Standardization of management of occupational exposure to HIV/blood-borne infections and evaluation of post-exposure prophylaxis in Europe

Grant no. SI 2.322294

Final scientific report

The Project Leader
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The aims of the project were:
1. To implement and standardize the management of occupational exposures to blood-borne infections in Europe, including post-exposure prophylaxis (PEP).
2. To issue European Recommendations
3. To assess current policies and activities on the management of occupational exposures and PEP in EU countries
4. To monitor the use, failures -if any-, and toxicity of PEP
5. To evaluate the effectiveness of rapid HIV serological assays, and highly sensitive direct HIV assays in the management of HIV exposures
6. To analyze the utility for gene sequencing methods of source’s HIV isolates in guiding the choice of PEP regimens. This part of the project was not performed because of availability of new literature data showing the limited usefulness of expected results, and due to logistic difficulties and costs.

Main Results

Recommendation for Post-Exposure Prophylaxis against HIV Infection in Health Care Workers in Europe

Nine European countries participated in the project coordinated by the National Institute for Infectious Diseases “Lazzaro Spallanzani” in Rome, Italy: Croatia, Denmark, France, Germany, Italy, Portugal, Spain, Switzerland, and the United Kingdom.

National guidelines and recommendations, local bulletins, written protocols, published data or presentations from national and international conferences, and any other document relevant to occupational exposures to HIV in HCWs and antiretroviral PEP were collected, in order to define the state of the art.

A literature review was conducted using the key terms HIV, AIDS, occupational infection, health care workers, occupational risk, occupational exposure, and antiretroviral prophylaxis, searching the MEDLINE and AIDSline databases of MEDLARS (National Library of Medicine, Bethesda, MD). The bibliographies of selected articles were also searched for pertinent studies.

Representatives of the participating member countries, who are expert in the field of blood-borne pathogens transmission prevention and PEP, were also asked to fill an ad-hoc structured questionnaire, in order to assess current guidelines, policies, and data on occupational exposures to HIV and the management of antiretroviral PEP in HCWs. The
questionnaires were reviewed and entered into a database at the coordinating centre to compare the results within the participating countries. Identified differences and analogies, existing experiences and scientific evidences regarding the main issues in this field were analyzed and discussed during a consensus meeting held in Rome, Italy, on January 18-19, 2002. Members of the working group were convened to discuss the first draft of the European recommendations on PEP against HIV. Subsequently, a second draft was produced incorporating comments and judgments of the working group. They reviewed the second draft and submitted comments, which were incorporated into a third and final version of the document, issued in March 2002.

The final document on the state-of-the-art on current policies and activities on the management of occupational exposures and PEP in EU countries, and the Recommendations for Post-Exposure Prophylaxis against HIV Infection in Health Care Workers in Europe, were:

- presented by the Italian project coordinator, Dr. Stefania Cicalini, during the XIV International AIDS Conference in Barcelona, Spain, July 7-12 2002. A report of this presentation appeared on the Reuters;
- published in the European bulletin (Thomas T, Puro V. Towards a standard HIV post exposure prophylaxis for healthcare workers in Europe. Eurosurveillance Weekly 20 August 2002; issue 34);

Moreover, the recommendations are

- available through the internet
  - on the website of the Istituto Nazionale Malattie Infettive L. Spallanzani (www.inmi.it),
  - on the website of the Robert Koch Institute (www.rki.de/INFEKT/AIDS_STD/EXPO/HIV.HTM) in the original version and in the German translation,
  - are going to appear on the website of EPINETAC, the Spanish National Registry of Occupational Exposures.
- going be published in the Croatian journal Infektologski glasnik in the Croatian translation.
In Germany, in the process of the revision of the German-Austrian HIV-PEP Guidelines, these were carefully checked against the European recommendations for consistency.

In France, during the revision of the French HIV-PEP Guidelines, these were carefully checked against the European recommendations for consistency, and a text from the French Ministry of Health is awaited.

In Portugal, the European Recommendations were made available to those hospitals offering PEP treatment since June 2002.

The recommendations, and the rationale from which these were derived, are currently under preparation to be submitted as a scientific publication to a widely circulating, peer-reviewed journal.

**European Registry of Occupational Post-Exposure Prophylaxis**

The European Registry of Occupational Post-Exposure Prophylaxis was instituted in January 2002. The data collection forms and the protocol were discussed and approved during the first steering committee. The forms and an explanatory document were distributed by the national coordinators in each country.

In Italy, the forms in the Italian version were sent to all of the participants to the Italian Registry of Antiretroviral Post-Exposure Prophylaxis, were published in the Giornale Italiano delle Infezioni Osperdaliere, and are available on the website of the Istituto Nazionale Malattie Infettive L. Spallanzani (www.inmi.it).

In Germany, clinical centres for HIV/AIDS treatment, the occupational health insurances for health care workers, the organisation for occupational medicine (Arbeitsmediziner) and a German journal for occupational health issues were asked to support the European Registry of Occupational Post-Exposure Prophylaxis. The Registry was announced during the Munich AIDS Day in February 2002 and during the discussion of the German-Austrian HIV-PEP Guidelines. These documents are also available on the website of the Robert Koch Institute (www.rki.de/INFEKT/AIDS_STD/EXPO/HIV.HTM).

In Denmark, the five centres offering PEP treatment were all enrolled in the Registry.
In the UK, the Advisory Group on Occupational Exposures, CDSC, decided that centres would be more likely to contribute their data if it was routinely collected data. Therefore, the coordinating centre in Italy provided a comparison table so that the data set collected at a national level in the UK could be matched to the EuROPEP form.

In Spain, during February 2002 all of the hospitals participating in the EPIINETAC Project (65 hospitals throughout Spain) were contacted and asked to participate in the EuROPEP Registry, and the forms translated into Spanish were sent to those centres who voluntarily enrolled in the project.

In France, a surveillance system had already been implemented since July 1999 to monitor the characteristics of HCW seeking advice for PEP, the use and toxicity of PEP and the follow-up testing in the first six months after exposure. All PEP cases collected within this surveillance were enrolled in the Registry.

In Portugal, 10 district hospitals offering PEP treatment were enrolled in the Registry. The national coordinators are going to make the forms available on a website, to enhance participation.

