Haut Conseil de la Santé Publique

High Council for Public Health

OPINION

relating to the management of health-care worker (HCW) in care settings who are victims of an AEB/AEV from a patient who is a confirmed index case of Ebola virus disease

4th december 2014

These data may evolve as knowledge progresses and the epidemiological situation evolves. It is advisable to refer to the latest version on line.

On 20th November 2014, the High Council for Public Health (HCSP) was briefed by the General Directorate for Health relative to the management of individuals who are accidentally exposed to blood/ virus (AEB/AEV) in a professional setting from a patient who is a confirmed index case of Ebola virus disease (EVD).

The HCSP was requested to provide information relating to the following:

- Assessment of the risks related to AEB and AEV in the management of EVD as a function of the type of exposure and contact: contact with the healthy skin, damaged skin or mucous membranes; type and volume of the body fluid.
- Procedure for immediate disinfection following accidental exposure: type and concentration of the disinfectants to be used; duration of disinfectant exposure.
- Potential prophylaxis to be set up in the event of accidental exposure in liaison with the National Agency for the Safety of Medicines (ANSM): drugs to be used, indications, prescription conditions.
- Modalities and organization of victim follow-up.

The HCSP draws attention to a certain number of findings published in the opinions dated 10 April, 10 September, and 24 October 2014 [1,2,3]

- The virus is transmitted by contact with blood or biological fluids such as stools, vomit, urine, sweat, semen, amniotic fluid, tears, saliva and breast milk.
- The viral burden of the biological fluids of a patient infected with the Ebola virus is major: it may reach 10^9-10^{10} PFU/g (plaque forming unit/g) in diarrheal stools or vomit [4] and 10^7 PFU/g in serum [5].
- The degree of infectiousness of the Ebola virus is poorly known but it would appear that small quantities of the virus (a few PFU) are able to transmit the disease [6].
- In view of the risks incurred, a person infected by the Ebola virus and symptomatic is to be considered highly contagious.
- The onset of contagiousness is related to viremia and thus the emergence of the initial symptoms (including fever). The more advanced the disease, the more contagious the patient. The resolution of symptoms in survivors is correlated with the resolution of the

risk of contagion (however, the virus may persist in sperm; cf. HCSP Opinion: "Transmission of Ebola virus after clinical recovery").

- Management in the event of fortuitous and brief contact, without personal protective equipment and without care giving, with a febrile person who is ambulatory (able-bodied) and able to take care of him/herself was defined in the opinion dated 24 October 2014 [3].

The HCSP has reviewed the following:

- **Regarding the risks incurred by health-care workers in West Africa**
  - As at 21 November 2014, the number of healthcare professionals affected by the virus was 588 cases, of which 337 fatal cases (observed lethality: 57%) for all the countries affected by the epidemic or having treated repatriated patients (Guinea, Liberia, Nigeria, Sierra Leone, Mali, Italy, United States and Spain) [7].
  - Healthcare workers treating patients with EVD are at a high risk of infection if they do not comply with the recommendations: wearing of the recommended personal protective equipment (PPE) and strict compliance with the infection control and prevention measures [8]. Other risk factors include psychological distress, prolonged work, stress related to heat and dehydration due to wearing cumbersome PPE and ergonomic difficulties relating to handling corpses and specimens [8].
- **Regarding the risks incurred by health-care workers in industrialized countries**
  - Accidental transmissions to HCWs from repatriated Ebola patients, while limited in number, have been reported in industrialized countries, without precise details having been published.
  - According to the data reported, the environment was highly contaminant with profuse diarrhea; all the source patients died.
- **Regarding the risk level of Ebola virus transmission depending on the type of contact with the patient infected by the virus**
  - Reported by the European Center for Disease Prevention and Control (ECDC) [9], the risk levels are included in the Ebola Contact Procedure and Opinion of the HCSP dated 24 October 2014 [3].
  - On 22 October 2014, the ECDC published recommendations for the follow-up of contacts and particularly HCWs exposed to biological fluids following caring for a patient 'confirmed case'. The concept of "very high" risk in such settings is reported [10].
  - The levels of exposure have been transposed to the AEB/AEV setting (accidental exposure to the virus); cf. table 1.
- **In the event of AEB/AEV occurring in a community setting**

