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PROPOSED RECOMMENDATIONS FOR THE MANAGEMENT OF HIV POST-EXPOSURE PROPHYLAXIS AFTER SEXUAL, INJECTING DRUG OR OTHER EXPOSURES IN EUROPE

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Post-exposure prophylaxis (PEP) is the standard of care for a healthcare worker (HCW) accidentally exposed to an HIV infected source person (occupational exposure), but this is not the case for non-occupational exposures. Very few national guidelines exist for the management of non-occupational exposures to HIV in Europe, contrarily to the occupational ones. The administration of non-occupational post-exposure prophylaxis (NONOPEP) for HIV may be justified by: a biological plausibility, the effectiveness of PEP in animal studies and occupational exposures in humans, efficacy in the prevention of mother to child HIV transmission, and cost effectiveness studies. These evidences, the similar risk of HIV transmission for certain non-occupational exposures to occupational ones, and the conflicting information about attitudes and practices among physicians on NONOPEP led to the proposal of these European recommendations. Participant members of the European project on HIV NONOPEP, funded by the European Commission, and acknowledged as experts in bloodborne pathogen transmission and prevention, met from December 2000 to December 2002 at three formal meetings and a two day workshop for a literature review on risk exposure assessment and the development of the European recommendations for the management of HIV NONOPEP.

NONOPEP is recommended in unprotected receptive anal sex and needle or syringe exchange when the source person is known as HIV positive or from a population group with high HIV prevalence. Any combination of drugs available for HIV infected patients can be used as PEP and the simplest and least toxic regimens are to be preferred. PEP should be given within 72 hours from the time of exposure, starting as early as possible and lasting four weeks. All patients should receive medical evaluation including HIV antibody tests, drug toxicity monitoring and counseling periodically for at least 6 months after the exposure.

NONOPEP seems to be a both feasible and frequent clinical practice in Europe. Recommendations for its management have been achieved by consensus, but some remain controversial, and they should be updated periodically. NONOPEP should never be considered as a primary prevention strategy and the final decision for prescription must be made on the basis of the patient-physician relationship. Finally, a surveillance system for these cases will be useful to monitor NONOPEP practices in Europe.

Introduction

Post-exposure prophylaxis (PEP) is the standard of care for a healthcare worker (HCW) accidentally exposed to an HIV infected source person (occupational exposure), but this is not the case for non-occupational exposures. Very few national guidelines exist for the management of non-occupational exposures to HIV in Europe, contrarily to the occupational ones. The administration of non-occupational post-exposure prophylaxis (NONOPEP) for HIV may be justified by: a biological plausibility, the effectiveness of PEP in animal studies and occupational exposures in humans, efficacy in the prevention of mother to child HIV transmission, and cost effectiveness studies. These evidences, the similar risk of HIV transmission for certain non-occupational exposures to occupational ones, and the conflicting information about attitudes and practices among physicians on NONOPEP led to the proposal of these European recommendations. Participant members of the European project on HIV NONOPEP, funded by the European Commission, and acknowledged as experts in bloodborne pathogen transmission and prevention, met from December 2000 to December 2002 at three formal meetings and a two day workshop for a literature review on risk exposure assessment and the development of the European recommendations for the management of HIV NONOPEP.

Post-exposure prophylaxis (PEP) is now the standard of care when a healthcare worker (HCW) is accidentally exposed to a source person known to be infected with HIV (occupational exposure), but this is not the case for non-occupational exposures.

We considered as non-occupational exposure all accidental and sporadic incidents in which contact with blood or other body fluids (semen, vaginal secretions, etc.) that pose a potential risk for HIV infection occurred, excluding exposures of HCWs in a healthcare or laboratory setting. Non-occupational exposure includes unprotected sexual exposure, sexual exposure involving a broken or slipped condom, injecting drug users (IDUs) sharing equipment, accidental needlestick injuries, bite wounds, mucosal exposure, etc. Exposure to tears or sweat is not considered to be a risk for HIV transmission.