Preliminary results

Between 01/09/2001 and 30/11/2002, the EuROPEP collected information on 531 cases of occupational PEP in health care workers. The distribution of cases by country is reported in Table 1.

<table>
<thead>
<tr>
<th>Country</th>
<th>N. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Italy</td>
<td>238 (44.8)</td>
</tr>
<tr>
<td>France</td>
<td>179 (33.7)</td>
</tr>
<tr>
<td>Spain</td>
<td>38 (7.2)</td>
</tr>
<tr>
<td>Denmark</td>
<td>29 (5.5)</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>23 (4.3)</td>
</tr>
<tr>
<td>Portugal</td>
<td>9 (1.7)</td>
</tr>
<tr>
<td>Germany</td>
<td>6 (1.1)</td>
</tr>
<tr>
<td>Switzerland</td>
<td>7 (1.3)</td>
</tr>
<tr>
<td>Croatia</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Total</td>
<td>531 (100)</td>
</tr>
</tbody>
</table>
The distribution by job category is reported in Table 2.

Table 2. Distribution of cases by job category of the exposed HCW– EuROPEP, 9/01-11/02

<table>
<thead>
<tr>
<th>Job category</th>
<th>N.</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physician (staff)</td>
<td>94</td>
<td>(17.7)</td>
</tr>
<tr>
<td>Phys. (intern)</td>
<td>22</td>
<td>(4.1 )</td>
</tr>
<tr>
<td>Medical student</td>
<td>8</td>
<td>(1.6 )</td>
</tr>
<tr>
<td>Student nurse</td>
<td>18</td>
<td>(3.4 )</td>
</tr>
<tr>
<td>Nurse</td>
<td>219</td>
<td>(41.3)</td>
</tr>
<tr>
<td>Nurse aid</td>
<td>29</td>
<td>(5.5 )</td>
</tr>
<tr>
<td>Technician</td>
<td>27</td>
<td>(5.1 )</td>
</tr>
<tr>
<td>Housekeeper</td>
<td>38</td>
<td>(7.2 )</td>
</tr>
<tr>
<td>Midwife</td>
<td>4</td>
<td>(0.8 )</td>
</tr>
<tr>
<td>Other</td>
<td>70</td>
<td>(13.3)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>531</td>
<td>(100)</td>
</tr>
</tbody>
</table>

HCWs were mostly exposed through needlestick (71%) and mucous membrane contamination (35%) (Note: more than one type of exposure could be present).

Following occupational exposure, PEP was started after a mean of 6 hours. However, it should be noted that 149 HCWs (28%) did not work in the same hospital where PEP was provided.

The distribution of source patients by serostatus is reported in Table 3. Following the occupational exposure, source patients were tested mostly with conventional assays (n=125). Only 5 subjects were tested with rapid assays.

Table 3. Distribution of source patients by serostatus

<table>
<thead>
<tr>
<th>Source patient</th>
<th>Serostatus</th>
<th>No.</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unknown</td>
<td></td>
<td>111</td>
<td>(20.0)</td>
</tr>
<tr>
<td>Known</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- already known</td>
<td>HIV+</td>
<td>267</td>
<td>(51.3)</td>
</tr>
<tr>
<td>- tested</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV+</td>
<td>16</td>
<td>(3.0 )</td>
<td></td>
</tr>
<tr>
<td>HIV-</td>
<td>109</td>
<td>(20.5)</td>
<td></td>
</tr>
<tr>
<td>Not available</td>
<td>5</td>
<td>(0.9 )</td>
<td></td>
</tr>
<tr>
<td>- untested</td>
<td></td>
<td>23</td>
<td>(4.3 )</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td>531</td>
<td>(100)</td>
</tr>
</tbody>
</table>

Data regarding different variables were not available in all cases, resulting in variation in the denominators used in the analysis.
Among HIV-infected sources, 75 were co-infected with HCV, 11 with HBV, and 7 with both viruses. Primary HIV infection was reported in 26, while 65 were asymptomatic and 36 symptomatic. Mean CD4+ cell count/mL was 356 (median 289, range 1-1705); viral load was undetectable in 44 subjects, between threshold limit and 999 copies/mL in 22, 1,000-9,999 copies/mL in 19, 10,000-99,999 in 33, 100,000-1,000,000 in 25. Forty patients were naïve, 29 were at their first antiretroviral treatment and 55 were experienced. Current antiretroviral treatment was available in 124 cases; in 11 cases, the choice of the prophylactic regimen was influenced by known resistance in the source.

Of the 503 healthcare workers for whom initial prophylactic regimen was available, 352 (70%) were started on a 3-drug regimen (AZT+3TC+IDV 36%; AZT+3TC+NFV 41%). One-hundred fifty-one cases (30%) received two drugs only (AZT+3TC 98%), however, most of these cases were enrolled before the European recommendations were issued. Nevirapine was used in 7 cases.

Overall, mean treatment duration in exposed HCW was 19 days (median 28, range 1-57), including 101 HCW who interrupted PEP after the source tested HIV negative. In the remaining subjects, prophylaxis was completed in 71% of cases; 12% of HCW interrupted PEP because of adverse reactions, 7% because of personal choice, and 4% because of other reasons.

No case of seroconversion was observed in the EuROPEP Registry as of November 30, 2002.

**Recommendations for the Management of Health Care Workers Occupationally Exposed to HBV and HCV in Europe**

The nine European countries participating in the project provided national guidelines and recommendations, local bulletins, written protocols, published data or presentations from national and international conferences, and any other document relevant to occupational exposures to hepatitis B virus (HBV) and hepatitis C virus (HCV) in HCWs and vaccination against HBV, in order to define the state of the art.
A literature review was conducted using the key terms HBV, HCV, occupational infection, health care workers, occupational risk, occupational exposure, hepatitis B vaccination, searching the MEDLINE database of MEDLARS (National Library of Medicine, Bethesda, MD). The bibliographies of selected articles were also searched for pertinent studies.

Representatives of the participating member countries, who are expert in the field of blood-borne pathogens transmission prevention, were also asked to fill an ad-hoc structured questionnaire, in order to assess current guidelines, policies, and data on occupational exposures to HBV and HCV, vaccination against HBV, management of post-exposure anti-HBV prophylaxis and follow-up in HCWs. The questionnaires were reviewed and entered into a database at the coordinating centre to compare the results within the participating countries.

