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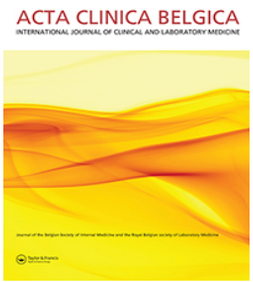

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ORIGINAL PAPER

Belgian guidelines for non-occupational HIV post-exposure prophylaxis 2017

Agnès Libois[a], Eric Florence[b], Inge Derdelinckx[c], Jean Cyr Yombi[d], Sophie Henrard[e], Françoise Uurlings[f], Stefaan Vandecasteele[g], Sabine D. Allard[h], Rémy Demeester[i], Filip Van Wanzeele[j], Nathalie Ausselet[k] and Stéphane De Wit[a]

[a]Department of Infectious Diseases, CHU Saint-Pierre, Université Libre de Bruxelles (ULB), Brussels, Belgium; [b]Institute of Tropical Medecine, Antwerp, Belgium; [c]Department of Internal Medicine, University Hospitals Leuven, Leuven, Belgium; [d]Department of Internal Medicine, Infectious Diseases and Tropical Medicine Unit, Cliniques Universitaires St Luc, Brussels, Belgium; [e]Centre de Référence SIDA, Unité de Traitements des Immunodéficiences, Hôpital Erasme, Route de Lennik 808, Bruxelles, Belgium; [f]Infectious Diseases Department, Liège University Hospital, Liège, Belgium; [g]Department of Nephrology and Infectious Diseases, AZ Sint-Jan Brugge, Brugge, Belgium; [h]Department of Internal Medicine and Infectious Diseases, Universitair Ziekenhuis Brussel, Brussels, Belgium; [i]Department of Internal Medicine and Infectious Diseases, CHU de Charleroi, Charleroi, Belgium; [j]Department of General Internal Medicine, Infectious Diseases and Psychosomatics, Ghent University Hospital, Ghent, Belgium; [k]Infectious Disease Department, CHU UCL Namur-Godinne, Belgium

ABSTRACT

We present the updated Belgian guidelines for the use of non-occupational HIV post-exposure prophylaxis (NONOPEP). This document is inspired by UK guidelines 2015, adapted to the Belgian situation and approved by all AIDS reference centers in Belgium. When recommended, NONOPEP should be initiated as soon as possible, preferably within 24 h of exposure but can be offered up to 72 h. The duration of NONOPEP should be 28 days. These current guidelines include epidemiologic estimations, which can be used to calculate the risk of infection after a potential exposure and help to decide whether or not to start prophylaxis. We review which medications to use in the context of the last Belgian NONOPEP convention, provide a checklist for initial assessment, and make recommendations for monitoring individuals receiving NONOPEP.

KEYWORDS

HIV; post-exposure prophylaxis

News and summary of recommendations

(1) Decisions whether or not to start prophylaxis should be taken on a case by case basis, taking into account the kind of risk the patient has encountered and factors increasing the risk of transmission. The risk of an individual acquiring HIV following exposure can be calculated by multiplying the risk that the source is HIV infected and the risk per exposure.

NONOPEP is recommended when there is a significant risk of HIV transmission (risk > 1/1000).

NONOPEP may be considered if the transmission risk is between 1/1000 and 1/10,000.

NONOPEP is not recommended if the transmission risk is < 1/10.000.

(2) NONOPEP should be initiated as soon as possible, preferably within 24 h of exposure but can be offered up to 72 h. The duration of NONOPEP should be 28 days.

(3) Proactive attempts should be made to establish the HIV status of the source. Whenever possible, prophylactic regimen should be adapted to the HIV genotype and resistance profile of the source person.

(4) NONOPEP is not recommended if the source is on antiretroviral therapy (ART) with a confirmed and sustained (>6 months) plasma viral load (pVL)<200 copies/ml.

(5) NONOPEP is not recommended following fellatio with ejaculation as the risk of transmission is estimated to be < 1/10.000 (except if suspicion of primary infection and oropharyngeal trauma).

