

# MANAGEMENT OF NON-OCCUPATIONAL POST EXPOSURE PROPHYLAXIS TO HIV (NONOPEP) : SEXUAL, INJECTING DRUG USER OR OTHER EXPOSURES

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**EUROPEAN PROJECT ON NON-OCCUPATIONAL  
POST EXPOSURE PROPHYLAXIS (EURO-NONOPEP)**

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**PURPOSE :**

To standardize and to assess the feasibility of a guideline on non occupational post-exposure prophylaxis of the HIV infection in Europe.

**OBJECTIVES :**

MAIN OBJECTIVES:

- 1- To collect and describe the existing recommendations of non occupational post exposure prophylaxis for HIV in the participant countries.
- 2- To establish an European prospective registry of potentially HIV non occupational exposure individual, by mean of the national registries.

SECONDARY OBJECTIVES.

- 1- To describe the knowledge and attitudes of health professional and the groups at high risk of acquiring HIV infection.
- 2- If it possible, to assess the effectiveness of non occupational post exposure prophylaxis for HIV.



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## 1- INTRODUCTION AND JUSTIFICATION

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Post-exposure prophylaxis (PEP) is now the standard of care when a health care worker (HCW) is accidentally exposed to a source person known to be HIV infected (occupational exposure), but this is not the case for non-occupational exposures (see definition in point 2 below),

Although there is no prospective controlled trial or retrospective case-control studies to support its potential efficacy, non occupational post exposure prophylaxis (NONOPEP) is becoming used more and more. Faced with a request for NONOPEP for HIV, physicians have to deal with several questions such as the magnitude of the risk of the exposure or whether to prescribe anti-retroviral therapy (ART) or not. Several questions regarding the prescription of NONOPEP remain unanswered including which combination to choose? What should be the duration of the follow-up? Which laboratory tests are necessary? NONOPEP demand is not negligible in Europe (1,2,3,4), nor is it in the other continents (5,6,7,8,9,10,11). Curiously, in most of the European countries there are no formal national guidelines for the management of possible sexual, injecting-drug-use, or other non-occupational exposures to HIV(12).

Several factors justify the administration of NONOPEP:

- 1- The biological plausibility of NONOPEP for 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 (13,14). As a matter of fact, 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 (15). 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 nodes settlement could prevent the establishment of a systemic infection.

2.- The results of different animal studies have shown the plausibility in preventing HIV infection, by administering ART after an exposure to HIV, for animals (16). 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 and during 4 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 is the prevention (17). 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 12h after the exposure, the third at 36 hours and the fourth group 72h after the vaginal exposure. In the first group, all except one of the macaques became infected. None of the macaques from the second and third group became infected, and one out of three macaques became infected after 16 weeks in the fourth group. These data confirm that the time elapse between the exposure and the beginning of ART is a important factor which can affect NONOPEP efficacy. The delayed infections further support the need for an adequate follow-up period after NONOPEP to monitor for delayed sero-conversions(18).

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. An other issue raised from this study was the increase in the risk of acquiring HIV when some enhancing existed such as: the depht or extent of the injury, whether there was visible blood on the device, advanced stage of HIV disease in the source person(19)...

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 randomized 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 randomized to placebo (20). In spite of contact between the child's blood and the HIV status of his/her mother, AZT prevented the infection in the majority of cases.

4.- In 1997, an article was published describing the cost effectiveness of Tri-therapy with Zidovudine, Lamivudine and Indinavir following moderate to high risk occupational exposure (21). An other 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 nearly certain that the source person is infected, and receptive vaginal sex only when the source person is know to be HIV positive (22). Assuming that it is not only the cost effectiveness which can predominate in a public health decision, further studies on it are necessary.

Guidelines for the management of occupational HIV exposures exist in the USA and in most European countries; on the other hand, very few national guidelines for NONOPEP have been elaborated in Europe (12).

The above-mentioned studies encourage us to propose and standardize 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 (23-29).



An other argument to propose NONOPEP guidelines is the results of a French study in which the existence of NONOPEP recommendations had an impact on physicians behavior, improving their acceptability and attitude regarding NONOPEP(30) and probably the risk assessment. Furthermore, a survey has been conducted among European physicians as part of the EURO-NONOPEP project coordinated by the CEESCAT, and presented above. The results clearly showed clearly that there were significantly more prescriptions after NONOPEP requests(76% vs 61%  $p=0,007$ ), as well as more ARV emergency start kit available(92% vs 44%,  $p<0,001$ ), in the countries with national guidelines. Similarly, the exposure risk assessment and the management of NONOPEP requests improved among this group of physicians in comparison to the group without national guidelines.

