only a handful of patients at a time. Many patients were treated with invasive monitoring, vasopressors, renal replacement therapy, ventilation and experimental drugs. The case fatality rate (CFR) was below 20% [12].

US/Europe	West Africa
Critical care setting	O
High staff to patient ratio	O
Multidisciplinary expertise	O
Laboratory investigations	Π
Invasive monitoring (CVP,APM)	O
Advanced nutrition (NGF, TPN)	O
Blood products (PRC, FFP, Plts)	O
NIV, IV, RRT	O
Experimental therapies	O

Table 1: Comparison of standards of care in US/Europe and West Africa. Central venous pressure (CVP), arterial pressure monitoring (APM), nasogastric feeding (NGF), total parental nutrition (TPN), packed red cells (PRC), fresh frozen plasma (FFP), platelets (plts), non-invasive ventilation (NIV), invasive ventilation (IV), renal replacement therapy (RRT).

The situation in West Africa was, in contrast, stark, with limited staffing numbers, skill levels and access to drugs and equipment [13,14]. Many Ebola treatment centres (ETC's) relied on a handful of physicians to manage upwards of 50 patients. The level of care achieved consisted generally of basic physiological observations, Intravenous (IV) fluids and electrolytes, IV or Intramuscular (IM) antibiotics, antimalarial and analgesia [14,15]. The initial paucity of experience in managing large numbers of EVD patients, a lack of understanding of the disease pathophysiology [16], invalidated assumptions regarding EVD survivability [13], and fear of infection amongst HCW's [17], meant that clinical care was initially often limited to isolation, oral therapy and palliative care [14]. The lack of domestic resources and infrastructure [2], high numbers of infected HCW's [3,4] and well slow international response [18] resulted in national healthcare services being overwhelmed early on [19], compounding poor outcomes. In contrast to the low CFR in Europe and US, CFR in West Africa averaged 75% over the course of the outbreak for laboratory confirmed cases [20].

The working environment

Figure 1 represents a typical ETC design. Early in the outbreak many ETCs or EVD wards were makeshift and did not follow the red/green zone design or flow pathway, leading to inadequate infection prevention and control (IPC) and contributing to nosocomial infections [3,4,21]. Typically, personal protective equipment (PPE) in West Africa consisted of rubber boots, body length suit, face-mask,

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FACTORS	CONSEQUENCES
Restricted time inside red zone due to heat	Limited clinical assessments, in particular fluid and respiratory status
Cognitive impairment due to heat, dehydration, exhaustion, stress	Difficulties in monitoring fluid output and balance
Sensory impairment due to PPE	Inability to treat certain EVD complications and non-EVD diagnoses
Low staff/patient ratios	Inability to complete IV fluid infusions, medications, and patient feeding and hygiene
Limited staff medical training/education	Limited transfer of clinical information from red to green zone
Restricted staff skill mix	Nosocomial transmission of EVD and other infectious diseases
Limited range of drugs and equipment	Delayed administration of emergency therapy
Restricted patient visibility from green zone	
Complex, demanding and critically ill patients	

Table 2: Challenges in caring for EVD patients in West Africa and their consequences.

CHALLENGES	SOLUTIONS
Clinical assessment, in particular hydration status and fluid losses	Daily weights, nappy changes, nappy weights, bucket weights, IVC USS, urinary catheters
Fluid and electrolyte replacement	Onsite portable biochemistry, empirical fluid and electrolyte regimes, simplified child IV fluid regimes, loperamide, pressure bags
Special patients (obstetric, encephalitic, paediatric)	Survivor care givers, relative care givers, tele-expertise, placement of patients at front of ward, pre-made specialist (e.g. obstetric) kits, IO cannulae
Emergency admissions	Pre-made admission therapy packs, therapy at triage, distribution of work, door to therapy time of 30 mins.
Nosocomial transmission of EVD	Patient education, staff (HC and WASH) education, separation of patients, hand-washing stations across ward
Post-EVD sequela	Early follow up, patient education, hotline for ocular symptoms
Delivery of care	Timetabled red zone entries, role assignment, survivor care givers
Palliative care	SC cannulae, staff education, appropriate drugs
Nutrition	Relative meals, simple to eat foods, NG feeding in selective cases, dextrose additions to IV fluids, discharge food packs

