**Post Exposure Prophylaxis for Ebola Virus Disease**

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**Background**

The on-going Ebola epidemic in West Africa evolved rapidly from a small outbreak in Guinea into an unprecedented global public health emergency. As of September 6, 2015 28,183 cases and 11,306 deaths have been reported. (1). In addition to its unprecedented scale, the Ebola outbreak has resulted in the infection of at least 881 healthcare providers (HCP) and claimed the lives of 513, further depleting an already precious resource (1). The devastating effects on healthcare infrastructure and numbers of healthcare providers will continue to plague the affected countries for decades to come. While the rates of new infections have declined substantially, transmission continues and future outbreaks are inevitable

Infections among HCPs are a reality of the current and prior Ebola outbreaks and often have served as the initial indication that an outbreak has started. The most effective protection for HCPs is the implementation of environmental and administrative controls as well as appropriate personal protective equipment, that limit contact with infectious patients and body fluids containing high levels of virus, but aggressive clinical care requires close contact with infected patients (2-5). Accidental exposures occur in the course of caring for patients with Ebola virus disease (EVD), as well as also in laboratory workers involved in handling clinical samples or undertaking filovirus research (6). Furthermore, person-to-person transmission of Ebola virus (EBOV) in households and community settings like burials have been major factors in the prolonged nature of the current outbreaks in Liberia, Sierra Leone, and Guinea(7). These situations are all ones in which an effective means of post-contact or post-exposure prophylaxis (PEP) could prove life saving for exposed individuals and could also serve to augment traditional public health measures to reduce community transmission.

Despite pre-clinical work on filovirus-specific countermeasures for many years, there are currently no licensed vaccines or antivirals for EVD(8). However, several strategies have shown efficacy for PEP or early therapy in non-human primate (NHP) models of EVD. These include the use of vaccines displaying the Ebola glycoprotein (GP), passive immunotherapy with concentrated Ebola-specific immunoglobulin, monoclonal antibodies, and agents that interrupt virus replication including siRNAs, phosphorodiamidate morpholino oligomers (PMOs), and viral RNA polymerase inhibitors (Table 1). Recently, the recombinant vesicular stomatitis virus vaccine vaccine expressing EBOV glycoprotein (rVSV-ZEBOV) was found to be effective for ring prophylaxis among community and household contacts (9). However, it is critical to view the data from the perspective of a PEP strategy for people with exposures and *potential* infection rather than as a treatment for a patient with *confirmed* EVD, since efficacy and risk-benefit relationships will differ in these two circumstances. To this end, we review first potential PEP interventions with respect to animal model and clinical data, and second the limited clinical data on actual use for PEP in healthcare providers, laboratory workers exposed to filoviruses, and high-risk community contacts of EBOV-infected patients.

**Vaccines**

**Recombinant vesicular stomatitis virus vaccine**. Complete protection against a filovirus related to EBOV, Marburg virus, in NPHs was achieved with the administration of a live-attenuated rVSV vaccine expressing the Marburg virus GP 20-30min after challenge with a lethal dose of Marburg virus (10). When treatment was delayed 24 and 48 hours post challenge, 1/6 and 4/6 animals died from Marburg infection, with no delay in time to death in vaccinated animals (11). These findings imply that there may be a critical window of efficacy for PEP with the rVSV vaccine. Similarly, a rVSV vaccine expressing the Ebola Sudan GP demonstrated complete protection when given to rhesus macaques 20-30min post lethal challenge with Ebola Sudan (12). In contrast, protection of NHPs, was only 50% when treated with an rVSV vaccine expressing the Ebola Zaire GP 20-30min after lethal challenge with homologous virus, indicating variable strain-specific efficacy (13, 14). Collectively, the rVSV platform demonstrates time-critical protection when administered after lethal filovirus exposure, as PEP, in NHP models, with the highest efficacy against Marburg and Ebola Sudan viruses and reduced efficacy against Ebola Zaire. However, the NHP model differs from human EBOV disease in two important respects: the onset of clinical illness is faster and it is uniformly lethal. It is plausible that vaccination may have greater efficacy as PEP in humans than shown in these NHP studies.