Although there have been no prospective controlled trials or retrospective case-control studies to support its potential efficacy, non-occupational post-exposure prophylaxis (NONOPEP) is used increasingly frequently. Faced with a request for NONOPEP for HIV, physicians must deal with several questions such as the magnitude of the risk of the exposure or whether or not to prescribe antiretroviral therapy (ART). NONOPEP demand is not negligible in Europe [1-3], nor is it in other parts of the world [4-8]. Several questions regarding the prescription of NONOPEP remain unanswered, however, including which combination of antiretrovirals to choose, the duration of the follow up, and which laboratory tests are necessary.

Curiously, guidelines for the management of occupational HIV exposures exist in the United States and in most European countries; yet very few national guidelines for the management of possible sexual, injecting drug use, or other non-occupational exposures to HIV have been developed in Europe [9].

Background

Several factors justify the administration of NONOPEP:

- 1- The biological plausibility of NONOPEP for preventing HIV infection.
- 2- Scientific literature on the effectiveness of the ART used for post-exposure prophylaxis in animals and occupational exposures in humans.
- 3- Efficacy studies on the prevention of mother to child HIV transmission.
- 4- Studies on cost effectiveness and cost benefit of HIV post-exposure prophylaxis.

1. One of the characteristics regarding the pathogenesis of HIV infection is the period of time between the HIV exposure and the replication of the virus in the lymph nodes [10]. Immediately after HIV exposure, there is an infection of dendritic cells at the site of the inoculation. These infected cells will migrate to the regional lymph nodes during the first 24-48 hours [11]. The beginning of HIV systemic infection is marked by the settlement of the infected dendritic cells in the lymph nodes. In theory, administering ART as a prophylaxis during this period and before the lymph node settlement could prevent the establishment of a systemic infection.

2. The results of different animal studies have shown plausibility in preventing HIV infection, by administering ART after an exposure to HIV [12]. In 1995, the results of a study showing the prevention of SIV infection in macaques were published. Administering an antiretroviral compound (PMPA (tenofovir)) 24 hours after virus inoculation, for four weeks, prevented SIV infection in all of the macaques. Protection was incomplete if tenofovir was administered at 48 or 72 hours after the exposure, or if the duration of treatment was 3 or 10 days only. This suggests that the earlier ART is given, the more effective the prevention [13]. In 2000, Otten et al published data from a study in which macaques received an atraumatic intravaginal inoculum of HIV-2. One group of macaques did not receive ART, the second group received tenofovir 12 hours after the exposure, the third at 36 hours, and the fourth at 72 hours. In the first group, all but one of the macaques became infected. None of the macaques from the second and third group became infected, and one in three macaques in the fourth group became infected after 16 weeks. These data confirm that the time elapse between the exposure and the beginning of ART is an important factor which can affect NONOPEP efficacy, and support the need for an adequate follow up period after NONOPEP to monitor for delayed seroconversions [14].

In a retrospective case-control study, AZT given after an occupational percutaneous exposure to a HCW was associated with an 81% decrease in the risk of HIV infection. Another issue raised by this study was the increase in the risk of acquiring HIV when some enhancing factor existed, such as the depth or extent of the injury, the presence of visible blood on the device, or an advanced

extent of the injury, the presence of visible blood on the device, or an advanced stage of HIV disease in the source person [15].

3. Data from human studies regarding the prevention of mother to child HIV transmission also support the probability of the efficacy of an HIV post-exposure prophylaxis. In a randomised trial, the administration of AZT to HIV infected pregnant women was associated with a 2/3rd reduction in HIV infections in babies whose mothers had been given AZT pre and intra partum (and who themselves had received AZT post partum) versus those randomised to placebo [16]. Despite contact between the child's blood and the HIV status of its mother, AZT prevented infection in the majority of cases.

4. In 1997, an article was published describing the cost effectiveness of tritherapy with zidovudine, lamivudine and indinavir following moderate to high risk occupational exposure [17]. Another cost effectiveness study on post-exposure prophylaxis following potential sexual HIV exposure in humans concluded that in the following cases PEP is cost effective: receptive anal sex when it is almost certain that the source person is infected, and receptive vaginal sex only when the source person is known to be HIV positive [18]. Assuming that it is not only cost effectiveness that can predominate in a public health decision, further studies are necessary.