Table 3: Examples of solutions to overcome specific challenges.

hood and goggles [or visor], outer apron and two pairs of gloves [22]. Undoubtedly, the biggest factor impeding care was PPE in the context of extreme humidity and temperatures exceeding 40°C. Donning PPE takes a minimum of 15 minutes with safety checks, often resulting in staff sweating profusely before having even entered the red zone. As a result, 45-60 minutes was a typical limit for time inside the red zone during the day and 90 minutes at night. Even with these limits, 'man-down' incidents in which a staff member in the red zone suffered a syncopal or near syncopal episode still occurred. 'Man-down' incidents were dangerous both for the affected individual and the staff members tasked with rapidly decontaminating and doffing the affected individual. These time limits whilst necessary severely restricted the time that could be spent with patients, which was further exacerbated by low staffing. Thus, on a typical ward round, a single physician would have 15-30 patients to review in 45-60 minutes. This together with restricted visibility, hearing and dexterity as a result of PPE [23] significantly limited the quality of care provided to patients, many of whom were critically ill. This was compounded by cognitive and motor impairments in staff secondary to heat exhaustion [24], dehydration [25] and stress [26].

The disease

In our experience, the clinical spectrum of EVD ranged from mildly symptomatic e.g. occasionally fever alone, to high volume diarrhoea and vomiting, haemorrhage, encephalopathy, and multi-organ failure. Vomiting and diarrhoea were the most common clinical features of organ dysfunction, with some patients experiencing greater than 20 episodes of diarrhoea/day. Marked hypotension, even in the context of presumed hypovolemia, was oddly and relatively rare. Extensive bleeding e.g. gastrointestinal haemorrhage though relatively uncommon, was invariably a pre-terminal event. Likewise was true of a multifactorial encephalopathy presumably resulting from viral encephalitis [27] and / or renal or liver failure [28]. Profound fatigue was a hallmark of advanced disease, with some patients unable to open their eyes or lift their heads limiting mobility and oral intake. Severe myalgia, in part likely due to myositis/rhabdomyolysis [29] further limited mobility, whilst chest/abdominal pain, possibly due to viral esophagitis/gastritis/colitis [30] further restricted oral intake. Hypoglycemia was common, particularly in children and was probably due to poor intake, liver dysfunction [28] and catabolism [31]. Whilst extremes of age were usually associated with a poor prognosis, it is not clear why some individuals experienced minimal symptoms whilst others deteriorated rapidly, though host genetics, viral mutations, inoculation route and dose, nutritional status, age, comorbidities [e.g. HIV] may all play a part. Many patients were reluctant to attend ETC's due to fear and distrust despite severe symptoms [32], making delayed presentation common. Therefore, overall many patients presented late, had one or multi organ impairment/failure, were critically ill and required a high level of care.

Clinical Care

Clinical assessment

PPE, heat and stress impairs visibility, hearing, touch and cognition [23-26] hampering quality clinical assessment. We therefore focused on estimating volume status given the large volume losses that some patients suffered and the potential to correct this deficit. Sphygmomanometers were not always available and given that hypotension was rare, the use of clinical signs such as jugular venous pressure and skin turgor were often the only way of assessing volume status. In one of the author's centres, bedside ultrasonography was available which was of great help