It is likely that the mechanism of protection through active immunization is multifactorial, including early innate immune responses, NK cell recruitment, and potentially viral interference, as the rVSV-ZEBOV vaccine replicates significantly faster than wild type Ebola virus (13, 15). Subsequent adaptive immune responses include the production of neutralizing and non-neutralizing antibodies and virus specific cell-mediated immune responses. Humoral responses among vaccinated NHPs are species specific. In a pre-exposure vaccine study, complete protection of NHPs was achieved when the EBOV challenge was given 7 days after vaccination, but only 66% were protected when the virus challenge occurred 3 days after vaccination, confirming as expected that the protective efficacy of the rVSV vaccine is time dependent (16). In NHPs vaccinated with an rVSV expressing the Marburg GP, 0% mounted a detectable IgM response on Day 3 but this increased to 100% by Day 6 (10). Similarly, 0%-20% of vaccinated NHPs mounted a detectable IgG response on Day 6 but 58-80% had detectable IgG antibodies on Day 10 with titers greater than 1:100 (10, 11). In NHPs vaccinated with an rVSV vaccine containing the Ebola Sudan GP, 100% had detectable IgM on Day 6 and 100% IgG by Day 10 (17). In contrast, only 14% of animals vaccinated with rVSV-ZEBOV had detectable IgM on day 6 and this only increased to 43% on Day 14, with only 28.5% having detectable IgG on Day 10 and 57% by Day 14 (13). This delay in generating effective humoral responses may in part explain the reduced efficacy when vaccination is delayed even 24 or 48 hours post challenge (18).

In phase 1, placebo-controlled, double-blinded randomized controlled trials, including more than 200 participants in total, the rVSV-ZEBOV vaccine demonstrated dose-related reactogenicity and immunogenicity at doses ranging from 3x105 to 5x107 plaque forming units (PFU)(19, 20). The vaccine elicits higher neutralizing antibody titers at higher doses and, although none of the volunteers had detectable antibodies on day 7, all the volunteers had detectable IgGs at 28 days post-vaccination (90-95% had detectable antibodies at day 14 post vaccination) (21). Transient lymphopenia, reductions in platelets count and rVSV-ZEBOV viremia are recognized side effects. Furthermore, rVSV-ZEBOV dissemination to skin and joints were observed in some cases; up to 22% of the patients experienced arthralgia at a median of 11 days after injection. Most recently, the rVSV-ZEBOV vaccine demonstrated a vaccine efficacy of 100% (95% CI 74.7-100.0; p=0.0036) in a cluster-randomized ring vaccination strategy of high-risk contacts of a confirmed case of EVD (22). In this trial,, 48 clusters (4,123 individuals) were randomized to receive immediate vaccination and 42 clusters (3,528 individuals) to receive delayed vaccination after 21 days. No cases of EVD developed in the group of contacts that received the vaccine immediately, in contrast to 16 confirmed infections in the delayed vaccination group 10 days or more after receiving the vaccine. Of note, some vaccinated individuals were diagnosed with EVD within 6 days of immunization, suggesting that the vaccine may not protect against incubating infection (23). Whether vaccine recipients with early breakthrough infections had reduced EVD mortality remains to be determined. Although the timing required for the development of protective immunity in humans is not currently known, data from this trial suggests it may occur within one week. The incubation period of Ebola virus in humans is on average 9 days and likely shorter after percutaneous exposure (9, 24). Taken together, it is not yet clear from the data whether or not vaccine-induced immunity is sufficiently rapid to utilize active immunization for PEP in humans, even if vaccine were given as quickly as possible following exposure.

Other vaccines

Several other Ebola vaccines are in development but there are no published animal or clinical data to inform their use as PEP. Unlike rVSV, some of these are viral-vectored but non-replicating vaccines, which are generally used in heterologous, prime-boost immunization regimes. From first principles, these may be well less suited to the demands of PEP and the need to induce a protective immune response as rapidly as possible.