  In the event of AEB/AEV occurring with a secondarily-diagnosed index patient, the healthcare worker member victim of the AEB/AEV is to make immediate contact with the accredited reference healthcare establishment (ESRH) for immediate management and follow-up organization.
- **Regarding knowledge of the specific treatments liable to be used for prophylaxis**
  - **Several drugs have been shown to be active on Ebola virus (favipiravir, brincidofovir, BCX 4430, Zmapp, TKM 100802 and AVI-7537). The treatments differ in several respects**:
    - *In terms of mechanism of action*:
    - Favipiravir, brincidofovir and BCX4430 are all nucleos(t)ide analogs inhibiting RNA-polymerase.

- Zmapp is a combination of 3 monoclonal antibodies each of which targets a surface-glycoprotein epitope of the Ebola virus: c13C6, c2G4 and c4G7.
- TKM-Ebola is a combination of 2 interfering RNA molecules targeting the L-polymerase and genes for protein VP35.
- AVI-7537 is an antisense oligonucleotide that inhibits synthesis of protein VP24.

▪ *In terms of administration route*: oral route for the 3 nucleos(t)ide analogs and parenteral route for the other treatments.

▪ In terms of the level of information:

- In terms of efficacy with respect to Ebola virus infection: data are available (in the form of a report or publication) on the pertinent model (non-human primate) for favipiravir, Zmapp, TKM-Ebola and AVI-7537, while for the other drugs only *in vitro data* and *in vivo* data generated in rodent models are available.
- In terms of safety: clinical experience with target populations other than patients infected by the Ebola virus are available for favipiravir and brincidofovir. Zmapp, TKM-Ebola, favipiravir and brincidofovir have also been administered in a very limited compassionate framework in the context of Ebola virus infection.

Table 1 - Level of the risk of Ebola virus transmission from a patient with confirmed EVD to a health-care worker by type of exposure

Contact type	Risk level	
	Presence of diarrhea and/or vomit and/or blood	
	NO	YES
Close contact (less than 1 meter), without personal protective equipment (PPE), face to face with a febrile but able-bodied patient. No direct contact or projection of biological fluids.	Low	High
Direct contact without protection with materials soiled by biological fluids from an Ebola infection case.	High	Very high
Cumulative incidents during the various stages of undressing reported by the interested party or observed by the teammate or supervisor.	Low	Very high
Transcutaneous exposure, AEB or mucosal exposure to blood or a body fluid (including diarrheal stools and vomit), biological tissues or contaminated clinical specimens from a patient.	Maximum	Maximum

- Regarding the availability of the treatments, only favipiravir and brincidofovir have no availability limits at the present time. However, the Chimerix company is not currently envisaging provision of brincidofovir for post-exposure prophylaxis.
- **Thus, to date, in light of the antiviral effect of favipiravir vis-à-vis the Ebola virus, the oral administration route and its availability, the antiviral favipiravir (authorized in Japan for influenza treatment) is a potential candidate for post-exposure prophylaxis.**