The above mentioned studies encouraged us to propose and standardise this prophylaxis for non-occupational exposure, despite some difficulties, including the extrapolation of animal study data to humans, the specificity of the mother to child transmission, the difference between occupational and non occupational exposures, the difficulty of the risk assessment in non occupational exposure, the reports of PEP failures to prevent HIV infection after occupational exposure in at least 21 instances with different ART [19-23].

Another argument for introducing NONOPEP guidelines is the results of a French study in which the existence of NONOPEP recommendations at national level had an impact on physicians' behaviour, improving their acceptance of and attitude towards NONOPEP [24] and probably on their risk assessment. Furthermore, a survey about knowledge of, attitudes towards and practices of NONOPEP for HIV has been conducted among European physicians, as part of the same project that led to the present recommendations [25]. The results clearly showed that in the countries with national guidelines there were significantly more prescriptions made following requests for NONOPEP (76% versus 61%, $p=0.007$), as well as more antiretroviral emergency starter kits available (92% versus 44%, $p<0.001$). Similarly, the exposure risk assessment and the management of NONOPEP requests improved among this group of physicians in comparison with the group without national guidelines.

Finally, the probability of HIV transmission by certain non-occupational exposures is estimated to be higher than the risk of percutaneous occupational exposure. Furthermore, the characteristics of both situations - occupational and non-occupational - are different. In the case of occupational exposures, it is possible to start ART earlier, the HIV status of the source is usually known, and the follow up of the exposed person is more feasible. In the case of a non-occupational exposure, however, the time delay between exposure and ART initiation is frequently longer, the possibility of knowing the HIV status of the source person is lower, and the rate of lost-to-follow-up is higher, hence the need for specific guidelines for these non-occupational exposure situations.

Methods

In September 2001, the European Commission (Directorate-General for Health and Consumer Protection, (DG-SANCO)) funded a project on non-occupational post-exposure prophylaxis to HIV (Euro-NONOPEP Project - project number 2000CVG4-022), coordinated by the Centre d'Estudis Epidemiològics sobre la Sida de Catalunya (Center for Epidemiological Studies on HIV/AIDS of Catalonia, CEESCAT), with the participation of 14 European countries. One of the main objectives of this project was the development of the European recommendations regarding the management of HIV NONOPEP. In this perspective, the national representatives from each participant country were contacted and integrated into the project, on the basis that they were responsible for the national registry or multicentre group, or had been designated by national healthcare agencies. The representatives of participating member countries were acknowledged to be experts in the field of bloodborne pathogen transmission prevention and PEP.

A steering committee was established to take responsibility for the logistic and scientific aspects of the project, with participation of members from five of the participating countries (Spain, France, the United Kingdom, Italy and Belgium). Concerning the development of the European recommendations, the steering

committee members reviewed previous recommendations, risk assessment, possible prophylaxis regimens and their cost effectiveness, and shared and updated information at three meetings, in December 2000, June 2001 and December 2002. For this review, data from the published literature and abstracts from recent scientific conferences were taken into consideration.

Reviewed data were presented and discussed by representatives of all participant countries in the project during the first of a two day workshop on 19-20 October 2001. The national representatives were divided into two working groups, one to achieve consensus on the risk assessment of non-occupational post-exposure prophylaxis, and the other to achieve consensus on the treatment and clinical follow up protocols for non-occupational post-exposure prophylaxis. The results are presented in this paper.

Results and discussion

Literature review on risk exposure assessment.-

Table 1 shows the different risk estimates of HIV transmission by non-occupational exposures, according to a literature review. It is important to remember that these estimates of transmission are not absolute. Every risk exposure depends on the type of exposure, but also on cofactors such as follows: a) infectivity of the source, taken as a high plasma viral load, increases the risk of transmission in all cases [37]; b) genito-oral ulcers, sexually transmitted infections or bleeding increase the risk of transmission for a sexual exposure [34], and c) for accidental needlestick exposures, fresh blood, a deep injury or intravenous injection all increase the risk of HIV transmission [15].