(6) In the event of a new high-risk sexual exposure during the last two days of the NONOPEP course, NONOPEP should be continued for 48 h after the last high-risk exposure.

(7) In Belgium, antiretrovirals prescribed in the context of NONOPEP are free of charge if prescribed by an AIDS reference center. However, the budget allocated by the INAMI/RIZIV does not allow the prescription of the preferred treatment combination.

(8) Counseling to reduce future risk behavior is essential.

(9) The possibility of pre-exposure prophylaxis (PrEP) in patients with repeated indication of NONOPEP treatment or with ongoing high-risk behavior needs to be discussed.

CONTACT Agnès Libois agnes_libois@stpierre-bru.be

Background

Non-occupational post-exposure prophylaxis (NONOPEP) is a recommended public health intervention to prevent human immunodeficiency virus (HIV) transmission after a sexual or percutaneous exposure. Once HIV crosses a mucosal or cutaneous barrier, it takes up to 48–72 h before it can be detected within regional lymph nodes and up to five days in blood. This allows a therapeutic window of maximum 72 h for NONOPEP initiation, consisting in antiretroviral drugs after a risk exposure [1]. Data from animal transmission models, perinatal clinical trials, observational studies of healthcare workers receiving prophylaxis after occupational exposure, and observational and case studies of NONOPEP have shown an efficacy of this intervention. Data from macaque studies demonstrated the best efficacy if the treatment is taken within 24–36 h post-exposition and a decreasing and partial efficacy until 72 h post-exposition [2]. Comparing a treatment for 3, 10, or 28 days, macaque study has shown the best efficacy when prophylaxis is taken for a total of 28 days [2]. Based on these data, NONOPEP is recommended to be started as soon as possible after exposure, preferably within 24 h of exposure, but can be offered up to 72 h. The duration of NONOPEP should be 28 days. The only case-control study done on occupational post-exposure prophylaxis showed that zidovudine reduces transmission by 81% in health care workers exposed to needle stick injuries [3].

Because of ethical and operational challenges in humans, no randomized controlled clinical trials have been or will be conducted to evaluate the efficacy of NONOPEP. Cohort studies with patients receiving a 28-day regimen of antiretroviral therapy tend to confirm the efficacy of NONOPEP, with most of seroconversions being associated to poor adherence to prescribed NONOPEP regimen or to ongoing high risk behavior following treatment [4–6].

In Belgium, there is a convention with the national health insurance (INAMI/RIZIV) concerning the reimbursement of NONOPEP. NONOPEP has to be prescribed by an AIDS reference center. Antiretrovirals drugs are free of charge for persons fulfilling the indication but consultations and tests are not. Recently, a new convention of INAMI/RIZIV with the AIDS reference centers decreased the budget for NONOPEP by 37%, limiting affordable drug options. Consequently, treatment has to be adapted and prophylaxis recommended by the majority of guidelines worldwide (tenofovir disoproxil fumarate/emtricitabine plus raltegravir) can't currently be given in Belgium [7,8]. This should change once more generic drugs will become available.

Methods

These current guidelines are an update of the 2009 Belgian NONOPEP guidelines established by all AIDS reference centers (non-published). This document is inspired by the UK guidelines 2015 and adapted to the Belgian situation [7].

UK guidelines followed processes outlined in the BASHH Framework for Guideline Development and are based on a comprehensive literature review on NONOPEP and HIV transmission (Medline, Embase, Cochrane Library were searched from January 1990 to November 2014 for all articles relating to HIV post-exposure prophylaxis (985 abstracts reviewed)) [9]. UK guidelines were adapted to the Belgian situation by the first author and each recommendation was discussed and approved in a series of meetings with experts from all AIDS reference centers in Belgium.

Evaluation of the risk of transmission after potential exposure

The probability of HIV transmission depends upon the exposure characteristics, the infectivity of the source and the host susceptibility.

The risk of an individual acquiring HIV following an exposure can be calculated by multiplying the risk that the source is HIV-positive (estimated HIV prevalence) and the risk per exposure.