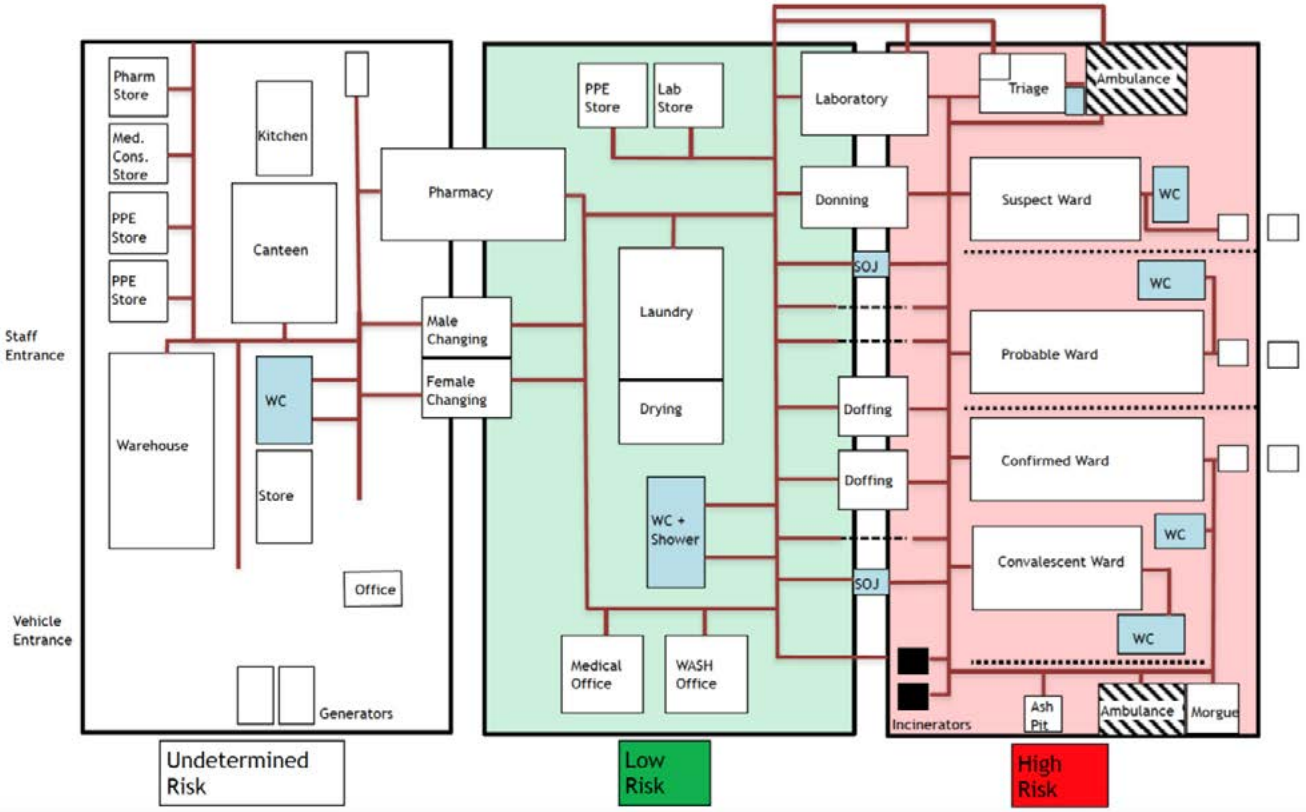

Figure 1: Schematic of a typical ETC. An ETC consists of a high-risk zone (red zone), which includes a triage unit, wards for suspect EVD patients and wards for confirmed EVD patients. A low risk zone (green zone) houses a PPE donning station, medical/nursing stations and the pharmacy. All staff entering the red zone must wear full PPE. Staff and patient flow in the red zone is strictly 'one-way', from triage to suspect wards, confirmed wards and then discharge or decontamination. Contraflow movement would risk introducing EVD into the suspect wards. Exiting the red zone requires passing through decontamination and doffing. Visibility from the green zone to the middle and ends of the wards in the red zone is very limited, hampering observation and monitoring of patients.

in assessing volume status. Not infrequently, a collapsing inferior vena cava (IVC) was demonstrated in newly admitted patients with vomiting and diarrhoea helping to guide the degree of fluid responsiveness [33]. A collapsing IVC was also sometimes seen despite aggressive fluid resuscitation (>8 litres per day) and peripheral edema, suggesting misdistribution and ongoing intravascular depletion.