TABLE 1

Summary of HIV transmission risk by type of non-occupational exposure

Type of exposure (from a source known to be HIV positive)	Risk of HIV transmission per exposure	Ref.
Accidental needlestick injury	0.2%-0.4%	[15]
Mucosal membrane exposure	0.1%	[26]
Receptive oral sex	From 0 to 0.04%	[27,28]
Insertive vaginal sex	≤ 0.1%	[29-32]
Insertive anal sex	≤ 0.1%	[29-32]
Receptive vaginal sex	0.01%-0.15 %	[29,31,33,34]
Receptive anal sex	≤ 3%	[28,32,34]
IDUs sharing needle	0.7%	[35]
Transfusion	90-100%	[36]

The figures of risk for the first type of accidental exposure in table 1 refer to accidental needlestick injuries in healthcare workers or healthcare setting, and can not be directly applied to accidents with abandoned needles.

Some of the reviewed articles in the literature about estimates on transmission risk of insertive vaginal and anal sex come from North America, where a high proportion of men are circumcised. Therefore the risk for uncircumcised men may be underestimated.

When the HIV status of the source person is unknown, the risk assessment is usually based on the type of exposure, on the estimated HIV prevalence in the source HIV group and/or the HIV prevalence in the source person's country of origin.

Recommendations

In general, physicians facing a request for non-occupational post-exposure prophylaxis to HIV should take the following steps:

1- Evaluate the HIV status and risk behaviour history of reported source of HIV exposure (person belonging to a high risk group for HIV or coming from a country with high HIV prevalence) and, if possible, test the source person for HIV antibodies.

2- Evaluate the risk for HIV transmission regarding the type of exposure, as well as the presence of factors that would increase the risk (e.g., use or non-use of a condom, details of the exposure as receptive or insertive intercourse, anal or vaginal intercourse, presence of visible genital ulcers for a sexual

anal or vaginal intercourse; presence or visible genital ulcers for a sexual exposure; number of persons sharing equipment for IDU; and depth of injury for any other needlestick exposure).

3- Determine the time elapsed between the exposure and the presentation for medical care before deciding to prescribe an antiretroviral therapy. PEP should be given within 72 hours from the time of exposure.

4- All patients should receive medical evaluation including testing for HIV antibodies at baseline and periodically for at least 6 months after the exposure, as well as testing for other bloodborne pathogens such as HBV and HCV, and for sexually transmitted infections (STIs) if indicated.

5- In the case of prescribing ART, treatment must start as early as possible. Drug toxicity monitoring should include a complete blood count, renal and hepatic chemical function tests at baseline, and again at least 6 weeks after the exposure.

6- For women sexually exposed to HIV, a pregnancy test must be undertaken, and the result taken into account before any prescription. Consult obstetricians or other experts in the care of HIV infection during pregnancy. Similarly, for children, consult specialist paediatrician in the care of HIV infection.

7- The exposed individual should be counselled to prevent additional exposure, and to improve ART adherence in the case of prescription.

8- NONOPEP should never be considered as a primary prevention strategy.

The indications of NONOPEP for sexual, IDU, needlestick and other exposures are shown in boxes 1 to 4 respectively, according to the criteria expressed by the consensus group. It should be stated that at-risk sexual exposures are 'unprotected intercourse', either without condom or with broken or slipped condom.

Box 1

Indications of NONOPEP for sexual exposures

1. HIV source person known as HIV positive

- | | |
|--|--------------------|
| • Receptive anal sex | PEP is Recommended |
| • Insertive anal sex | PEP is Considered |
| • Receptive vaginal sex | PEP is Considered |
| • Insertive vaginal sex | PEP is Considered |
| • Receptive oral sex with ejaculation | PEP is Considered |
| • Splash of sperm into eye | PEP is Considered |
| • Receptive oral sex without ejaculation | PEP is Discouraged |
| • Female to female sex | PEP is Discouraged |

In the case of rape or the existence of any **high risk factors** (for both, source person or exposed individual): high viral load of the source partner, menstruations, other bleeding during intercourse, genital ulcer, STI.