- Dosage
  - With regard to the dosage to be envisaged in the post-exposure context, even if the patient has no detectable viremia during the incubation phase, the critical aspect is to achieve sufficient plasma exposure before emergence of viremia and thus limit the risk of potential progression toward the disease. Thus, if post-exposure prophylaxis is envisaged in the context of Ebola virus infection, the dosage should the same as determined for treatment of a confirmed case.
  - All the simulations conducted ultimately resulted in definition of the favipiravir dosage: a loading dose of 6,000 mg (2,400 mg at H0 and H8 + 1,200 mg at H16) on day 1, followed by a maintenance dosage of 1,200 mg b.i.d. [11]. This dosage is markedly higher than that for which clinical experience was through the development program in the influenza indication.
- Time to initiation
  - Post-exposure treatment should be initiated as rapidly as possible and in a maximum time interval of 10 days (median duration of Ebola virus incubation period).
- Post-exposure treatment duration
  - In light of the high dosage envisaged, uncertainties with regard to the degree of safety and no follow-up for exposure durations beyond 5 days (in the context of influenza treatment) treated duration covering the whole incubation period (up to 21 days) would be debatable.
  - Thus, a compromise has been defined, *empirically*, with a total duration of post-exposure treatment of 14 days, which would cover the mean duration of incubation.
- Monitoring modalities
  - Regarding the implementation of pre-exposure prophylaxis at national level in the reference centers:
  - In light of the uncertainty with respect to the risk profile at the dosage envisaged, subjects treated in a post-exposure setting are to be closely monitored, which will necessitate hospitalization whose duration is to be modulated as a function of the patient's tolerance.
  - Monitoring must at least include liver function tests (ALT, AST, gamma-GT) and renal function tests, uric acid assay, CBC and monitoring of coagulation parameters (laboratory monitoring is to be conducted on D1, D3, D5, D10 and D14), intensified gastrointestinal tolerability monitoring and electrocardiographic monitoring (QT interval).
  - Ebola PCR is to be implemented at least on D14 (end treatment) and D21 post-exposure (to be adapted in liaison with the Viral Hemorrhagic Fever (VHF) National Reference Center (CNR) as a function of the clinical picture).
  - It is to be noted that in the absence of fever or clinical signs, victims of AEB/AEV are not contagious and the specimens could therefore be processed in the standard manner.

➢ Regarding the knowledge relating to specific vaccines or use of sera from convalescent patients

- Two candidate vaccines are undergoing phase I clinical trials in the context of prevention of Ebola virus fever, which is responsible for the current epidemic in West Africa. Publications report a degree of efficacy in a post-exposure primate model of vaccines prepared from recombinant vesicular stomatitis virus (VSV), in which VSV protein G is replaced by an Ebola virus surface glycoprotein. The very preliminary information on the first subjects who have received investigational vaccine VSV-ZEBOV

in a phase I clinical trial does not evidence any serious adverse reactions in the week following injection. However, the data currently available are not sufficient to propose use of the vaccine in the context of AEB/AEV.

- Use of convalescents' sera is one of the therapeutic approaches identified by the World Health Organization (WHO) in the context of the Ebola virus epidemic. However, in the current state of our knowledge, use remains empirical and efficacy studies should be conducted.

➢ **Regarding the position of the World Health Organization (WHO) with respect to compassionate use of treatments in the absence of human safety and efficacy data**

- Use of drugs for which the data required for regulatory approval are not available raises an ethical problem with respect to the West African epidemic in which the lethality rate is about 50%. The panel convened by WHO in August 2014 unanimously concluded *" that it would be acceptable on both ethical and evidential grounds to use as potential treatments **or for prevention** unregistered interventions that have shown promising results in the laboratory and in animal models but have not yet been evaluated for safety and efficacy in humans, provided that certain conditions are met'* [12]. The potential use of the medications prophylactically is addressed in the background document [13].

➢ **The status of the drugs in the context of post-exposure prophylaxis is covered by the regulatory text**

- The ministerial order dated 18 September 2014 authorizing the use of treatments for patients contaminated by the Ebola virus indicates in article 1: "
- By way of derogation the medications containing the following substances may be imported, stored, prescribed, dispensed and administered for treatment of persons contaminated by the Ebola virus in the reference healthcare establishments (ESR) and armed forces teaching hospitals (HIA) included in the list posted on the website of the Ministry of Social Affairs, Health and Women's Rights: favipiravir; TKM-100-802; ZMapp; ZMabs". [14,15].
- A new ministerial order is to be worded as follows: By way of derogation, the medicinal product containing the drug substance favipiravir may be imported, stored, distributed, prescribed, dispensed and administered for the treatment of persons exposed to the Ebola virus in the reference healthcare establishments (ESRH) and armed forces teaching hospitals (HIA) included in the list posted on the website of the Ministry of Social Affairs, Health and Women's Rights".