Identified differences and analogies, existing experiences and scientific evidences regarding the main issues in this field were analyzed and discussed during a consensus meeting held in Rome, Italy, on June 14-15, 2002. Members of the working group were convened to discuss the first draft of the European recommendations for the management of health care workers occupationally exposed to HBV and HCV. Subsequently, a second draft was produced incorporating comments and judgments of the working group. They reviewed the second draft and submitted comments, which were incorporated into a third and final version of the document.

The recommendations, and the rationale from which these were derived, are currently under preparation to be submitted as a scientific publication to a widely circulating, peer-reviewed journal.
Annexes

- Recommendations for Post-Exposure Prophylaxis against HIV Infection in Health Care Workers in Europe (European recommendations for HIV PEP.pdf)
- Recommendations for the Management of Health Care Workers Occupationally Exposed to HBV and HCV in Europe (European Recommendations for HBV-HCV exposure.pdf)
- Abstract (http://www.aids2002.com/Program/ViewAbstract.asp?id=/T-CMS_Content/Abstract/200206290751295929.xml) (http://www.aids2002.com/Program/ViewAbstract.asp?id=/T-CMS_Content/Abstract/200206290751305978.xml), and poster (HIV PEP state of art in Europe.pdf; Proposed recommendations for HIV PEP.pdf) of the presentations at the XIV International AIDS Conference in Barcelona, Spain, July 7-12 2002; CD ROM containing the presentations on the epidemiological situation regarding HIV, HBV and HCV in each participating country developed by the representatives of the member states, and the presentations on the state of the art and the rationale of the proposed guidelines made by members of the coordinating centre.

CD ROM contents:

First Steering Committee
- Project Summary (Dr. Gabriella De Carli)
- HIV State of the art (Dr. Stefania Cicalini)
- Rationale HIV (Dr. Vincenzo Puro)
- HIV Croatia (Prof. Slavko Schonwald)
- HIV Denmark (Dr. Suzanne Lunding)
- HIV France (Dr. Florence Lot)
- HIV Germany (Dr. Ulrich Marcus)
- HIV Italy (Dr. Stefania Cicalini)
- HIV Portugal (Dr. José Luis Boaventura)
- HIV Spain (Dr. Magda Campins)
- HIV Switzerland (Dr. Enos Bernasconi)
- HIV UK (Tania Thomas)

Second Steering Committee
- Nosocomial HBV HCV (Dr. Paola Scognamiglio)
- HBV in France (Dr. Arnaud Tarantola)
- HBV_HCV State of the art (Dr. Stefania Cicalini)
- Rationale (HBV_HCV) (Dr. Gabriella De Carli)
- HBV_HCV Croatia (Prof. Josip Begovac)
- HBV_HCV Denmark (Dr. Ulla Balslev)
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- HBV_HCV Portugal (Dr. José Luis Boaventura)
- HBV_HCV Spain (Dr. Magda Campins)
- HBV_HCV Switzerland (Dr. Raoul Kammerlander)
- HBV_HCV UK (Dr. Lara Payne)
Recommendations for Post-Exposure Prophylaxis against HIV infection in Health Care Workers in Europe

March 2002
This is a document from the European Project on

“Standardization of the management of occupational exposure to HIV/blood-borne infections and evaluation of post-exposure prophylaxis in Europe.”

FUNDING: European Commission, Directorate-General Health Care and Consumer Protection. Unit F4. Project number SI2.322294

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Dr. Yohanka Alfonso Contreras
Recommendations for Post-Exposure Prophylaxis against HIV infection in Health Care Workers in Europe.

Definition of health care worker (HCW) and occupational exposure

HCW is defined as a person whose activities involve contact with patients or with blood or other body materials from patients in a health-care or laboratory setting.

Occupational exposure is defined as any at risk accidental exposure to at risk body materials during working activity.

Policies

All preventive efforts should be made to reduce the risk of occupational exposures (i.e. development of educational programs, implementation of standard precautions, provision of safety devices and personal protective equipment, implementation of safer procedures, etc)

- **Educational Programs**
  - All HCWs should be informed and educated about:
    - the possible risk of HIV transmission from an occupational exposure
    - the importance of seeking urgent advice following any occupational exposure
    - the knowledge about efficacy and toxicity of drugs used for PEP
    - the benefits from prompt administration of PEP

- **Reporting an occupational exposure**
  - Every health authority should identify designated health care providers to whom HCW can be urgently referred to in case of occupational exposure.
  - Local health policies should specifically identify who will be responsible for the management of occupational exposures, for the provision of PEP and for clinical and serological post-exposure follow up.
  - All HCWs should be made aware of how to report an exposure and to whom it should be reported.

- **Availability of PEP**
  - The availability of PEP should be publicly advertised in order that it may be immediately and readily accessible and initiated as soon as possible following an occupational exposure.
  - In health settings where PEP is not available:
    - start kits should be available, and/or
a collaborative connection should be established with those centres where PEP may be provided, and information about where and how the drugs may be obtained should be publicly advertised.

**PEP When?**

The issue of PEP should be evaluated following an occupational exposure with the potential for HIV transmission, based on the type of exposure, the type of body fluid or material involved, and source patient’s evaluation.

**Type of exposures:**

1. percutaneous injury
   - PEP recommended
2. exposure of mucous membrane including the eye
   - PEP considered
3. exposure of non intact skin
   - PEP considered
4. exposure of intact skin
   - PEP discouraged
5. bite
   - PEP considered

**Type of materials:**

1. blood
   - PEP recommended
2. body materials containing visible blood
   - PEP recommended
3. cerebrospinal fluid
   - PEP recommended
4. concentrated virus in a research laboratory or production facility
   - PEP recommended
5. semen; vaginal secretions; synovial, pleural, peritoneal, pericardial, or amniotic fluid, and tissues
   - PEP considered
6. urine, vomit, saliva, faeces, tears, sweat, sputum
   - PEP discouraged
**Source patient**

1. **Source patient known to be HIV-infected**

   PEP recommended

   Available clinical information about stage of infection (i.e. primary acute infection, asymptomatic, symptomatic, AIDS diagnosis), CD4+ T-cell count, results of viral load testing, current and previous antiretroviral therapy, and results of any already available genotypic or phenotypic viral resistance testing should be collected for consideration in choosing the most appropriate PEP regimen. If this information is not immediately available, initiation of PEP, if indicated, should not be delayed; changes in the PEP regimen can be made after PEP has been started, as appropriate.