- | | |
|---------------------------------------|--------------------|
| • Insertive anal sex | PEP is Recommended |
| • Insertive vaginal sex | PEP is Recommended |
| • Receptive vaginal sex | PEP is Recommended |
| • Receptive Oral sex with ejaculation | PEP is Recommended |
| • Female to female vaginal-oral sex | PEP is Considered |

2. Unknown HIV status of the source person

A - The source person is from a group or from an area of **high** HIV prevalence (at least 15%).

- | | |
|---------------------------------------|--------------------|
| • Receptive anal sex | PEP is Recommended |
| • Receptive vaginal sex | PEP is Considered |
| • Insertive anal sex | PEP is Considered |
| • Insertive vaginal sex | PEP is Considered |
| • Receptive oral sex with ejaculation | PEP is Considered |
| • Other situations | PEP is Discouraged |

In the case of rape or the existence of any **high risk factors** (for both: source person or exposed individual): menstruations, other bleeding during intercourse, genital ulcer, STD.

- | | |
|----------------------|--------------------|
| • Insertive anal sex | PEP is Recommended |
|----------------------|--------------------|

• Insertive anal sex	PEP is Recommended
• Insertive vaginal sex	PEP is Recommended
• Receptive vaginal sex	PEP is Recommended
• Receptive oral sex with ejaculation	PEP is Recommended

B - The source person does **not** belong to a group with high risk activities or is from an area of **low** HIV prevalence.

• Receptive anal sex	PEP is Considered
• All other situations	PEP is Discouraged

In the case of rape or the existence of any **high risk factors** (for source person or exposed individual): menstruations, other bleeding during intercourse, genital ulcer, STD.

• Receptive anal sex	PEP is Considered
• Receptive vaginal sex	PEP is Considered
• Insertive anal sex	PEP is Considered
• Insertive vaginal sex	PEP is Considered
• Receptive oral sex with ejaculation	PEP is Considered
• All other situations	PEP is Discouraged

Box 2

Indications of NONOPEP for IDU exposures

1. Source person known to be HIV positive

• Needle or syringe exchange	PEP is Recommended
• Any equipment* sharing within IDU group	PEP is Considered

2. Source person HIV status is unknown

• Needle or syringe exchange	PEP is Discouraged
• Any equipment* sharing within IDU group	PEP is Discouraged

In case of the prevalence of HIV infection in concerned IDU population >15%

• Needle, syringe or any equipment* exchange	PEP is Considered
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* Such as cookers to melt the drug, cotton used as filter, or water to rinse the syringe

Box 3

Indications of NONOPEP for other needle exposures

• Needlestick from abandoned needle	PEP is Discouraged
• Aggression with a needle	PEP is Discouraged

If extreme factors exist: needle of someone known to be HIV positive, or in 'high risk area' (prevalence of HIV infection in the IDU population concerned >15%), injection of blood or deep injury, fresh blood in syringe, etc.

• Aggression with a needle	PEP is Considered
• Needlestick from abandoned needle with visible fresh blood	PEP is Considered

Box 4

Indications of NONOPEP for other exposures: non-intact skin, mucosal, bite, etc.

- Source person is HIV positive,
or is from a group or from an area

or is from a group or from an area with high HIV prevalence (at least 20%)	PEP is Considered
• HIV source person status unknown, or is not from a group or from an area with high HIV prevalence	PEP is Discouraged

The drug selection was based on the antiretroviral drugs approved by the United States Food and Drug Administration [38], and the belief that a combination of drugs with activity at different stages in the viral replication cycle have proved to be superior to monotherapy regimens, and a three drug regimen (tritherapy) superior to bitherapy.

Guidelines for the treatment of HIV infection recommend the use of three drugs [39]. It is supposed that a three drug therapy will also be the most effective in the case of NONOPEP, when there is a real risk of HIV transmission. Any complete treatment has to take four weeks duration.