Estimating fluid balance was frustratingly difficult, due to the logistics of working in the red zone short shifts resulting in a lack of continuity of care, language and cultural barriers, and lethargic/confused patients being unable to communicate. Some of the methods used to employ included weighing patients, nappies or hygiene buckets daily and recording the number of nappy changes or diarrheal episodes. None of these methods were accurate enough. Indwelling urinary catheters were not routinely used due to the time needed to insert them under sterile technique and for catheter care and patients sometimes removing them with resultant bleeding. In hindsight however, we think that despite the risks and time involved, their more regular use was warranted. Fluid overload and pulmonary edema were uncommon, perhaps because of difficulties in matching large volume losses. Diagnosing pulmonary edema was difficult however due to the restrictions in clinical assessment, the inability to use stethoscopes and the unavailability of oxygen saturation probes in some centres and lack of imaging.

Clinical therapy

Given the large volume losses and poor oral intake often encountered, we believe that the most critical aspect of clinical care that could contribute to improved survival was fluid and electrolyte replacement. Thus appropriate fluid resuscitation was the mainstay of our management. Outwith this, the standard therapeutic regime used consisted of multivitamins, zinc, analgesia, empirical oral antimalarial (IV/IM if critically ill or in infants), proton pump inhibitors if epigastric/chest pain or critically ill, IV antibiotics if diarrhoea (in case of gut bacterial translocation [34]) or critically ill, thiamine if malnourished or confused, glucose if conscious level reduced, and vitamin K if bleeding. Some of the authors used loperamide for large volume diarrhoea [35], though the appropriateness of this given the possibility of an inflammatory colitis is unclear.

Sudden death in convalescing patients which did occasionally occur, was probably due to pulmonary embolism or cardiac arrhythmias secondary to severe electrolyte disturbances following prolonged high output fluid loss and possibly "refeeding syndrome". The authors worked both at centres in which on-site biochemistry was present throughout and at centres where it became available later. The difference that biochemistry made to electrolyte replacement cannot be overestimated. Without it electrolyte replacement therapy was crude and guided for example by the number of diarrheal episodes per day. This was far from ideal given the wide range of electrolyte disturbances and presence of renal impairment in some patients [28]. The use of routine electrolyte monitoring from the outset of the outbreak would probably have significantly reduced the number of deaths. Some blood chemistry analysers, particularly handheld ones performed poorly in

the red zone however, likely as a result of environmental conditions and chlorine contact.

Delivery of therapy

Each 24 hour period was generally split into two 6 hour day shifts and one 12 hour night shift. On average, a staff member would make 2 red zone entries per shift sometimes 3 in exceptional circumstances. Therefore, it was not possible to provide a continuity of care. Managing emergencies, e.g. a seizing patient was particularly challenging due to the time taken to don PPE. A timetabled system of red zone entries eased some of these challenges with allocation of specific tasks (e.g. medication, IV fluids, cannulation, hygiene, feeding) to specific teams at set times. Backup teams were used for admission and discharge procedures as well as emergency red zone entries. This system provided simple, yet effective and efficient, care to a large number of patients. Combined with simple clinical protocols, this system enabled the regular delivery of standardized care, reduced staff errors (as their focus was generally on one specific task) and reduced the number of tasks left incomplete (e.g. medication delivery).

The use of Ebola survivor caregivers, who would stay within the red zone in light PPE (gloves, apron) for extended periods, was invaluable for the care and supervision of young children and dependent adults. However, their use is not without ethical issues and unresolved questions. It is unknown whether individuals can be re-infected with Ebola, especially in the context of immune suppression (e.g. HIV). As a result, not all ETC's nor all the authors utilized survivor caregivers.