Risk of HIV transmission = risk that source is HIV positive x risk per exposure

1. NONOPEP is recommended when there is a significant risk of HIV transmission (risk > 1/1.000).
2. NONOPEP may be considered if the transmission risk is between 1 in 1.000 and 1 in 10.000.
3. NONOPEP is not recommended if the transmission risk is < 1/10.000.

Estimated HIV prevalence in Belgium

- MSM: 5% in general gay venues in Flanders, 9% in Brussels, 14.5% in high risk venues (cruising)[10].
- Female sex workers:<1% in Western Europe, 1–2% in Central Europe, 2.5–8% in Eastern Europe.
- Male sex workers: 14% (reported from 27 countries)
- African heterosexuals: the prevalence in the Country of origin varies widely according to the UNAIDS statistics [11]. In Democratic Republic of Congo, estimation of HIV prevalence in adults between 15 and 49 years was 0.8% in 2015. Other Sub-Saharan African countries reported much higher prevalence figures especially in the Southern African Countries. HIV prevalence among adults was as high as 28.8, 22.7, and 19.2% in Swaziland, Lesotho and South Africa, respectively. The prevalence of HIV infection among the migrant community in Belgium has been estimated at 5.9% among women and 4.2% among men [12]. The risk of HIV acquisition post-migration was estimated to be as high as 45% in a recent European study [13].

- Prevalence in the general Belgian population (outside high risk group) is estimated to be between 0.01 and 0.02%.

HIV prevalence in other countries can be found in the UNAIDS Gap report [14].

Box 1. Factors increasing the risk of HIV transmission

(1) A high plasma viral load (pVL) in the source, particularly during primary HIV infection
(2) Breaches in the mucosal barrier: ulcer, trauma following sexual assault or first sexual intercourse
(3) Menstruation or other sources of bleeding
(4) Sexually transmitted infection
(5) Ejaculation
(6) Non-circumcision

Estimated risk per exposure

The risk of HIV transmission per exposure from a known HIV-positive individual not on ART is summarized in Table 1.

Estimations have been deduced from cohort and modeling studies. For receptive oral sex with ejaculation, the risk is estimated < 1/10.000. Although, modeling studies have estimated the risk to be 4/10.000, no seroconversion was observed after 19,000 unprotected orogenital exposures with an HIV-positive partner in a cohort study [15].

Some factors may increase the risk of HIV transmission (Box 1). These factors must always be considered and discussed during a NONOPEP consultation.

Therefore, although the calculated risk of HIV transmission supports the decision whether or not to initiate NONOPEP, the final decision will be made on a case-by-case basis.

Recommendations for prophylaxis

The recommendations are summarized in Table 2. A risk-benefit analysis should be undertaken for every individual presenting following an exposure and the decision to initiate NONOPEP made on a case-by-case basis. This should consider both the risk of the source being HIV-positive, the risk of transmission according to exposure, and the pVL in the source, if known.

Proactive attempts should be made to establish the HIV status of the source. NONOPEP is not recommended if the source is on cART with a confirmed and sustained (>6 months) pVL < 200 copies/ml.

NONOPEP is not recommended following fellatio with ejaculation but can be considered in case of suspicion of primary HIV infection and oropharyngeal trauma.

Others situations

- Needlestick from a discarded needle in the community: NONOPEP not recommended
- Oral insertive sex, cunnilungus, or semen splash in the eye: not recommended as there has been no documented HIV transmission via this route
- Aggression with a needlestick: consider if visible blood, deep injury
- Human bite: generally not recommended, consider if blood in the mouth of assaulter
- Blood on non-intact skin/mucosal: consider

Antiretroviral regimen

Once the indication of NONOPEP has been made, an accurate medical history needs to be taken, including the use of over-the-counter medications, vitamins, minerals, herbal remedies, and recreational drugs.