Finally, as summarized in chapter 3, the probability of HIV transmission by certain non-occupational exposures is estimated 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. On the contrary, in the case of a non occupational exposure, the time of ART initiation is frequently longer, the possibility of knowing the HIV status of the source person lower, and the rate of lost to follow up higher. Hence the need for specific guidelines for these situations of non-occupational exposures.

One of the main objective of the EURO-NONOPEP project is the elaboration of the communal European recommendations regarding the management of HIV NONOPEP. In this perspective, the national representatives who attended the first General Workshop of this project, on the 19<sup>th</sup> and the 20<sup>th</sup> of October 2001, drew up a consensus draft regarding the European NONOPEP guidelines, to standardize the management of non occupational exposures. These recommendations were based on the actual knowledge on NONOPEP, and in particular its cost effectiveness and the risk exposure assessment of several types of non occupational exposures. We also made use of the CDC recommendations and reports on the management of occupational and non occupational exposure to HIV. Every country is quite free to adapt these recommendations to its HIV infection epidemiological situation, and its own NONOPEP policies, specially regarding the attitudes indicated as “considered”...

As NONOPEP effectiveness is not finally established, it is necessary to initiate a National and European surveillance system to collect information about persons who seek medical care after possible non occupational exposure for HIV. This system will assess the viability, the medication toxicity and eventually the effectiveness by gathering the characteristics of the reported exposures, the details of the ART used, the toxicity and the adherence to the ART, and eventual sero-conversions.

## 2- DEFINITION OF NON-OCCUPATIONAL EXPOSURE

We considered as non occupational exposure for HIV, all accidental and sporadic situations in which contact with blood or other body fluids (semen, vaginal secretions, or other body fluids) potentially at risk for HIV infection occurred, after having taken preventive measures, excluding exposures to HCW in the health care or laboratory setting. That is to say: unprotected sexual exposure, sexual exposure with broken or slipped condom, intravenous drug users (IDUs) sharing material, accidental needle stick, non occupational HCW exposure, bite wound, mucosal exposure....

Neither tears nor sweat exposures are considered as at risk for HIV transmission.

## 3-LITERATURE REVIEW OF RISK EXPOSURE ASSESSMENT

Table 1 shows the different risk of HIV transmission by non-occupational exposures, according to a literature review.

Table 1. Summary of HIV transmission risk by type of non-occupational exposure

TYPE OF EXPOSURE (from a source known as HIV positive)	RISK OF HIV TRANSMISSION PER EXPOSURE	REFERENCES
Accidental needle stick	0,2%-0,4%	19
Mucosal membrane exposure	0,1%	31
Receptive Oral Sex	Varied from 0 to 0,04%	32, 33
Insertive vaginal sex	≤ 0,1%	34 - 37
Insertive anal sex	≤ 0,1%	34 - 37
Receptive vaginal sex	0,01%-0,15 %	34, 36, 38, 39
Receptive anal sex	≤ 3%	33, 37, 39
Sharing IDUs needle	0,7%	40
Transfusion	90-100%	41

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 co-factors such as follows:

- Infectivity of the source: High plasma viral load increases the risk (42)
- Genital oral ulcers, STD or bleeding increase the risk a sexual exposure (39)
- For accidental needle stick exposure, fresh blood, a depth injury or intravenous injection increases the risk of HIV transmission.(19)

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

## 4- PEP RECOMMENDATIONS

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Facing a request for non occupational post exposure prophylaxis for HIV, the physicians should take the following steps into consideration:

- 1- To evaluate the HIV status and risk behavior history of the reported source of HIV exposure (person belonging to a HIV high risk group or coming from a country with high HIV prevalence) and, if possible, to test the source person for HIV-antibodies.
- 2- To 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 exposure; number of persons sharing material; depth of any per-cutaneous exposure ...for IDUs).
- 3- To 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 HIV-antibodies tests at baseline and periodically for at least 6 months after the exposure, as well as other blood-borne pathogens such as HBV and HCV or tests for sexually transmitted diseases (STD) if indicated.
- 5- In the case of prescribing ART, treatment has to start as early as possible. Drug toxicity monitoring should include a complete blood count, renal and hepatic chemical function tests at baseline, and periodically for at least 6 months after the exposure.
- 6- For HIV-sexually exposed women, a pregnancy test has to 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 pediatrician in care of HIV infection.
- 7- The exposed individual should be counseled to prevent additional exposure, and to improve the ART adherence in the case of prescription.
- 8- **NONOPEP should never be considered as a primary prevention strategy.**

## A- Sexual exposures:

It should be stated that at risk sexual exposures are “**unprotected intercourses**”(without condom or with broken or slipped condom).