With high patient numbers and the discussed difficulties in fluid balance estimation, we often used simple IV rehydration regimes guided by the number of estimated diarrheal episodes per day. For example, <5 episodes/day=3-4L/day, 5-10 episodes/day=5-6L/day, 10-20 episodes/day=6-8L/day. As patients were often unable to eat due to fatigue and pain, we sometimes added 50% glucose to Hartmann's solution to reduce hypoglycemic events. The WHO child fluid resuscitation protocols [36] were challenging to follow when there were large numbers of patients and few doctors. Resultantly, we often used our own simplified version of these. We were mindful, however of the risks associated with aggressively fluid resuscitating infants and children [37], particularly in the context of IV fluids running in the absence of staff in the red zone. Despite best efforts, patients did not always receive the amount of IV fluid prescribed. Difficulties from PPE, confused patients removing cannulas bleeding back into the IV fluid bag, children accidentally wrapping giving sets around their necks and staff having to exit the red zone unexpectedly all contributed to interruptions in fluid therapy. Fluids were sometimes delivered as a supervised bolus therefore, though rarely in infants or children. Intraosseous needles and infusions were a safe and viable alternative, particularly in children [38]. Nasogastric tubes were another alternative for fluid replenishment, as well as nutrition although not routinely utilized owing to bleeding risks and difficulty in confirming placement. Nutrition was an important focus of clinical care, though adequate and regular nutrition was difficult due to symptoms and the time required feed unwell patients. Readymade therapeutic foods such as BP 75/100 and Plumpy'nut were generally well tolerated and administrated more efficiently than standard meals.

Emergency admissions

At times, there could be unpredictable, rapid and dramatic increases in the number of admissions. At the Makeni ETC, for example, a large outbreak occurred in a nearby isolated rural village in February 2015, with an increase in the average daily admission rate, peaking at 20/day. The key to managing multiple simultaneous admissions in an efficient manner was robust coordination and communication between clinical staff inside the red zone and the green zone. In the event of multiple admissions, triage would often be conducted for one patient, whilst a second underwent venepuncture/cannulation. Critically unwell patients (e.g. reduced conscious level, prostration, marked tachypnea) were rapidly assigned to suspect or probable wards on the basis of contact history, with a subsequent in-depth history taken if possible. We aimed to start IV/IM antibiotic and antimalarial therapy +/- IV fluids within 15 minutes of arrival if a patient appeared critically unwell in triage. This was aided by having 'admission packs' pre-prepared each morning.

Occasionally, asymptomatic relatives would accompany patients in ambulances. Parents would often come with children and insist on also being admitted. In such scenarios, we would counsel the relative as to the risks of EVD transmission. If the relative still insisted on staying, we would provide basic IPC education and light PPE for them to use whilst caring for their relative. In many cases a relative acting as a career was actually of great benefit. Where the clinical picture and contact history were highly suggestive of EVD, we made significant efforts to discourage relatives from staying. Under no circumstances were relatives allowed to accompany a patient to the confirmed ward.

Special patient populations (obstetric, infant, encephalopathic and palliative patients)

Some specific patient groups proved particularly taxing. The breadth of patients admitted to an ETC ranged from pregnant women and newborns to elderly patients. Thus, the required clinical expertise was not always available on site. The availability of specialist advice by telephone, such as staff from the Médecins Sans Frontières (MSF) maternity ETC in Sierra Leone, was invaluable.

Delivering a baby in PPE is exhausting and labor-intensive, presenting significant risk to staff owing to bodily fluid exposure. During delivery, an almost continuous presence of appropriately skilled staff is needed. In the event of delivery a rolling rota of pairs, drawing on staffs that were on their off days, was utilized. Staffs were trained to deliver a baby from the side of the woman, avoiding direct fluid splashes to the face, whilst wearing additional PPE such as elbow length gloves. Pre-prepared obstetric packs containing delivery equipment and emergency drugs were useful.