Regimens recommended by the vast majority of recent national and international guidelines comprise tenofovir disoproxil fumarate/emtricitabine (Truvada®) + dolutegravir (Tivicay®) or tenofovir disoproxil fumarate/emtricitabine (Truvada®) + raltegravir (Isentress®). These antiretrovirals are well tolerated, result in high levels of adherence and have little potential of drug–drug interactions. Elvitegravir/cobicistat/emtricitabine/tenofovir alafenalide (Genvoya®) or elvitegravir/cobicistat/

Table 1. Risk of HIV transmission per exposure from a known HIV-positive not on ART.

Type of exposure	Estimated risk of HIV transmission per exposure from a known HIV-positive individual not on cART	References
Receptive anal intercourse	1 in 90	[16–22]
Receptive anal intercourse with ejaculation	1 in 65	[16–23]
Receptive anal intercourse no ejaculation	1 in 170	[23]
Insertive anal intercourse	1 in 666	[16,18,19,24]
Insertive anal intercourse not circumcised	1 in 161	[23]
Insertive anal intercourse and circumcised	1 in 909	[23]
Receptive vaginal intercourse	1 in 1000	[16,21,25–31]
Insertive vaginal intercourse	1 in 1219	[20,21,25–31]
Sem en splash to eye	<1 in 10,000	[32]
Receptive oral sex (giving fellatio)	< 1 in 10,000	[19,26,31,33]
Insertive oral sex (receiving fellatio)	< 1 in 10,000	[18,31]
Blood transfusion (one unit)	1 in 1	[34]
Needlestick injury	1 in 333	[3,33,35]
Sharing injecting equipment (includes chemsex)	1 in 149	[32]
Human bite	< 1 in 10,000	[36,37]

Table 2. Overview of the Belgian NONOPEP prescribing recommendations.

Characteristics of source person	HIV positive with unknown/ detectable viral load	HIV positive treated with viral load <200 copies/ml for > 6 months	Unknown HIV statusFrom high risk/prevalence group[2] or high risk area[3]	Unknown HIV statusFrom low risk/prevalence group[2] or low risk area[3]	Rape (except if condom used or rapist with proven recent negative HIV status)
Receptive anal	Recommended	Not recommended [1]	Recommended	Not recommended	Recommended
Insertive anal	Recommended	Not recommended	Considered	Not recommended	NA
Receptive vaginal	Recommended	Not recommended	Considered	Not recommended	Considered
Insertive vaginal	Recommended	Not recommended	Considered	Not recommended	NA
Receptive oral with ejaculation	Not recommended except if cofactors 1 and 2 (see Box1)	Not recommended	Not recommended except if cofactors 1 and 2 (see Box 1)	Not recommended	Not recommended except if cofactors 1 and 2 (see Box 1)
Receptive oral without ejaculation	Not recommended except if cofactors 1 and 2 (see Box1)	Not recommended	Not recommended except if cofactors 1 and 2(see Box 1)	Not recommended	Not recommended except if cofactors 1 and 2 (see Box 1)
Sharing or injecting equipment	Recommended	Not recommended	Recommended	Not recommended	

[1]Whenever possible, provide source confirmed pVL < 200 copies/ml for > 6 months
[2]High risk/prevalence group: High risk/prevalence groups include men who have sex with men (MSM), bisexual men, injection drug users, male and some female prostitutes, people participating in group sex or having multiple sexual partners, (ex-)prisoners
[3]High-risk area: prevalence > 1% (http://www.unaids.org/en/resources/campaigns/2014/2014gapreport/gapreport) Latin America, sub-Saharan Africa, eastern asia, and ex-urss countries
NA: not applicable

emtricitabine/tenofovir disoproxil fumarate (Stribild®) may be considered as an alternative regimen, although drug–drug interactions are of concern in the NONOPEP target population (e.g. regular use of recreational drug).

Currently, in Belgium, affordable regimens within the RIZIV/INAMI convention are:

Lamivudine/Zidovudine (Combivir®) (1 tablet bid) together with one of the following: lopinavir/ritonavir (Kaletra®) (2 tablets bid) or, atazanavir 200 mg (Reyataz® 200 mg) (2 tablets qd) or atazanavir 300 mg (Reyataz® 300 mg) (1 tablet qd) and ritonavir (Norvir®) (1 tablet qd).