**Human and chimpanzee adenovirus vaccines.** Adenovirus-based EBOV vaccines are non-replicating vaccines that have also demonstrated promise in mice, guinea pigs and non-human primate models (29-32). A human adenovirus serotype 5 (Ad5) vectored vaccine protected 67% (6/9) and 25% (1/4) cynomologus macaques when delivered 30 minutes or 24 hours prior to infection respectively, and 25% of rhesus macaques when administered 24 hours post challenge. The use of interferon or rNAPc2 as adjuvants were not found to improve vaccine pre- or post-exposure efficacy(33). Human-derived adenovirus based vectors are limited, however, by the presence of pre-existing immunity to the vectors: human Ad 5 vectors failed to protect animals immune to Ad5 (34).

More recently, a chimpanzee type 3 adenovirus-vectored vaccine (ChAd3), which has low prevalence of preexisting vector-directed immunity in humans, demonstrated complete protection in cynomologous macaques when given before virus exposure (34). A preliminary report demonstrated that the ChAd3 vaccine expressing the ZEBOV glycoprotein was safe and immunogenic with a dose dependent rise in detectable antibodies (35). No data on using this vaccine for PEP in NHPs have been published. The durability of the immune response to the ChAd3 vaccine initially raised concerns as protection decreased from 100% to 50% in cynomologous macaques when the animals were challenged 5 weeks and 10 months following vaccination (34). However, boosting with modified vaccinia Ankara (MVA) 8 weeks after the initial vaccination resulted in complete protection even 10 months after vaccination (34). The percentage of volunteers that achieved detectable antibodies at 14 and 28 days post vaccination with the monovalent chimpanzee adenovirus (52-67% and 63-90% respectively) were lower in comparison to the rVSV vaccine (90-95% and 100% respectively) (20, 35).

Adenoviral vectors derived from rare human serotypes are another strategy to overcome pre-existing immunity to Ad5 vectors in human populations and include adenovirus 26 and 35. Recombinant adenovirus 26-vectored vaccines have been shown to be immunogenic and completely protect NHPs when used as part of a heterologous prime-boost strategy with Ad35 (Geisbert, T JV 2011 4222). A phase I study of a heterologous prime-boost regimen using Ad26 expressing the Ebola Zaire-Mayinga GP and MVA-Bavarian Nordic filo-vector (MVA-BN) is ongoing (NCT02376426).

**Other vaccines.** A non-replicating virus-like-particles (VLP) vaccine, composed of EBOV GP, NP and VP40, administered intraperitoneally or intramuscularly at the dose of 50 mcg 24 hours after challenge with EBOV protected an average of 93% mice. Viremia and cytokine levels were reduced in treated mice, correlating with higher antigen staining in untreated animals. Further analysis revealed a higher EBOV specific IgG level in VLP-treated mice, and that T cell-independent B cells response may be sufficient to elicit protection (36). As part of the protective effect, VLP treatment seemed to induce early type I IFN responses. Virus-like-particle vaccine efficacy has not been confirmed in NHPs. Many different types of EBOV vaccines are in development, but no published data are available with regard to their potential efficacy for PEP in NHP models.

**Specific Antibodies**

Passive immunotherapy as a PEP strategy has demonstrated efficacy in NHPs and has recently been used in HCPs exposed during the 2013-2015 epidemic. Based on anecdotal reports of possible benefit with the use of convalescent blood products in treating EVD and evidence that a strong humoral immune response is associated with survival, various passive immune strategies, including convalescent plasma, hyperimmune goat and equine serum, and monoclonal antibodies, have been evaluated as PEP (6, 37-39). Some animal data describes early treatment of clinically apparent disease with passive immunotherapy. This is not strictly PEP, but it is widely assumed that treatment is more challenging and that potential efficacy in PEP can be extrapolated although not precisely defined by these models.