   - If genotypic or phenotypic viral resistance tests are not already available, they should not be performed.

2. **Source patient serostatus unknown**

    PEP considered

    Inform the source patient and ask for informed consent to HIV testing.

    - Efforts should be made to assure “immediate” results in order to prevent unnecessary initiation of PEP.

    - Rapid HIV-antibody test could be useful for the diagnosis of HIV infection in the source patient, facilitating the prompt beginning of PEP in the exposed HCW and limiting unnecessary treatment.

3. **Source patient who denies his/her consent to HIV test**

    PEP considered

    Consider the likelihood of HIV infection in the source:

    - risk behaviors
    - results of previous laboratory investigations
    - clinical symptoms (e.g. acute syndrome suggestive of primary infection or undiagnosed immunodeficiency disease)
4. **Source patient unknown or who cannot be tested**

   PEP considered

   Consider the likelihood of HIV infection in the possible source:
   - prevalence of HIV infection on a specific unit

5. **Source patient HIV-seronegative**

   PEP discouraged

   In the absence of clinical or epidemiological likelihood of HIV infection in the source patient, p24 HIV antigen testing or biomolecular analyses are not recommended.

**Timing of PEP**

PEP should be initiated as soon as possible following an occupational exposure.

The time interval from exposure after which PEP should be discouraged is 72 hours.

**Duration of PEP**

PEP should be administered for 4 weeks.

**PEP What?**

Any combination of antiretrovirals approved for the treatment of HIV-infected patients can be used in PEP regimens.

- **Triple combination therapy is recommended** as first line PEP regimen.

Suggested first-choice treatment (i.e. start kits) in case of exposure to a source patient with unknown HIV serostatus, or HIV-positive but never treated

- 2 NRTI + 1 PI or 1 NNRTI
- i.e. ZDV/3TC (Combivir) + NFV or EFV
• Dual NRTI combination therapy could be considered an option on a case-by-case evaluation (i.e. pregnancy).

• Nevirapine is not indicated for a full course of PEP because of the reported severe hepatotoxicity, and could be considered only if no other choice exists. An initial single dose of Nevirapine could be considered, on a case-by-case evaluation.

• Zidovudine (ZDV) is the only drug to date for which there is evidence of a reduction of risk of HIV transmission following occupational exposure. It is reasonable that ZDV is included in all first line PEP treatments, if not otherwise contraindicated (i.e. resistance in the source patient).

• A simplified regimen should be used whenever possible, in order to increase adherence.

• If constitutional adverse reactions are reported which could be controlled through the administration of symptomatic drugs, this could enhance adherence to the prescribed regimen, with the ultimate goal of achieving treatment completion in the exposed HCW.

• Any information available in the source patient’s medical record and history taking about previous and current antiretroviral treatment may be important in the choice of PEP regimen. Consider the possibility that the virus may be antiretroviral resistant:
  - prolonged treatment with any antiretroviral
  - clinical progression of disease
  - persistently increasing viral load and/or a decline in CD4 T-cell
  - lack of virological response to a change in therapy
  - antiretroviral drug profiling (i.e., genotypic or phenotypic viral resistance tests), if available

• *Ad hoc* genotypic and/or phenotypic resistance tests are not recommended.

• When prescribing PEP, check for:
  - any existing medical conditions and any medications (auto-medication, drugs) an exposed HCW may be taking, in order to prevent toxicity and drug interactions.
**PEP in pregnancy**

- Women should be asked about the possibility of pregnancy
- If pregnancy cannot be excluded, a pregnancy test should be performed
- Pregnancy *per se* should not preclude the use of HIV PEP
- The decision to use PEP during pregnancy should involve discussion with the exposed HCW regarding the risk of HIV infection, the risk of transmission to her baby, and the potential benefits and potential risks for her and her baby, in order to help her reach an informed personal decision about the use of PEP.
- Because teratogenic effects were observed in primates after drug exposures similar to those representing human therapeutic exposure, the use of *efavirenz* should be avoided in pregnant women.
- Recent reports of fatal and nonfatal lactic acidosis in pregnant women treated throughout gestation with a combination of *d4T* and *ddI* have prompted warnings about the use of these drugs during pregnancy.
- *Indinavir* is associated with hyperbilirubinemia and it should not be administered shortly before delivery.

**Follow-up**

All HCWs occupationally exposed to HIV should receive follow-up counseling, post-exposure testing and medical evaluation regardless of whether they have received PEP or not.

**Toxicity monitoring:**

Regular medical follow-up during PEP treatment is necessary to monitor acceptability and possible toxicity of drugs, according to toxic profiles of the drugs included in the PEP regimen.

Routine laboratory tests could be performed on a case-by-case basis. Complete blood cell count, ALT, AST, creatinine, glucose, amylase blood levels and urine test could be performed at baseline and thereafter at 15 days, and, only if altered, at 30 days.

**HIV serological follow-up:**

HIV testing should be performed shortly after exposure and thereafter at 6 weeks, 3 and 6 months. The routine use of direct virus assay (HIV p 24 antigen or tests for HIV-RNA) to detect infection in exposed HCW is not recommended.
Visits and clinical evaluation are recommended at 6 weeks, 3 and 6 months, and in the case of development of signs/symptoms. Patients should be strongly encouraged to promptly report signs/symptoms, and should be counseled in order to prevent secondary transmission during the follow-up period.

Management of occupational HIV infection and of PEP failure

Therapy for primary HIV infection is based on theoretical considerations, and the potential benefits should be weighed against the potential risks. Therefore, in case of seroconversion, the infected HCW should be immediately referred to a specialist in the management of HIV infection. Any case of PEP failure should be thoroughly investigated, in order to avoid misclassification and to gather important information that could be beneficial to others. Standardized mechanisms for the prompt reporting of cases of HIV infection despite PEP should be implemented to support the epidemiological as well as clinical management of cases.

[inserire link a EUROPEPform.pdf]
[inserire link a FollowUpEUROPEPform.pdf]
European Recommendations for the Management of Health Care Workers Occupationally Exposed to Hepatitis B Virus and Hepatitis C Virus

November 2002
This is a document from the European Project on
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DEFINITIONS

Health care worker (HCW) is defined as a person whose activities involve contact with patients, or with blood or other body materials from patients, in a health-care or laboratory setting.