However, these regimens are frequently associated with side effects (asthenia and inability to attend work, gastro-intestinal side effects, jaundice, and others), resulting in reduced levels of adherence. In the CHU Saint-Pierre cohort, adherence for regimens comprising lopinavir/ritonavir (Kaletra®) + stavudine (Zerit®)+lamivudine (Epivir®) was 60% [5] . A prospective trial in Barcelona comparing tenofovir disoproxil/emtricitabine plus either lopinavir/ritonavir or raltegravir, in the context of NONOPEP, showed a better adherence and less adverse events in patients receiving tenofovir disoproxil/emtricitabine and raltegravir [38]. Moreover, regimens including a protease inhibitor have a higher potential of drug–drug interaction. There is an urgent need to shift to regimens associated with better adherence, less side effects and low potential potential of drug interaction. In the near future, generic drugs should allow the implementation of such regimens.

Whenever possible, the prophylactic regimen should be adapted to the source person's HIV genotype and resistance profile.

In the event of a new high-risk sexual exposure during the last two days of the NONOPEP course, NONOPEP should be continued for 48 h after the last high-risk exposure.

Prevention of others diseases

As the route of transmission can be shared, hepatitis B (HBV) and sexually transmitted infection (STI) prophylaxis have to be considered. There is no post-exposure prophylaxis for hepatitis C (HCV).

HBV prevention

In case of potential non-occupational exposure to hepatitis B (HBV), the recommendations depend on the HBV status of the source, the HBV vaccination status of the patient and the type of exposure. If the patient is vaccinated against HBV and has a documented hepatitis B surface (HBs) antibody (Ab) titer of ≥ 10 IU/ml, no further measures need to be taken.

HBV vaccination is integrated in the recommended and free childhood vaccination schedule since 1999.

Table 3. Recommendations concerning HBV prophylaxis following non-occupational exposure.

	Patient not (or not fully) vaccinated*	Patient vaccinated[$] but no post-vaccination testing performed
HBs Ag positive source	Anti-HBV Ig[#] and start (or complete) HBV vaccination[&]	One Engerix B® booster
HBV status source unknown	Start (or complete) HBV vaccination	No additional measures

HBs Ag: hepatitis B surface antigen.
[*]Or 'non-responder' (i.e. lack of HBs Ab following adequate vaccination or titer HBs Ab < 10 IU/ml).
[#]Preferably within 24 h of risk exposure and no later than 7–14 days. Anti-HBV IgG are not reimbursed and are expensive.
[&]In vaccination non-responders after two series of 3 HBV vaccine: 2 doses of anti-HBV Ig (with an interval of 1 month), no vaccination.
[$]Vaccination needs to be written proved.

Then persons born in Belgium after 1999 are probably vaccinated.

Table 3 resumes the recommendations to follow if the patient is not (or not fully) vaccinated against hepatitis B or if no HBs Ab titer is available.

STI prevention

In rape, test for STI at baseline and give a post-exposure treatment with ceftriaxone and azithromycine as lost of follow-up is frequently observed in this subgroup [5]. In other situation, systematic prophylaxis for STI is not indicated.

Follow-up

- At baseline : Blood chemistry and hematology, HIV serology, syphilis, HBV serology (Ag Hbs, anti-Hbs, anti-Hbc) and HCV IgG, pregnancy test (women).
- At 2 weeks: blood chemistry and hematology depending on medical indication (generally not necessary if regimen with raltegravir (Isentress®)/ dolutegravir (Tivicay®) and tenofovir disoproxil fumarate/emtricitabine (Truvada®)).
- PCR forgonorrhea and Chlamydia (at least one week after the sexual intercourse)
- HIV and syphilis serology at 6–8 weeks and 12–16 weeks. Follow up of HCV serology according to the situation

Counseling associated with NONOPEP is essential as it can enhance efficacy by reducing further risk behaviors.

For individuals who repeatedly present for NONOPEP or with ongoing high-risk behavior, consider pre-exposure prophylaxis.

Disclosure statement

No potential conflict of interest was reported by the authors.

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