➢ **Considering the various recommendations in the event of occupational exposure to the Ebola virus published by the CDC [16], Public Health Agency of Canada [17] and WHO [18, 19] ;**

The HCSP recommends:

➢ **All cases of AEV due to exposure to blood, a biological fluid, secretion or excretion from a "suspected", "possible" or "confirmed" case are, <u>imperatively and immediately</u>, to give rise to measures of general nature and specific measures in the event of confirmed EVD in the source patient.**

➢ **General measures**

❖ **In all cases**:

- secure discontinuation of the ongoing tasks;
- victim evacuation from the healthcare area;
- secure removal of the PPE with scrupulous compliance with the written procedures.

- ❖ **In the event of AEB** (needle sticks or percutaneous wounds):
  - mild and non-traumatic washing with soap and water of the skin area affected by the wound or needle stick;
  - disinfection with 0.5% sodium hypochlorite for 10 minutes.
- ❖ **In the event of AEV on healthy skin**:
  - mild and non-traumatic washing with soap and water of the skin area affected by the wound or needle stick;
  - disinfection with 0.5% sodium hypochlorite for 10 minutes.
- ❖ **In the event of AEV on the mucosa** (e.g. conjunctiva):
  - abundant rinsing with normal saline or, failing that, with water or an eyewash solution;
  - without any chlorine solution or disinfectant.
- ❖ **In the event of an incident occurring during the undressing procedure following care giving**, observed by the interested party or his/her teammate:
  - thorough washing of the hands with soap and water;
  - thorough washing of the skin area involved;
  - complementary skin disinfection with 0.5% sodium hypochlorite solution;
  - thorough rinsing with normal saline or, failing that, with water, or an eyewash solution in the event of splashing or contact with the ocular mucosa;
  - thorough rinsing with water in the event of splashing or contact with the oral mucosa.
- ❖ **All cases of AEV from a suspect, possible or confirmed case** is to give rise to:
  - assessment of other potential exposures (e.g HIV, HBV and HCV);
  - verification of HBV status, immunization/vaccination if necessary; in this context, the HCSP recommends that personnel members liable to give care to persons infected with the Ebola virus should be correctly immunized against HBV;
  - assessment of the psychological impact;
  - information of the victim so that the HCW is informed of the expected risks and benefits of chemoprophylaxis.

➢ **Specific measures in the event of EVD confirmation for the index patient:**

All AEV/AEB from a confirmed case are, imperatively and immediately, to undergo reporting, assessment of the risk related to exposure and decision-making as to the pertinence of post-exposure chemoprophylaxis.

❖ **The assessment is to be conducted at two levels:**

Local level

- All AEV/AEB are to be immediately reported and require collegial review by the local crisis unit, urgently, in the timeliest manner.
- The local crisis unit (infectious diseases specialist, hygienist, occupational physician, virologist):
  - determines the risk level: the assessment is based on the levels defined in Table 1 (Level of risk of Ebola virus transmission from a patient with confirmed EVD to a health-care worker by exposure type);
  - determines the pertinence of post-exposure chemoprophylaxis; hospitalization will be necessary in the event of chemoprophylaxis:

- in the event of low-risk exposure: no chemoprophylaxis;
- in the event of high or very high risk exposure: decision after collegial discussion;
- in the event of maximum risk: chemoprophylaxis is indicated;
- special case: in the event of exposure and the impossibility of urgently obtaining a PCR for the index case, chemoprophylaxis may be initiated, following discussion and pending the PCR result;
- optimally determines the circumstances of exposure in order to take corrective measures if necessary;
- reviews the scope for post-exposure vaccination;
- gives the victim all the information available, particularly with regard to the expected risks and benefits of chemoprophylaxis (handover of the ANSM information document).