Occupational exposure is defined as any at-risk accidental exposure to at-risk body materials during working activity.

1) GENERAL POLICIES

Exposure prevention is the primary strategy to reduce the risk of occupational bloodborne pathogen infections. All preventive efforts should be made to reduce the risk of occupational exposures. Health care organizations should have a system readily available to their personnel that includes educational programs, written protocols for prompt reporting, evaluation, counselling, treatment, and follow-up of occupational exposures that might place HCWs at risk of acquiring a bloodborne infection.

1.a Educational programs and training

All HCWs should be informed, educated and trained about:

- The possible risks and prevention of bloodborne infections after an occupational exposure
- The measures to prevent bloodborne pathogen exposures
  - Implementation of standard precautions
  - Provision of personal protective equipment and safety devices
  - Implementation of safer procedures.
  - Hepatitis B (HBV) vaccination
- The principles of post-exposure management and the importance of seeking urgent advice following any occupational exposure immediately after it occurs, as certain indicated interventions [Hepatitis B Immunoglobulins (HBIG), hepatitis B vaccine, and HIV Post-Exposure Prophylaxis (PEP)] must be initiated promptly to maximize their effectiveness.

1.b Reporting an occupational exposure

Every health authority should have designated health care providers to whom HCWs can be urgently referred to in case of exposure.
Local health policies should specifically identify who will be responsible for the management of occupational exposures, for the provision of PEP and for clinical and serological post-exposure follow-up.

HCWs should be made aware in advance of the medico-legal and clinical relevance of reporting an occupational exposure.

Access to clinicians who can provide post-exposure care should be available during all working hours, including nights and weekends.

All HCWs should be aware of how to report an exposure and to whom it should be reported to, and have ready access to expert consultants to receive appropriate counselling, treatment and follow-up.

2) HEPATITIS B VACCINATION

- HCWs should be vaccinated against hepatitis B, with a standard vaccination schedule.
- Before entering nursing and medical schools and before employment in health care settings, vaccination or demonstration of immunization against hepatitis B virus is strongly recommended.
- Pre-vaccination screening is not routinely indicated.
- HCWs should be tested for antibody title against HBsAg (anti-HBs) 1-2 months after completion of a 3-dose vaccination series.
- New vaccines or alternative schedules that could determine a higher response rate or a stronger response should be used if available.

2.a Definitions

Primary 3-dose vaccination: three standard doses (according to manufacturers) of recombinant hepatitis B vaccine administered intramuscularly in the deltoid region at 0, 1, and 6 months.

Responders: subjects with post-vaccinal anti-HBs levels, determined at 1-2 months from the last dose of vaccine, equal to or greater than 10 mIU/mL.

Non responders: subjects with post-vaccinal anti-HBs levels, determined at 1-2 months from the last dose of vaccine, lower than 10 mIU/mL.
A minority of the expert panel suggests a more conservative approach, in which those HCWs who have post-vaccinal anti-HBs levels between 10 and 100 mIU/mL are considered as low-responders or hypo-responders. For these subjects, the same recommendations used for non-responders could be applied.

2. Post-vaccination management

HBV vaccination responders (anti-HBs ≥10 mIU/mL):
- Subjects considered as responders are protected against HBV infection.
- Routine booster doses of hepatitis B vaccine are not recommended for known responders, even if anti-HBs levels become low or undetectable.
- Periodic antibody concentration testing after completion of the vaccine series and assessment of the response is not recommended.

HBV vaccination non responders (anti-HBs <10 mIU/mL)
- 5-10% of the adult population will not respond to standard hepatitis B vaccination.
- Risk factors for vaccine non response include: male gender, older age, cigarette smoking, obesity, immunodeficiency, renal failure, intragluteal vaccine administration, and certain HLA haplotypes.
- Persons who do not respond to the primary vaccine series should be tested for HBsAg, and anti-HBc [see section 2c].
  If HBsAg/anti-HBc negative:
  - A 4th dose should be administered and then the HCW should be retested for response 1-2 months later;
  - If no response has been elicited, a full-course of conventional vaccine at the standard doses should be completed (i.e. a 5th and 6th dose should be administered), and HCWs should be then retested for response again 1-2 months after the last dose of vaccine.
  - Possible alternative strategies to overcome non response to standard HBV vaccination are:
    o Vaccines containing S subunit, pre-S1 and pre-S2 particles
    o Three intradermal 5 μg doses of standard vaccine, given every two weeks
    o Combined hepatitis A and hepatitis B vaccines
    o High-dose standard vaccine series
Non responders to vaccinations who are HBsAg-negative should be considered susceptible to HBV infection and should be counselled regarding precautions to prevent HBV infection and the need to obtain HBIG prophylaxis for any known or probable exposure to HBsAg-positive blood.

**HCWs with HCV infection or other liver diseases**

More severe hepatic injuries, with higher fatality rates, have been reported in subjects superinfected with HBV-HAV or HBV-HCV, or with chronic HCV hepatitis co-infected with HBV or HAV. Combined hepatitis A and hepatitis B vaccine is suggested in case of susceptible HCWs with HCV infection or other liver diseases.

**HCWs who are HBsAg-positive**

Persons who prove to be HBsAg-positive should be counselled regarding prevention of HBV transmission to others and regarding the need for medical evaluation.

2.c Management of isolate anti-HBc

- Isolated anti-HBc positive HCWs should be tested for IgM anti-HBc and HBV-DNA, possibly with sensitive PCR assays, to determine whether these subjects are low-level HBsAg carriers and in the window phase or not.

- If negative for IgM anti-HBc and HBV-DNA, anti-HBs response to vaccination can distinguish between:
  
  o anamnestic response: subjects who are infected with HBV (anti-HBs titre exceeding or equal to 50 mIU/mL 30 days after the 1\textsuperscript{st} dose of vaccine)
  
  o primary response: subjects who have false positive results (anti-HBs titre exceeding or equal to 10 mIU/mL 30 days after the 3\textsuperscript{rd} dose of vaccine).

- True positive subjects with isolated anti-HBc (those with anamnestic response) have resistance to HBV re-infection and do not need vaccination or HBV PEP.