**Polyclonal antibodies**. Hyperimmune goat serum was effective in a guinea pig model of EVD up to 72 hours post infection, with maximal efficacy at 24 hours post infection. The lack of adverse local or general reactions after hyperimmune goat serum was tested in 7 human volunteers and suggests a favorable safety profile (40). Hyperimmune equine serum was also found to protect baboons from EVD. Neutralization titers correlated with improved PEP effectiveness, as the preparation with the highest virus neutralization assay titers provided >80% survival when given within the first hour following infection (as compared with only 6% survival in baboons given a preparation with 4 fold lower titer) (40, 41). Efficacy decreased to 29% protection when given 2 hours after infection, even in high neutralisation titer preparations. None of the surviving baboons developed viremia, suggesting that the mechanism of protection of passive immunotherapy was most likely the neutralization of virus, although other antibody-mediated actions might be contributory. The same equine preparation was tested by USAMRIID in mice, guinea pigs, and cynomologus macaques. Although guinea pigs were completely protected when treated with hyperimmune globulin at the same time as infection, only 5/20 mice survived. None of the NHPs treated with equine hyperimmune immunoglobulin the same day as the inoculation survived, although they displayed a delayed onset of viremia and clinical signs compared with controls (42) (43). In addition to a different NHP model (cynomologus macaques vs baboons), the difference in efficacy between the two studies may have to do with a difference in viral inoculum, highlighting the difficulties of developing animal models that closely reflect human disease..

Convalescent blood products, including whole blood and plasma from EVD survivors have been administered to infected patients in Africa and in infected HCPs repatriated to the United States and Europe, with unclear benefit (38, 44-50). The efficacy of convalescent plasma as a treatment in EVD was evaluated in three separate studies in Liberia, Guinea, and Sierra Leone during the current Ebola epidemic. Preliminary results from one nonrandomized and non-controlled trial suggest that transfusion of 500ml of convalescent plasma with unknown levels of antibodies was not associated with a significant improvement in survival(51). Results from the other trials are expected soon. In at least one patient, the use of convalescent plasma was associated with acute respiratory distress syndrome that was attributed to transfusion acute lung injury (TRALI) that resolved with supportive care (52). Convalescent plasma has not been used for PEP and the potential adverse effects of different PEP interventions need to be considered in light of the risk of infection of the exposed individual as well as the potential of benefit of the intervention.

**Monoclonal antibodies.** Monoclonal antibodies have demonstrated promise as PEP in animal models and have been used in uncontrolled treatment of HCPs exposed during the West Africa epidemic (53-56). Although the neutralizing monoclonal antibody KZ52 completely protected guinea pigs when given 1 hour after infection it failed to reduce mortality in NHPs (57, 58). MB-003, a cocktail of 2 neutralizing mouse/human chimeric monoclonal antibodies (mAbs) (c13C6 and c6D8) and one non-neutralizing mAb (h13F6), generated in mice against Ebola-Mayinga, provided 67% (4/6) protection when given 24 or 48 hours after EBOV-Kikwit challenge in rhesus macaques (59).

ZMAb, a cocktail of 3 EBOV GP-specific murine mAbs (1H3, 2G4, and 4G7), produced by mice immunization with rVSV-ZEBOV, completely protected (4/4) cynomolgus macaques with no side effects when treatment was begun 24 hours after challenge with Ebola-Kikwit and continued daily for three days(54). When treatment was delayed until 48 hours after infection, 50% of animals recovered. All survivors displayed evidence of virus-specific humoral and cell-mediated immune responses suggesting that the antibody cocktail did not prevent infection. Adjunctive treatment with recombinant human adenovirus serotype 5 virus expressing consensus human IFNα (Ad5-IFNα) resulted in the same survival rates in cynomologus macaques boosted at 24 hours post infection and treated 96 hours after challenge. When Ad5-IFNα was given during the first injection of ZMAb starting 72 hours after infection, 75% (3/4) of cynomologus macaques and 100% (4/4) of rhesus macaques survived(60). None of the antibodies included in this preparation are cross reactive with Marburg virus or other Ebola species, highlighting the strain specificity of monoclonal antibodies and therefore a potential difficulty in preparing for future outbreaks. (54).