National level

- Collegial opinion of the ANSM for validation.

❖ Protocol for post-exposure chemoprophylaxis

- All AEB/AEV require an urgent decision with regard to implementation of the favipiravir chemoprophylaxis protocol:
  - a loading dose of 6,000 mg (2,400 mg at H0 and H8 + 1,200 mg at H16) on day 1,
  - followed by a maintenance dose of 1,200 mg b.i.d. for 14 days.
- When the chemoprophylaxis decision has been made, administration is to be implemented in the timeliest manner.

❖ **In that context, the HCSP stresses the need to constitute a stock of favipiravir in each Accredited Reference Healthcare Establishment (ESRH) in order to enable urgent initiation (H24) of post-exposure favipiravir treatment.**

❖ Scheduling and medical follow-up

All AEV/AEB require scheduling of medical and paramedical follow-up of the victim by the reference infectious diseases specialist of the ESRH:

- During hospitalization, over the first 5 days at least, and subsequently in outpatient settings in the event of good tolerability, setup of twice-daily body temperature monitoring for 21 days with the requirement of calling the emergency number 15 in the event of emergence of fever or clinical signs with a view to evaluation by the reference infectious diseases specialist of the ESRH.
- Monitoring must at least include liver function tests (ALT, AST, gamma-GT) and renal function tests, uric acid assay, CBC and monitoring of coagulation parameters (laboratory monitoring is to be conducted on D1, D3, D5, D10 and D14), intensified gastrointestinal tolerability monitoring and electrocardiographic monitoring (QT interval).
- It is to be noted that in the absence of fever or clinical signs, victims of AEB/AEV are not contagious and the specimens could therefore to be processed in the standard manner.
- Ebola PCR is to be implemented at least on D14 (end treatment) and D21 post-exposure (to be adapted in liaison with the Viral Hemorrhagic Fever (VHF) National Reference Center (CNR) as a function of the clinical picture).
- Discontinuation of favipiravir on day 14 of treatment is to be confirmed by a negative Ebola virus PCR result.

- **Lastly, the HCSP draws attention to the following:**
  - **the absence of quarantine irrespective of the AEV;**
  - **in the event of chemoprophylaxis, the need for clinical and laboratory monitoring by the reference infectious diseases specialist of the ESRH;**
  - **in other cases, the need for twice-daily outpatient monitoring ensured by the Regional Healthcare Agency (ARS) in the event of low or very low risk exposure. Self-monitoring is possible in the event of very low risk exposure.**

Opinion compiled by the expert group, members or non-members of the HCSP, with the specialized Commission for Transmissible Diseases and the Specialized Commission for the Safety of Patients, and with the ANSM Ebola Group. No conflict of interest has been identified.

Opinion validated by the Chairman of the High Council for Public Health.

Opinion translated by ANSM with the permission from HCSP. French and English versions available on the HCSP website : **http://www.hcsp.fr/Explore.cgi/AvisRapports**.

References

[1] Haut Conseil de la santé publique. Avis relatif à la conduite à tenir autour des cas suspects de maladie Ebola. 10 April 2014.

Available at: http://www.hcsp.fr/Explore.cgi/avisrapportsdomaine?clefr=414 (consulted on 24/10/2014).

[2] Haut Conseil de la santé publique. Avis relatif à la conduite à tenir autour des cas suspects de maladie Ebola : données complémentaires à l'avis du 10 avril 2014. 10 September 2014.

Available at: http://www.hcsp.fr/Explore.cgi/avisrapportsdomaine?clefr=456 (consulted on 24/10/2014).

[3] Haut Conseil de la santé publique. Conduite à tenir concernant l'identification et le suivi des personnes-contact d'un cas possible ou confirmé d'infection par le virus Ebola. 24 October 2014.