- In case of an exposure to an HBsAg positive source, subjects with “unresolved” isolate anti-HBc should be managed as susceptible.
3) MANAGEMENT OF OCCUPATIONAL EXPOSURES

3.a Immediate treatment of the exposure site

- Percutaneous exposure: encourage bleeding and wash with soap and water
- Cutaneous contaminations: wash with soap and water.
- Mucous membranes contamination: flush with water.
- Eyes should be irrigated with clean water, saline, or sterile irrigants.
- Although no evidence exists that using antiseptics/disinfectants reduces the risk of bloodborne pathogen transmission, their use is not contraindicated. In fact, relatively little is known about the inactivation of HBV and HCV by chemical germicides, because of the absence of available means to directly detect and quantify infectious virus particles. However, both viruses are enveloped and are supposed to be relatively sensitive to many chemical agents. Between topical products, widespread used products such as chlorhexidine gluconate or povidone iodine in infection control suggests that they should be examined for activity against HBV and HCV, even if their concentration is lower than in surface or medical device disinfectants.
- The application of caustic agents (i.e. bleach) or the injection of antiseptics or disinfectants onto the wounds is not recommended.

3.b Risk assessment

A) Evaluation of the exposure

The exposure should be evaluated for the potential to transmit HBV, HCV, and HIV, based on the type of exposure and the type of body material involved.

**At risk exposures:**

1. percutaneous injury
2. contamination of mucous membranes including the eyes, and non intact skin
3. injury by human bite resulting in an open wound

**At risk materials:**

1. blood, body materials containing visible blood
2. semen; vaginal secretions; cerebrospinal fluid, synovial, pleural, peritoneal, pericardial, or amniotic fluid, and tissues.
3. concentrated viruses in a research laboratory or production facility
B) Evaluation of the infectious status of the source patient

− Any report of an occupational exposure should be followed by the evaluation of HBV susceptibility in the exposed HCW, or the initiation of hepatitis B vaccination, if necessary, regardless of the source patient’s serostatus.

− The source patient’s serostatus for the presence of HIV antibody, HCV antibody, and HBsAg should be obtained.

− If the HBV, HCV, and HIV infection status of the source is unknown, the source person should be informed of the incident and an informed consent should be obtained in order to test for serologic evidence of bloodborne virus infection. Testing the source patient for HBsAg can be avoided in cases where the HCW is known to be protected by vaccine or natural immunity.

− Testing to determine the HBV, HCV, and HIV infection status of the source patient should be performed, with consent, and results should be readily available (immediately for HIV).

− Direct virus assays (e.g. HIV p 24 antigen, tests for HIV-RNA, HBV-DNA or HCV-RNA/HCV Ag) for routine screening of the source patient are not recommended.

− Qualitative HCV-RNA may be useful when there is immunosuppression or another condition (e.g. renal dialysis, infection with HIV, etc.) associated with the possibility of a false-negative HCV antibody result in the source.

− A source patient who does not consent to be tested after an HCW’s occupational exposure or a source patient unknown or who cannot be tested should be considered infected.

C) Evaluation of the susceptibility of the exposed HCW

− In case of an occupational exposure to an at risk bloodborne infection, baseline HBV, HCV, HIV immune status of the exposed HCW should be available.

− HCWs are considered susceptible to hepatitis B infection when tested negative for HBsAg, anti-HBc and anti-HBs level is <10 mIU/mL.

3.A.1 MANAGEMENT OF EXPOSURES TO HBV

The management of a possible occupational exposure to HBV differs according to the susceptibility and serostatus of the exposed HCW

When necessary, post-exposure prophylaxis with HBV vaccine, HBIG or both must be started as soon as possible, preferably within 24 hours from the exposure and no later than one week.
No data directly assess the efficacy of HBIG in post-exposure prophylaxis in HCW, however, the vast majority of the expert panel agrees about HBIG administration.

1) **Source patient HBsAg-positive**

   a) **HCW not vaccinated for hepatitis B virus**

   - Test for anti-HBs (obtain a rapid response)
     
     Ideally, in those subjects testing anti-HBs negative, testing for anti-HBc would avoid HBIG administration if the subject has natural immunity.
     
     - If anti-HBs < 10 mIU/mL, administer HBIG (0.06 ml/kg) as soon as possible after the exposure and repeat after 1 month.

   The expert panel was divided about the administration of the 2nd dose of HBIG, assuming that a protective response would be elicited after the first 3 doses of vaccine during the accelerated vaccination schedule.

   - Start the accelerated vaccination schedule as soon as possible and at 1, 2, and 12 months. Hepatitis B vaccine can be administered intramuscularly simultaneously with HBIG at a separate site (vaccine should always be administered in the deltoid muscle)
   
     - Test for anti-HBs at 1-2 months from the last dose to assess the response.

   b) **HCW incompletely vaccinated or who does not recall a complete vaccination schedule**

   Test for anti-HBs (obtain a rapid response)

   - If anti-HBs level < 10 mIU/mL, administer HBIG (0.06 ml/kg) as soon as possible, and complete the vaccination schedule according to available documentation, otherwise restart with an accelerated vaccination schedule at 0, 1, 2, and 12 months.
   
     - Test for anti-HBs (at 1-2 months after the last dose) to assess the response.

   c) **HCW previously vaccinated with an unknown antibody response**

   - Test for anti-HBs (obtain a rapid response)
     
     - If adequate, no treatment.
     
     - If inadequate, administer vaccine booster as soon as possible and one dose of HBIG.

   A minority of the expert panel would not administer HBIG in view of the high probability of the subject being responder.

   - Test for anti-HBs (at 1-2 months after the last dose) to assess the response
d) HCW non responder to primary vaccination
   - Administer one dose of HBIG (0.06 ml/kg) as soon as possible after the exposure
   A minority of the expert panel would not administer HBIG in view of the high probability of the subject being responder.
   - and a 2\textsuperscript{nd} dose of HBIG after 1 month
   The expert panel was divided about the administration of the 2\textsuperscript{nd} dose of HBIG, assuming that a protective response would be elicited after the first 3 doses of vaccine during the accelerated vaccination schedule.
   - Initiate hepatitis B vaccination as soon as possible after exposure, with an “accelerated” vaccination schedule at 0, 1, 2, and 12 months.
   - Test for anti-HBs (at 1-2 months after the last dose) to assess the response.

e) HCW previously vaccinated with 4 doses of vaccine or with two complete vaccine series but non responder (anti-HBs <10 mlU/mL)
   - Administer one dose of HBIG (0.06 ml/kg) as soon as possible after the exposure and a 2\textsuperscript{nd} dose of HBIG after 1 month
   - Possible use of an alternative vaccine.

f) HCW previously vaccinated and known responder (anti-HBs >10 mlU/mL)
   - No treatment

A more conservative approach suggested by part of the expert panel is as follows:
   - Test for anti-HBs (Considered)
     o If adequate, no treatment.
     o If inadequate, administer one dose of vaccine booster.