ZMapp, a third cocktail of 3 humanized monoclonal antibodies (c13C6, c2G4, and c4G7) composed of mAbs from ZMAb and MB-003, demonstrated even greater therapeutic efficacy with a 100% of protection when treatment was delayed until 3, 4, or even 5 days post infection.(55). Given the delay in treatment, the majority of animals displayed signs and symtpoms of EVD including fever, leukocytosis thrombocytopenia and evidence of viremia. Two animals in which ZMapp was initiated 4 days post virus challenge had clinical scores near the limit for mandated euthanasia yet these animals survived with ZMapp therapy. Clinical resolution of symptoms was observed by day 14 in all animals, compared with 100% death in control animals. Treatment with ZMapp reduced peak viral loads of up to 106TCID50 to undetectable levels by day 14. Although ZMapp is composed of antibodies that are directed against the Kikwit variant of EBOV, published amino acid sequences suggest that the epitopes of the strain found in Guinea had not mutated. Additionally *in vitro* binding assays revealed comparable neutralization of the Ebola Kikwit and Guinea strains. A significant limitation thus far has been production of monoclonal antibody, which in the case of ZMapp occurs in tobacco plants. MIL-77 is a cocktail of recombinant afucosylated humanized mAbs with the same sequence in the binding domain as ZMapp, produced in Chinese hamster ovarian cell lines (Jacobs, LID, 2015). In a limited number of Ebola-infected NHPs, treatment with MIL-77 has demonstrated similar or enhanced efficacy in comparison with ZMapp (Abstract from 7th filovirus meeting, Kobinger, Gary).

Monoclonal antibodies as therapeutic or PEP strategies are currently limited by both supply and strain specificity, but further refinements to mAb combinations and production are currently underway.. In the current epidemic, different preparations of monoclonal antibodies have been used for treatment of medically evacuated healthcare workers to the U.S. and Europe. (REF: Schibler, LID, 2015; Jacobs, LID, 2015; Petrosillo, BMK, 2015;.Lyon NEJM 2014, <http://www.who.int/medicines/ebola-treatment/outcomes_experimental_therapies/en/>); Liddell, ann intern med, 2015, sueblinvong, crit care med 2015;) but no conclusions can be drawn about their efficacy from this uncontrolled experimental use.

**Antiviral agents**

A number of different filovirus replication inhibitors have been evaluated therapeutically in animal models and their use can be considered in PEP.

**Favipiravir**. Favipiravir is a broad spectrum oral pyrazine compound that targets the polymerase of many RNA viruses and was approved in Japan for influenza virus infection treatment in March, 2014 (61) (62). Two phase III clinical trials have recently been completed in uncomplicated influenza (NCT02008344 and NCT02026349). In an immune deficient murine model of Ebola virus disease (C57BL/6 interferon alpha/beta receptor -/- knockout), complete protection was afforded when treatment (300mg/kg/day x 14 days) was started up to 6 days post EBOV challenge(63, 64). At the time of favipiravir administration, the animals were viremic and were already displaying signs of illness. Clearance of viremia occurred within 4 days of oral treatment. In another immunodeficient murine model, favipiravir (150mg/kg twice daily orally) protected 100% of animals from death when used as a PEP agent, approximately 1 hour post challenge (64). The dose used is approximately 10 fold higher than those needed for protection in lethal models of influenza in mice. Efficacy data against Ebola in NHPs has not been publically released but preliminary reports indicate dose-related antiviral effects and delays to death, but not overall survival benefit. Given its known safety profile, favipiravir has recently been evaluated in a non-comparative clinical trial in the treatment of EVD using a dose regimen that is about 50% higher (D1: H0 2400mg, H8 2400mg, H16 1200mg; D2-9 1200mg BID) than used in the influenza studies (66, 67). Preliminary analysis suggested a potential benefit only in the 15% of patients that presented with low viral load at admission (as defined by CT >20); n(68, 69). Taken together, the data suggest that favipiravir has relatively weak antiviral activity against EBOV. However, this may be sufficient for efficacy as PEP, when viral loads would be expected to be very low if infection has occurred at all. On this basis, favipiravir has been used as PEP in at least 5 HCPs with sharps exposures as detailed below, although no conclusions can be drawn about its efficacy from this uncontrolled experimental use (Jacobs, LID 2015, Kaiser, unpublished data).