Looking at the treatment combination, tritherapy (treatment with a combination of three drugs belonging to two different classes) is recommended; bitherapy (treatment with two nucleoside reverse transcriptase inhibitors (NRTI)) may also be an option. In general, any combination of drugs available for HIV infected patients can be used as PEP and the simplest and least toxic regimens are to be preferred.

When the source person has unknown HIV status, or is HIV positive but not treated, or HIV positive with an efficient first line therapy, the NONOPEP treatment recommended for the patient as first line treatment is 2 NRTI (a) + 1 protease inhibitor (PI) (b) or efavirenz, being the NRTI combinations zidovudine + lamivudine; or stavudine + lamivudine; and the PI, nelfinavir; or indinavir; or lopinavir/ritonavir combination.

Several remarks were made with respect to the NONOPEP:

- When there are several possibilities for the same active principle, the simplest pharmaceutical form must be used.
- Dual PI treatment is less appropriate.
- Indinavir and nelfinavir are frequently associated with side effects and intolerance.
- Do not use abacavir or nevirapine in a four week regimen, because of potential severe adverse events [40,41]. Only a single initial dose should be used, if necessary.

For a second line of prophylaxis, two possibilities arise: if the source person is HIV positive and has been treated by ART with any failure of treatment in his/her history (actual or previous), the NONOPEP must be adapted to the drug history and/or to resistance testing if available, and abacavir may be an option in this case. However, if the source person is HIV positive and has been treated by ART without treatment failure, and has an undetectable viral load, the same ART as that of the source person can be used.

Table 2 shows the patient follow up schedule established by consensus, but some remarks were made with respect to follow up:

- The assessment of other STIs (syphilis, gonorrhoea, chlamydia infection) and hepatitis B and C infections must always be considered.
- Viral load or p24 antigen tests in exposed person are not recommended, except in case of suspected primary HIV infection (fourth generation antibody/antigen tests are an option).
- If possible, deliver drugs for no longer than a 2 week period, to maximize likelihood of patient follow up.
- In case of ART prescribed, written informed consent is recommended.
- For pregnant women, efavirenz and amprenavir are contraindicated [39,42].

In any case, decisions should be made on a case by case basis and we recommend consulting an experienced specialist.

TABLE 2

Patient follow-up schedule

Laboratory tests recommended	Baseline	Week 2	Weeks 4-6	Months 3 and 6
HIV antibody tests	Yes		Yes	Yes
Haematological tests	Yes	Yes	Yes	
Creatininaemia, Transaminases,	Yes	Yes	Yes	

Glycaemia, Amylaseaemia				
Pregnancy test (if patient is female)	Yes			
Medical visit (counselling, compliance assessment, adverse events, clinical seroconversion)	Yes	Yes	Yes	Yes

Conclusion

According to the consensus process presented, the risk assessment and prescription of antiretroviral post-exposure prophylaxis can be made and prescribed in specific non-occupational situations of risk for HIV transmission that seem to be frequent in clinical practice. Most of the points and agreements expressed in these recommendations have been achieved by consensus, on the basis of indirect evidence, and some remain controversial; the maximum time elapsed from exposure to prescription may be reduced to 36 hours; the prevalence limit for unknown HIV status of source person may vary; biotherapy regimens should be considered more frequently, follow up schedule may be varied or shortened, etc. For this reason, the working group thinks that these recommendations should be reviewed and updated periodically according to new knowledge and evidence, if any.

Standardised recommendations have proved useful for improving counselling and care to HIV exposed individuals. However, every country is free to adapt these recommendations to its own HIV infection epidemiological situation, and its own NONOPEP policies, especially regarding the indications named as 'PEP is considered'. In fact several national recommendations for NONOPEP issued by ministries of health in Greece, Italy, Portugal and Spain were promoted following these European recommendations, adding to other previous and updated ones (Austria, France, Germany, Luxembourg, Sweden). In any case, the final decision for NONOPEP prescription must be made on the basis of the patient-physician relationship, bearing in mind that NONOPEP should never be considered as a primary prevention strategy. Finally, although it will be difficult to assess the NONOPEP effectiveness, a surveillance system for these cases will be useful to describe and to monitor NONOPEP practices in Europe.

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