Virus Persistence and Recrudescence after Ebola Virus Disease: What are the risks to Healthcare Workers?

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The 2013-2016 epidemic of Ebola virus disease (EVD) in West Africa has sometimes demonstrated stark limitations of our knowledge, but also provided an opportunity to enhance our understanding of this dangerous and often mysterious disease. Albeit unwelcome, the sheer magnitude of almost 30,000 cases in West Africa provides a much larger sample size from which observations can be made, augmented by the 27 cases seen in advanced medical settings in Europe and the United States where more detailed clinical observation and laboratory analysis were often possible. Perhaps at the top of the list of new and sometimes surprising findings are those that relate to sequelae, delayed virus clearance, and recrudescent disease in EVD survivors.

Prior to reports from the West Africa outbreak, only two controlled studies of EVD survivors had been published.[1,2] Both highlighted an array of sequelae lasting months to years, including extreme fatigue, anorexia, headache, arthralgia, myalgia, abdominal pain, sleep disturbance, hearing loss, and visual disturbances. However, neither study incorporated the detailed microbiological and physical examination (especially ocular, audiometric, and mental health exams) required for a thorough understanding of EVD sequelae and associated pathogenesis. Reports emerging in the wake of the massive outbreak in West Africa corroborate and expand earlier findings. These include the observation of new ocular symptoms in over 60% of EVD survivors, with sight-threatening uveitis in 18.1%, some of whom progress to early cataract formation.[3,4] Neurological deficits, including seizures, and various skin problems, have also been noted.[4] Lastly, mental health sequelae are unsurprisingly common in survivors and their family members and communities; included are sleep and memory disturbances, anxiety disorders, depression, posttraumatic stress disorder, and survivors' guilt.

The underlying pathogenesis of EVD sequelae is not well understood, but anecdotal observations increasingly suggest that at least some sequelae relate to virus persistence for months or even years in selected immunologically protected tissue compartments and fluids. These include the testes/semen, chambers of the eye, central nervous system/cerebrospinal fluid (CSF), and the fetus, placenta, and amniotic sac/fluid of women infected during pregnancy (Figure).[4] In many cases, only molecular evidence of viral RNA by RT-PCR is available, with no confirmatory cell culture, leaving open the question of whether the findings represent inconsequential residual RNA or infectious virus with continued risk of transmission.

Particularly vexing is the possibility of virus persistence during pregnancy. Maternal mortality in pregnant women with EVD is high, and fetal and neonatal mortality nearly 100%.[5] However, a few cases have been noted in West Africa in which women, possibly with asymptomatic infection or atypically mild disease, have recovered and remained pregnant, only to spontaneously abort a macerated and nonviable fetus in subsequent weeks or months.[4,6] Although the mothers' blood remained free of virus at the time of delivery, swabs of the fetus, placenta, and amniotic fluid in some cases have tested RT-PCR positive for Ebola virus.

Two cases of prolonged virus persistence associated with recrudescence have been well-documented. In the United States, Ebola virus was detected by PCR and cell culture from the aqueous humor of a medically evacuated healthcare worker with severe uveitis 14 weeks after disease onset and 9 weeks after clearance from the blood, which remained negative during the episode of uveitis.[7] Importantly, viral RNA was not detected in tear film or conjunctival swab specimens, suggesting that the virus remains confined to the intra-ocular compartment. In the United Kingdom, Ebola virus was noted by RT-PCR in both the CSF and blood in a medically evacuated healthcare worker who developed severe meningitis with seizures nine months after resolution of acute disease.[8] The RNA copy number was lower in the blood than in the CSF, and virus could be isolated in cell culture only from the CSF, leading to the conclusion that the viraemia was due to reseeding of the blood from the central nervous system. No obvious underlying immunosuppressive condition or trigger for virus reactivation could be identified in these cases.