**RNA Inhibition**. RNA interference is an alternative antiviral strategy. The use of a cocktail of siRNAs targeting genes encoding EBOV L protein, VP24, and VP35 in stable nucleic acid lipid particles (2mg/kg/dose bolus intravenous infusion) protected 66% of rhesus macaques from death when treated 30 min after infection and then again on days 1, 3, and 5; complete protection was afforded if treatment was given 30 min after infection and continued daily through day 6 (70). However siRNA preparations can also lead to a cytokine release syndrome, which was seen in early phase I clinical trials of TKM-100802 (71). TKM-100802, composed of siRNAs targeting genes encoding EBOV-Myinga L protein and VP-35 in a lipid nanoparticle formulation, has been used in at least 4 medically evacuated EVD infected patients in Europe and in the US during the current outbreak (45, 72). Several mutations occurring in the current circulating Makona EBOV variant raised concerns about efficacy of siRNAs, as inhibition is sequence-specific (73, 74). Consequently, a new lipid nanoparticle encapsulated siRNA cocktail targeting the L and VP35 proteins from the Makona variant, designated si-Ebola3, has been developed, and was 100% protective in NPHs when administered 72 hours after infection and continued for 7 days (75). A clinical trial of the si-RNA cocktail targeting the Makona variant (TKM-130803) was recently stopped in Sierra Leone due to a lack of efficacy, suggesting that siRNA treatment may be less effective in human EVD than in animal models for reasons that remain to be determined (76).

Antisense technology, with the use of positively charged phosphorodiamidate morpholino oligomers (PMOplus) (synthetic antisense oligonucleotide analogs resistant to degradation by RNAse H) acts by steric hindrance and can be designed against any viral target as long as the sequence is known (77). An EBOV-specific PMO targeting VP24 and VP35 (AVI-6002) was effective as very early PEP in animal models. Five of 8 (62.5%) rhesus macaques infected with Ebola survived if treated (40mg/kg per day SC or IP x 10 or 14 days) 30-60 min after infection. Surviving animals experienced decreased viremia, LFTs, and pro-inflammatory cytokines. Complete protection against Marburg challenge was afforded when AVI-6003 (pooled PMOplus targeting Marburg VP24, VP35, and L) was delivered IV 30-60min following infection (78). A recent study showed that AVI-7537, a PMOplus targeting only VP24 and administered daily (40 mg/kg, IV) for 7 days, protected 6/8 (75%) rhesus macaques, with no difference in viremia or renal and hepatic impairment between AVI-7537 and AVI-6002 (79). Notably these strategies are limited by the need for early PEP intervention (<1hour) and knowledge of the target sequence. These agents have been studied in phase 1 trials of tolerability and pharmacology but not yet in EVD patients or those exposed.

**Polymerase inhibitors.** Novel broad-spectrum synthetic adenosine analogues including GS-5734 and BCX4430 have been shown to protect animals through the inhibition of viral RNA polymerase (80-82). Mice treated with BCX4430 (timing of treatment related to infection not reported) were 100% and 90% protected against EBOV challenge respectively(82). In NHPs, BCX4430 administered for 12 days 30-120 minutes after virus challenge protected 4 of 6 (66.7%) monkeys when treated with 16mg/kg twice daily and 100% of animals if treated with 25mg/kg twice daily (83). Similarly, cynomolgus macaques were protected from Marburg infection when treated with 15mg/kg BCX4430 as late as 48 hours after infection and continuing twice daily for 14 days. Survival was associated with a decrease in viremia, LFT and coagulation testing abnormalities but effects of therapy on symptoms were not reported. GS-5734 has broad spectrum *in vitro* antiviral activity including against Ebola Zaire (Kikwit and Makona variants) as well as Ebola-Sudan, and Marburg virus with EC50 = 0.01 to 0.20uM in multiple human cell types (80, 81). Delayed treatment up to day 3 (after the detection of viremia) with 3mg/kg of GS-5734 protected 50% of NHPs whereas administration of a loading dose of 10mg/kg followed either by 3 or10 mg/kg/day for 11 days resulted in 100% survival (80, 81).