Some physicians encouraged medical termination of pregnancy for pregnant EVD patients [39,40]. The rationale included the belief though not based on substantive evidence that the fetus would never survive, with significant risks to the woman and wider community from a delivery outside the ETC. Given the lack of an evidence base to inform this decision, our general approach was only to broach abortion if the mother instigated discussion. Instead, we provided education and basic IPC equipment and training and arranged for delivery in the ETC.

Pediatric patients often deteriorated very rapidly and had a high mortality. Therefore, we had a low threshold for IV cannulation in an otherwise well pediatric admission, pre-empting difficulties once peripherally shut down. More generally, infants required a high level of care for feeding and hygiene with survivor caregivers proving invaluable. Otherwise, dedicated teams would be assigned for infant care and other teams were encouraged to check on infants routinely during their red zone entries. Infants and children, and other vulnerable groups were generally placed at the front of the ward to enable visibility

from the green zone. Given the presence of Ebola in breast milk and the possibility therefore that breastfeeding might increase the child's level of viremia, we discouraged breastfeeding and offered infant formula instead [41].

Some patients became confused as their disease progressed likely as a result of viral or metabolic encephalitis [27,28] and/or septic encephalopathy [42] compounded by an unfamiliar environment [32]. These patients posed a significant risk to staff and other patients as they would sometimes become aggressive and wander. Mock scenarios in full PPE were of use in training individuals to become familiar with managing an aggressive patient in the red zone. IM sedation was utilized to protect both patients and staff. Administering IM medication was dangerous due to the risk of needle stick injury however and required individualized risk assessment. Estimating the correct dose of sedation to calm a confused and aggressive patient but not render them unconscious, and was especially difficult when liver and renal functions were unknown.

Terminal patients were very challenging both ethically and practically. Palliative care in sub-Saharan Africa suffers from resource constraints, a paucity of clinical supervision and variable opioid availability [43]. Whilst conscious of its importance, timely and appropriate palliation was at times suboptimal owing to time pressures in managing high volumes of critically unwell patients. Furthermore, identifying a terminal patient was difficult due to the profound fatigue and lethargy seen in survivable EVD. In our experience, patients with gastrointestinal hemorrhage or a combination of marked delirium and severe derangements of renal or liver function would rarely survive. With such patients, best efforts were made to ensure comfort and dignity, utilizing opiate and benzodiazepines as needed. The use of a subcutaneous cannula minimized the need for multiple IM/IV injections in such patients and therefore patient discomfort and risks to staff.

Conclusion

The West African Ebola epidemic presented unprecedented political, epidemiological, logistical and social challenges [5] resulting in difficulties in providing good clinical care. Beliefs, based in part on CFR's in previous Ebola outbreaks, that there was little that could be offered to patients may have also contributed to delays in good clinical care [13]. These beliefs negated one of the major likely contributors to organ failure and death in EVD, namely hypovolemia secondary to diarrhoea and vomiting [13]. As it became increasingly recognized that patients could benefit from intravenous fluid, electrolyte replacement and nutritional support [13], the focus shifted to how such therapies could be delivered systematically within a resource limited setting. Working conditions proved challenging both for patient care and healthcare worker safety, despite the eventual large scale coordinated international response and resource influx. Nevertheless, improvements in care were made through clinical protocols and systems and procedures.

Had antivirals been available, successful administration would have faced many of the challenges highlighted in this article. Several of the antivirals trialed in West Africa required intravenous infusion over hours [44,45] which would have proved logistically difficult. It is doubtful that the delivery of these agents would have been systematically successful without significant improvements in PPE and ETC design. Further, since many patients presented late in the disease course, antiviral therapy would not have diminished the need for good and efficient clinical care. This is highlighted by the fact that almost all patients treated in the US and Europe required critical care despite presenting in early stages of the disease and many receiving antivirals early [12].

In future large scale EVD outbreaks in resource limited settings, it is imperative that a rapid, coordinated, well-staffed and resourced response is intertwined with robust procedural systems for care and innovative solutions to the constraints of working in PPE in a hot climate. Antiviral therapy alone will not prove to be a magic bullet.

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