Fortunately, recrudescent disease and viraemia after EVD appear to be rare. With the exception of sporadic cases of sexual transmission related to persistent virus in the semen, no cases of secondary transmission from survivors have been reported. Furthermore, accumulating evidence does not suggest prolonged shedding in other body fluids, at least in the absence of fever and other acute symptoms.[9,10] One theory for the apparent rarity of recrudescent cases is that such cases are the consequence of severe initial EVD, which is directly related to level of viraemia, with high viraemia seeding the immune-privileged sites. Indeed, both patients described above had very high viraemia and severe disease requiring intensive care (including, in one case, prolonged mechanical ventilation and haemodialysis). Without the intensive medical care usually afforded to medically evacuated patients in resource rich countries, such severe disease would usually be fatal in West Africa, leaving few survivors at risk of recrudescence. Alternatively, recrudescent disease in West Africa may simply be undetected or misattributed to malaria or other common causes of febrile disease due to a low index of suspicion and limited diagnostic capacity. Indeed, there are anecdotal reports of recrudescent disease and viraemia in West Africa, possibly related to underlying HIV infection, although this association has not been validated.

Even if infrequent, the possibility of recrudescent disease and virus shedding obligates developing appropriate guidelines for the management of EVD survivors that maximize health care worker protection while offering highest quality care without precipitation of undue fear and stigma. In the absence of evidence of external virus shedding (excluding virus in the semen) from asymptomatic EVD survivors, standard precautions are recommended for routine clinical examination and care.[11] In the UK all EVD survivors should be assigned to a designated infectious diseases unit where they will can receive routine follow up and guidance.[12] Should the patient become unwell, consultation with the designated infectious disease unit and the Rare and Imported Fever Service at Public Health England should be undertaken immediately to assess risk, arrange laboratory testing for EVD, and advise on appropriate infection prevention and control measures, including appropriate handling of biological samples.[13]

When in doubt, or in emergencies when expert guidance is not yet available, EVD survivors presenting with acute febrile or meningo-encephalitic syndromes should be placed in isolation and EVD infection prevention and control precautions applied, including the wearing of full personal protective equipment.[13,14] This applies, but is not limited to, attending to deliveries of women who were infected with Ebola virus while pregnant, performing emergency surgical procedures or attending to penetrating trauma that involves the eye, male genitourinary tract, brain and spinal cord, or female breast, and aliquotting specimens or performing centrifugation. Special attention should be given to appropriate waste, sharps and linen management, as well as strict adherence to environmental cleaning and decontamination protocols of reusable medical equipment. Blood, tissue and organ donation from EVD survivors is currently prohibited in the UK and should be deferred until further data are available on the precise duration of infectious virus in the various body compartments and potential triggers of virus reactivation. Should exposure to Ebola virus be suspected, various options for post-exposure prophylaxis exist, but must be considered experimental in the absence of systematically collected efficacy or safety data.[15]

The estimated over 10,000 EVD survivors from the West Africa outbreak present a moral imperative to provide the required medical care as well as an opportunity to collect the evidence necessary to inform future guidelines for effective and safe medical care of this vulnerable group.[4] The World Health Organization has published interim guidelines for clinical care of EVD survivors.[16] Acquiring the necessary scientific evidence must start with heightened yet non-stigmatizing surveillance and testing to document the duration of virus persistence in each body compartment or fluid and the nature and frequency of recrudescent disease and secondary transmission. Understanding the relationship between viral infectivity and detection of RNA by RT-PCR, a technique now widely available in the field during outbreaks, will be key to determining its practical utility in risk estimation. Full genome sequencing of Ebola viruses identified during acute infection and recrudescence may help shed light on the mechanisms of these events, especially the possibility of escape mutants.[17] Basic science research will also be needed to identify the implicated cellular reservoirs and immune mechanisms of virus persistence. Clinical research is also needed to identify the best strategies to both alleviate symptoms and eliminate virus in survivors. Various West African studies planned or currently underway promise in time to yield a wealth of new information, including the PREVAIL III study detailing sequelae and viral persistence in a 5 year controlled cohort of more than 1,500 Liberian EVD survivors.[18] Meanwhile, prudence not panic, is in order in the clinical management of EVD survivors.

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FIGURE LEGEND

Figure. Virus persistence after the day of disease onset in various body compartments in survivors of Ebola virus disease, as detected by reverse-transcription polymerase chain reaction (RT-PCR, green) and cell culture (blue). Red bars represent the day of the first negative RT-PCR detection in the patient's blood, when available. Reprinted with permission from Vetter *et al*.[4]