**Other therapies.** Recombinant nematode protein, rNAPc2, inhibits the tissue factor VIIa-mediated-coagulation pathway and has been evaluated as a treatment or PEP strategy given the association of hemorrhagic complications with death in filovirus disease. When administered to NHPs 24 hours post infection (subcutaneously, 30μg/kg daily) and continued daily for 8 days, only 33% (1/3) of challenged animals were protected but the mean time to death was prolonged (84). In rhesus macaques challenged with Marburg virus and treated 10 minutes post challenge with the same dose of rNAPc2 and continued daily for 14 days only 1 of 6 animals survived(85). Similar results were obtained with rhAPC when administered intravenously for 7 days starting 30-60 min after MARV challenge(86). These agents have not been tested in EVD patients to date.

Brincidofovir, an oral nucleotide analog, with activity against a range of DNA viruses and currently in phase III studies for treating adenovirus infections and preventing cytomegalovirus infections in transplant recipients, was reported to have some inhibitory effect on EBOV in cell culture. The possible anti-EBOV mechanism of inhibition *in vitro* remains to be determined. Brincidofovir was evaluated in an open label Phase II trial in Liberia (NCT02271347), but this trial was stopped due to a lack of enrollment, and no further studies are anticipated (87, 88).

**PEP in Humans**

The use of PEP in humans is limited to historical case reports of 5 individuals and at least 16 HCPs from the 2013-2015 ongoing epidemic.

**Earlier filovirus reports.**

In one case series, four scientists received PEP with goat hyperimmune serum following potential exposure while working in a bio-containment research facility (40). In two cases, the risk of exposure occurred in the setting of a hand injury suffered while washing cages that housed animals fatally infected with Ebola. A third case involved a needle stick that contained blood from an Ebola-infected monkey 4 days prior but had been treated with bleach for 1-2min before the injury. In these three cases, a single injection of goat hyper immune serum was administered with recombinant α-2-interferon (two injections daily for 14 days) and all survived without symptoms. The fourth person suffered a needle stick exposure during plasmapheresis of an Ebola-infected monkey with high viremia. Blood was then expressed from the puncture site, which was then washed with bleach. This individual was treated with a 6ml intramuscular injection of hyperimmune goat immunoglobulin intramuscularly and recombinant human α-2-interferon (two times daily x 12 days). The clinical course was complicated by an elevation in amylase, fibrinogen, prothrombin index, LFTs and symptoms that included myalgia, headache, arthralgia and malaise. This patient recovered and no virus or Ebola-specific antibodies were recovered from blood.

A second case report described a needle stick injury that occurred in a scientist while attempting to recap a needle containing high titer EBOV(26). A puncture site was visible but there was no bleeding. A single dose (5x107 plaque forming units) of the rVSV-ZEBOV was administered 48 hours after exposure. The vaccine was tolerated well except for a fever and myalgia that developed 12 hours after vaccination. The patient was transferred to a high-level bio-containment patient care area twice; once for fever and a second time for an unexplained incidental rise in D-dimer. Circulating vaccine virus was detectable by RT-PCR targeting EBOV GP (included in the vaccine) over 2 days post administration but was consistently negative for EBOV L protein (not included in the vaccine) during the 3-weeks follow up. Additionally, serologic investigation revealed only IgG titers to rVSV-ZEBOV, suggesting that infection was either subverted by the vaccine-induced immune response or more likely the patient was never infected.

**Makona variant Ebola virus reports**

Most recently, Ebola-specific PEP was considered in at least 12 HCPs who were providing direct clinical care in Sierra Leone including 8 who were repatriated to the United Kingdom, 2 to the United States, 1 in Belgium and 1 in Switzerland.

The eight that were repatriated to the UK were initially evaluated with a risk assessment algorithm and assigned a risk designation based on the circumstances of their exposure. Four individuals received PEP with favipiravir, and two with the highest risk exposures (penetrating sharps injuries with freshly used hollow bore needles) received mAb therapy in addition. None developed laboratory or clinical evidence of EBOV infection, but it is not possible to determine whether any infections were prevented by the use of PEP from this small, uncontrolled case series (24). Similarly, a nurse was repatriated to Switzerland after a moderate to high-risk exposure involving the penetration of 2 pairs of gloves by sharp plastic from trash containing biological fluids of EVD infected patients (Kaiser, personal communication). The HCP received a 7-day course of favipiravir as PEP, beginning 24 hours after exposure, and did not develop EVD.