### 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 case of raping 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, STD.

- 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 case of raping 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 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 high risk group or is from an area of **low** HIV prevalence.

- Receptive Anal sex ..... PEP is Considered
- All Other Situations..... PEP is Discouraged

In case of raping 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

## **B- IDU exposures:**

### **1- Source person known as HIV positive:**

- Needle or syringe exchange ..... PEP is Recommended
- Any material\* sharing inside IDUs group ..... PEP is Considered

### **2- Source person HIV status is unknown:**

- Needle or syringe exchange ..... PEP is Discouraged
- Any material\* sharing inside IDUs group ..... PEP is Discouraged

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

- Needle, Syringe or any material\* Exchange ..... PEP is Considered

\* Such as: cookers to melt the drug, cotton used as filter, or water to rinse the syringe



### C- Other needle exposures:

- Abandoned needle stick ..... PEP is Discouraged
- Aggression with a needle ..... PEP is Discouraged:

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

- Aggression with a needle ..... PEP is Considered
- Abandoned needle stick with visible fresh blood ... PEP is Considered

### D- Other expositions: Non intact skin, mucosal, bite, ... :

- 1- Source person is HIV positive, or is from a group or from an area of **high** HIV prevalence (at least 20%)..... PEP is Considered
- 2- HIV source person status unknown, or is **not** from a group or from an area of **high** HIV prevalence ..... PEP is Discouraged

## 5- ANTI-RETROVIRAL PROPHYLAXIS: DRUG SELECTION AND FOLLOW-UP SCHEDULE

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### A- Drugs selection:

We based the drugs selection on:

- a) the antiretroviral drugs approved by the FDA(43);
- b) the concept that a combination of drugs with activity at different stages in the viral replication cycle have proved to be superior to mono-therapy regimens, and a three drugs regimen superior to bi-therapy.

Guidelines for the treatment of HIV infection recommend the use of three drugs (44). It is supposed that a three drug therapy will be also the most effective in the case of NONOPEP, when there is a real risk of HIV transmission.

#### 1- Which Treatment combination?

Triple therapy (treatment with a combination of three drugs belonging to two different classes) is recommended.

Bi-therapy (treatment with two nucleoside reverse transcriptase inhibitors -NRTI- ) may be an option.

#### 2- First line treatment:

Source with unknown HIV status, or HIV positive but not treated, or HIV positive with an efficient first line therapy, the NONOPEP treatment recommended for the patient is as follows:

#### **2 NRTI (a) + PI\* (b) or Efavirenz**

(a): Zidovudine + Lamivudine;  
or Stavudine + Didanosine EC;  
or Stavudine + Lamivudine.

(b): Nelfinavir;  
or Indinavir;  
or Lopinavir/ritonavir.

When there are several possibilities for the same active principle use the simplest pharmaceutical form.

Dual PI is less appropriated.

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\* Protease inhibitor

Do not use Abacavir, or Nevirapine in a 4 weeks regimen, because of potential severe adverse events (45,46).

Only a single initial dose can be used if necessary.

### 3- Second line prophylaxis:

If the source person is HIV positive and treated by ART with any failure of treatment in his/her history (actual or previous):

Adapt the NONOPEP ART to the drug history and/or to resistance testing if available.

Abacavir may be an option in this case.

If the source person is HIV positive and treated by ART (without treatment failure) with undetectable viral load:

The same ART of the source person can be used.

## B- Duration of Treatment:

4 weeks.

## C- Patient follow-up:

Laboratory tests Recommended	Baseline	Week 2	Week 4-6	Month 3 and Month 6
HIV Anti body tests	Yes		Yes	Yes
Haematological tests	Yes	Yes	Yes	
Creatininemia, Transaminases, Glycaemia, Amylasemia.	Yes	Yes	Yes	
Pregnancy test (if patient is a woman)	Yes			
Medical visit: Counseling, Compliance assessment, adverse events, clinical seroconversion	Yes	Yes	Yes	Yes

**NB:** Consider the assessment of other STD (Syphilis, Gonorrhoea, Chlamydia infection) and of Hepatitis B and C.



## Remarks:

- Viral load or p24 antigen tests in exposed person are not recommended, except in case of suspected primary HIV infection (4<sup>th</sup> generation Antibody/Antigen tests are an option).
- If it is possible, deliver drugs for no more than a 2 weeks period, to improve the patient follow-up.
- In case of ART prescribed, written informed consent is recommended.
- For pregnant women, **Efavirenz and Amprenavir are contraindicated(44,47). Anyway, decision should be made on a case by case basis and we recommend to consult an experienced specialist.**

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