Available at: http://www.hcsp.fr/explore.cgi/avisrapportsdomaine?clefr=458 (consulted on 14/11/2014).

[4] Bray M, Davis K, Geisbert T, *et al.* A mouse model for evaluation of prophylaxis and therapy of Ebola hemorrhagic fever. J Infect Dis 1998; 178: 651-61.

Available at: http://jid.oxfordjournals.org/content/178/3/651.long] (consulted on 24/10/2014).

[5] Zampieri CA, Sullivan NJ, Nabel GJ. Immunopathology of highly virulent pathogens: insights of Ebola virus. Nature immunol 2007; 8: 1159-64.

[6] Franz DR, Jahrling PB, Friedlander AM, *et al*. Clinical recognition and management of patients exposed to biological warfare agents. JAMA 1997; 278: 399-411.

[7] InVS. EBOLA. Point épidémiologique semaine 42 (du 13/10 au 19/10/2014). http://www.invs.sante.fr/Dossiers-thematiques/Maladies-infectieuses/Fievre- hemorragique-virale-FHV-a-virus-Ebola/Point-epidemiologique-Ebola-Afrique-de-l-

Ouest/Virus-Ebola-Point-epidemiologique-en-Afrique-de-l-Ouest-au-20-octobre-2014

[8] WHO. Occupational health and safety risks. http://www.who.int/occupational_health/publications/ebola_osh/en/

[9] Source ECDC, Rapid Risk Assessment, Outbreak of Ebola virus disease in West Africa, 1st August 2014.

http://www.ecdc.europa.eu/en/publications/_layouts/forms/Publication_DispForm.aspx?List=4f55ad51-4aed-4d32- b960-af70113dbb90&ID=1141

[10] ECDC. Public health management of persons having had contact with Ebola virus disease cases in the EU. Technical Report, 22 October 2014. Available at: http://ecdc.europa.eu/en/publications/Publications/ebola-public-health-contact-management.pdf (consulted on 14/11/2014).

[11] Mentré F, Taburet AM, Guedj J, Anglaret X, Keita S, De Lamballerie X, Malvy D. Dose regimen of favipiravir for Ebola virus Disease. Lancet Infectious Diseases. http://dx.doi.org/10.1016/S1473-3099(14)71047-43

http://download.thelancet.com/pdfs/journals/laninf/PIIS1473309914710473.pdf

[12] WHO; Ethical considerations for use of unregistered interventions for Ebola viral disease Report of an advisory panel to WHO.
http://apps.who.int/iris/bitstream/10665/130997/1/WHO_HIS_KER_GHE_14.1_eng.pdf

[13] WHO. Consultation on potential Ebola therapies and vaccines. Background document: http://www.who.int/csr/disease/ebola/ebola-new-interventions-02-sep-2014.pdf?ua=1

[14] Arrêté du 18 septembre 2014 autorisant l'utilisation de traitements pour les patients contaminés par le virus Ebola.

[15] Arrêté du 22 septembre 2014 modifiant l'arrêté du 18 septembre 2014 autorisant l'utilisation de traitements pour les patients contaminés par le virus Ebola.

[16] CDC. http://www.cdc.gov/vhf/ebola/hcp/infection-prevention-and-control- recommendations.html

[17] Public Health Agency of Canada : http://www.phac-aspc.gc.ca/id-mi/vhf-fvh/ebola-ipc- pci-eng.php - a2

[18] WHO : http://www.who.int/occupational_health/publications/ebola_osh/en/

[19] WHO. Interim Infection Prevention and Control Guidance for Care of Patients with Suspected or Confirmed Filovirus Haemorrhagic Fever in Health-Care Settings, with Focus on Ebola. September 2014. http://apps.who.int/iris/bitstream/10665/130596/1/WHO_HIS_SDS_2014.4_eng.pdf?ua=1
&ua=1

Haut Conseil de la santé publique - High Council of Public Health
14 avenue Duquesne
75350 Paris 07 SP
www.hcsp.fr