Those who were assigned intermediate or maximal risk received PEP (including combinations of favipiravir and ZMAb, ZMApp or MIL77) while those who were deemed low risk were followed with heightened public health monitoring but received no PEP. Four of the eight suffered penetrating needle sticks with hollow bore needles while working in a high-risk area within an Ebola treatment unit in Sierra Leone. Two exposures occurred with needles that had been used in Ebola infected patients immediately prior to the injury, a third exposure occurred when a sterile needle penetrated potentially contaminated PPE; and the fourth from a needle of unknown previous use. All four followed needle stick protocols including “milking the wound” and washing the affected area with chlorine solution for “several minutes.” All four patients received treatment with favipiravir for ten days based on availability, efficacy in animal models, and human safety data (“high dose:” loading dose of 2400 mg, 2400 mg, and 1200 mg every 8 h on treatment day 1, followed by a maintenance dose of 1200 mg twice a day). Three healthcare workers tolerated “high dose” favipiravir without obvious adverse clinical effects. One healthcare provider, who was also receiving HIV PEP with tenofovir, emtricitabine, and raltegravir developed elevated transaminases (2-3x upper limit of normal) that resolved with cessation of both treatments. Monoclonal antibody therapy was also provided to the two healthcare providers who experienced a sharps injury with a needle that was previously used in an Ebola-infected patient (considered maximal risk exposure). Due to the complexity of administration, mAb therapy was delayed until the patient arrived in the UK and thus given on day 2 with two doses of 50mg/kg given 3 days apart. Two different preparations of monoclonal antibodies were used including a research-grade product including 4G7, 1H3, and 2G4 (ZMAb) and a clinical grade product containing 3 recombinant afucosylated humanized monoclonal antibodies (13C6, 2G4, and 4G7) produced in Chinese Hamster Ovary cell line (MIL77; Beijing MabWorks Biotech Co. Ltd.). None of these patients developed laboratory evidence of Ebola virus infection, although convalescent serologic studies were apparently not performed, and it remains possible that they were not actually exposed to infectious virus.

Two HCW repatriated to the United States were determined to have had significant exposures. In the first case, the needle pierced both outer and inner gloves and made brief skin contact. No bleeding was noted. The HCP was treated with an siRNA preparation (TKM-Ebola, Tekmira now Arbutusbio, Burnaby, British Columbia) for 5 days as PEP, and did not develop symptoms nor seroconvert. The second HCP experienced a clean needle stick that punctured two layers of potentially contaminated gloves and caused bleeding of the left thumb (27). 43 hours after the injury the patient was administered the rVSV-ZEBOV vaccine (1x108 PFU). The healthcare worker developed malaise, nausea, and a fever to 38.9° C 12 hours after vaccination.. Symptoms resolved between days 3-5. RT-PCR testing was positive for VSV nucleoprotein and EBOV GP (included in the vaccine), but remained negative for EBOV nucleoprotein and VP 40, demonstrating no evidence of EBOV infection. A very similar case was also described from Belgium (25). None developed EVD, but it is possible that none were actually exposed to virus.

**Concluding remarks**

NHP models of early treatment provide evidence of therapies that may be useful for PEP in humans. The therapeutic interventions that have demonstrated the most promise include mAbs, rVSV-ZEBOV vaccine and TKM-Ebola Guinea. However, the latter two appear effective only if delivered very soon after exposure in the NHP model. Given the low number of patients who have received PEP, it is not possible to determine the clinical efficacy of different therapies. However, information regarding the adverse effects from the various strategies is increasing. Some human subjects who received rVSV-ZEBOV or TKM-Ebola developed fever and symptoms consistent with natural EVD and required isolation in a bio-containment unit with medical support and the use of intensive personal protective equipment. Similar adverse effects have not been reported in the handful of patients who have received favipiravir, with or without mAb therapy, for PEP.

There is a clear need to develop standardized protocols for risk assessment and evaluate further therapeutic options for Ebola PEP, including choice of agent, duration of treatment, the role of combination therapy, and the duration of post-treatment monitoring. Designing clinical trials is challenging and careful, standardised observational data collection may be key to gaining further knowledge.

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