2) Source patient HBsAg-negative
   a) HCW not vaccinated for hepatitis B virus
      - Initiate hepatitis B vaccination according to the standard schedule.
      - Test for anti-HBs (at 1-2 months after the last dose) to assess the response.

   b) HCW incompletely vaccinated
      - complete the vaccination schedule according to available documentation, otherwise restart with a standard vaccination schedule.
      - Test for anti-HBs (at 1-2 months after the last dose) to assess the response.
c) **HCW previously vaccinated with unknown antibody response**
   - Test for anti-HBs antibodies
   - If anti-HBs level is < 10 mIU/mL, administer a booster dose of vaccine and retest for anti-HBs level after 1-2 months.
   - If still < 10 mIU/mL complete as a 2nd standard vaccination schedule.
   - Test for anti-HBs antibodies level after 1-2 months from the last dose of vaccine.

d) **HCW non responder to primary vaccination**
   - Repeat a complete standard vaccination schedule.
   - Test for anti-HBs antibodies level after 1-2 months from the last dose of vaccine.

e) **HCW previously vaccinated with 4 doses of vaccine or with two complete vaccine series, but non responder (anti-HBs <10 mlU/mL)**
   - Possible use of an alternative vaccine

f) **HCW previously vaccinated and known responder (anti-HBs >10 mlU/mL)**
   - No treatment.

3) **Source patient cannot be tested or serostatus unknown**
   - Treat as if the source were HBsAg-positive
   - A minority of the expert panel would consider the option of HBIG administration according to the probability of infection of source patient (e.g: drug user, coming from high endemicity country, etc.)

4) **HCW HBsAg –positive**
   - Clinical evaluation
   - Test for HDV

3.A.2 FOLLOW UP
In general, the serological follow-up of HCWs reporting an occupational exposure to HBV is not recommended when post-exposure has been managed according to the above mentioned recommendations.
However, for medico-legal reasons it could be appropriate to store a baseline blood sample or to test the HCW for HBsAg at baseline and after 6 months from the exposure.
3.B MANAGEMENT OF EXPOSURES TO HCV

Currently, there is no available prophylaxis for HCV: IG and antiviral agents are not recommended as prophylaxis after exposure to an HCV-positive source patient. Data from the literature suggest that therapy (IFN or PegIFN +/-Ribavirin) may prevent chronic HCV infection when administered to patients with acute HCV infection. However, while it is documented that viral clearance can spontaneously occur after acute infection, it is not clear whether treatment of the acute phase or during the first 6 months from infection is more effective than an early treatment of chronic hepatitis C.

Management of occupational exposure to HCV therefore depends on whether the early treatment of HCV infection is recommended or not (i.e. during acute symptomatic infection or during the first 6 months from infection).

Source patient anti-HCV positive

A) Treatment of acute HCV infection recommended
   – HCW should be advised to report any symptoms or signs suggestive of acute HCV infection
   – HCW should be counselled on how to avoid HCV transmission to others
   – Store a baseline blood sample of the exposed HCW
   – Test the HCW for anti-HCV antibodies (EIA) at baseline and at 6 months after the exposure. Positive results should be confirmed with a recombinant immunoblot assay or qualitative HCV-RNA.
   – Perform ALT activity at baseline, and then once a month for 4 months after exposure.
   – Qualitative HCV-RNA should be performed when an increased transaminase level is detected.
   – Extend follow-up to 12th month for any exposure to an HIV-HCV co-infected source.

A minority of the expert panel would perform anti-HCV antibodies also at 3 months as most seroconverters are already positive at 3 months, and in order to reduce loss to follow-up and the anxiety of the exposed HCW.

B) No treatment of acute HCV infection recommended
   – HCW should be advised to report any symptoms or signs suggestive of acute HCV infection
   – HCW should be counselled on how to avoid HCV transmission to others
   – Store a baseline blood sample of the exposed HCW.
– Test the HCW for anti-HCV antibody (EIA) at baseline and at 6 months after exposure. No other tests are recommended.
– Positive results should be confirmed with a recombinant immunoblot assay or qualitative HCV RNA.
– Extend follow-up to 12 months for any exposure to an HIV- HCV co-infected source

**Source patient anti-HCV negative**

– For medico-legal reasons, store a blood sample and/or test the HCW for anti-HCV antibody at baseline.
– In case of HIV infection, immunosuppression or other conditions (i.e. dialysis) associated with possible false negative results in the source, test the source for HCV RNA.
  o If positive, follow recommendations for exposure to an HCV positive source
  o If negative, no HCW follow up

**Source patient cannot be tested or serostatus unknown**

– Consider as anti-HCV positive
Management of post-exposure prophylaxis after occupational exposure to HIV in healthcare workers in Europe

Background: Although preventing exposure is the primary means of preventing HIV infection, post-exposure prophylaxis (PEP) with antiretroviral therapy is the recommended standard of care for the effective management of occupational exposure to HIV in HCWs. However, no general consensus exists on some issues.

In September 2001, the European Commission funded a project to evaluate and standardise the management of occupational PEP in Europe.

Objective: To assess current policies and activities on the management of occupational exposures and PEP in European countries.

Methods: Seven countries participated in the project: Italy (as the coordinating centre), Denmark, France, Germany, Portugal, Spain, and the United Kingdom. Croatia and Switzerland, shared the same aims of the project and have actively contributed to it, without being formally enrolled.

The coordinating centre requested the participating member countries to send national guidelines and recommendations, written protocols, local bulletins, published data or presentations from national/international conferences, and any other documents relevant to occupational exposures to HIV in HCWs and antiretroviral PEP in order to define the state-of-the-art.

Representatives of the participating countries were also asked to fill an ad-hoc structured questionnaire, developed in order to assess current protocols and policies, management and data on occupational exposure to HIV and other bloodborne pathogens in HCWs and antiretroviral PEP. The questionnaires were reviewed and entered into a database at the coordinating centre to compare the results within the different participating countries. The edited questionnaire were then sent to the representatives for revision and approval.

Current Guidelines and Registry for Post-Exposure Prophylaxis

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<td>ITALY</td>
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<tr>
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<tr>
<td>PORTUGAL</td>
<td>72 HOURS (HIGH RISK PEP)</td>
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<tr>
<td>SWITZERLAND</td>
<td>72 HOURS (EXCEPTIONS FOR HIGH RISK)</td>
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<tr>
<td>SPAIN</td>
<td>72 HOURS (HIGH RISK PEP)</td>
</tr>
<tr>
<td>UK</td>
<td>ASAP (HIGH RISK PEP UP TO 2 WEEKS)</td>
</tr>
</tbody>
</table>

Which type of PEP do you recommend?

- NRTI
- NNRTI
- NNRTI-including triple combination therapy

Genotypic Resistance Tests in the Source After An Occupational Exposure

- * Not recommended, but choice of the PEP regimen is based on the patient's previous ART and on the genotypic resistance test.
- ** Not recommended, but sometimes performed.

HIV Testing of the Exposed HCW During Follow up

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<td>UK</td>
<td>180 days</td>
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Which risk factors are considered when choosing triple PEP regimen?

- Age
- Month
- Year
- Sex
- Occupation
- Route of exposure
- Viral load
- Time to onset of symptoms
- HIV-RNA
- Other co-morbidities

Standardization of Management of Occupational Exposure to HIV Bloodborne Infections and Evaluation of Post-Exposure Prophylaxis in Europe

European Project number SI2.32294

Coordinating centre: NMI L. Spallanzani, Rome - Italy

<table>
<thead>
<tr>
<th>PROJECT LEADER:</th>
<th>Guido Ippolito</th>
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<tbody>
<tr>
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<tr>
<td>PROJECT COORDINATOR</td>
<td>Stefano Di Mario</td>
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<tr>
<td>DATA MANAGER:</td>
<td>Francesca Melotti</td>
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<td>DATA COLLECTOR:</td>
<td>Ilaria Rosati, Piero Fasano</td>
</tr>
<tr>
<td>SECRETARIAL SUPPORT:</td>
<td>Mariagrazia Angius, Yolanda Alvarez</td>
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Representatives

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<th>Country</th>
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CONCLUSIONS: Occupational PEP is widely prescribed in European countries, although differing in several aspects:

- Uniform guidelines should be developed to implement a rapid risk assessment, optimize availability and management, and minimize unnecessary treatments and related toxicity and costs.
Proposed European Recommendations for Post-Exposure Prophylaxis against HIV Infection in Healthcare Workers

Background and Objective

- Public Health Agencies in European countries issued recommendations for the use of post-exposure prophylaxis (PEP) in HIV-exposed healthcare workers (HCWs).
- However, management of occupational HIV PEP varies among European countries (see poster Lb0r01A), and several issues remain controversial.
- In September 2003, the European Commission funded a project, coordinated by Italy, to standardise the management of occupational HIV PEP in Europe. Nine countries participated in the project.

Methods

- In January 2004, during a 2-day consensus meeting, expert representatives from participating countries, reviewed and discussed available National recommendations and policies, data from local surveillance programs and current literature.
- Identified issues and controversies, existing guidelines and scientific and evidence regarding the main issues in this field were analysed.
- A proposal for European recommendations on PEP against HIV infection in HCWs was presented and discussed in detail during the meeting, to reach a consensus document.
- Edited recommendations have been sent for review to all representatives of the EuroPEP Project for approval before being distributed.

Conclusions

- A standardised management of PEP in European countries and the implementation of an European Registry could effectively:
  - Increase our understanding of efficacy and toxicity of antiretroviral drugs.
  - optimise the use of available resources to reduce the risk of HIV infection.
  - Improve occupational safety in the healthcare setting.

General Recommendations

- All efforts should be made to prevent occupational exposure.
- Every health authority should identify designated health care providers to whom HCW can be urgently referred to in case of occupational exposure.
- All HCWs should be made aware of how to report an exposure and to whom it should be reported.
- The availability of PEP should be publicly advertised in order that it may be immediately and readily accessible and initiated as soon as possible following an occupational exposure.
- The issue of PEP should be evaluated on the basis of the type of exposure, the body material involved, and the source patient’s evaluation.

Recommendations According to exposure

- Percutaneous injury
- Exposure of mucous membrane
- Exposure of non-intact skin
- Exposure of intact skin

According to material

- Blood
- Body materials containing visible blood
- Concentrated virus in a research lab, or production facility
- semen; vaginal secretions; synovial, pleural, peritoneal, pericardial, or amniotic fluid, and tissues
- Urine, vomit, saliva, faeces, tears, sweat, sputum

According to source patient

- Known to be HIV-infected
- Suspected HIV-infected
- Serostatus unknown
- Serology unknown
- Serology unknown
- Unknown or who cannot be tested
- HIV-negative

PEP Regimen

- Any combination of antiretrovirals approved for the treatment of HIV-infected patients can be used.
- Triple therapy (i.e. 2 NRTI + 1 PI or 1 NRTI) is recommended as a first line PEP regimen.
- Tenofovir is not indicated for a full course of PEP because of the reported severe hepatotoxicity.
- When prescribing PEP, check for any existing medical conditions and any medications (auto-medication, drug) an exposed HCW may be taking, in order to prevent toxicity and drug interactions.
- Drug adherence and tolerability should be monitored.
- Ad hoc genotypic and/or phenotypic resistance tests are not recommended.

Monitoring Recommendations

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<th>I.V. pr</th>
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<td>Ritonavir</td>
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Recommeneded standard initial regimen

Zidovudine 300 mg bid + lamivudine 150 mg po bid (or Combivir 3 bid)
Plus Nevirapine 250 mg bid

The routine use of direct virus assay (HIV p24 antigen or tests for HIV-RNA) to detect infection in exposed HCW is not recommended.
* Complete blood cell count, ALT, AST, creatinine, glucose, any baseline levels and urine test

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<td>ISTITUTO NAZIONALE PER LE MALATTIE INFETTIVE</td>
<td>Italy</td>
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<tr>
<td>Giuseppe Ippolito</td>
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