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Adherence to HIV post exposure prophylaxis: a multivariate regression analysis of a 5 years prospective cohort.

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Adherence to HIV post exposure prophylaxis

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Article main point

Adherence to nPEP is higher within MSM, older patients, native Belgians, patients having a health insurance and previous nPEP users. Patients on IDV/r/AZT/3TC as starter pack have similar treatment adherence compared to patients on LPV/r/d4T/3TC. Sexual assault survivors show reduced adherence to nPEP and are overexposed to deleterious effects of the absence of a health insurance in terms of compliance.

Highlights

- Increased treatment adherence to nPEP is associated with being MSM, having a health insurance, having had a previous nPEP treatment and with an older age.
- Reduced treatment adherence to nPEP is associated with sexual assault survivors and foreign patients.
- Sexual assault survivors are overexposed to the deleterious effect on compliance of not having a health insurance.
- Daytime consultations for nPEP are associated with increased treatment adherence when compared to nighttime consultations.

Abstract

Background:

Nonoccupational postexposure prophylaxis (nPEP) is a recommended public health intervention after a sexual or percutaneous exposure to human immunodeficiency virus (HIV).

Methods:

We conducted a prospective observational study recording consultations for nPEP at a reference HIV center in Brussels, Belgium from January 2011 to December 2015. We recorded attendance to follow-up, reported completion of nPEP and pharmacy records to measure adherence. Multivariate logistic regressions were performed to identify independent risk factors for adherence to nPEP and attendance to first follow up visit at the STI Clinic.

Findings:

Among 1881 patients receiving nPEP, 66.4% had a documented completion of a 28-day course of nPEP and 87.3% attended their first follow-up clinic visit. MSM (OR 1.40; 95%CI, 1.04-1.90) being a native Belgian (OR 1.50; 95%CI, 1.18-1.90) older age (OR 1.02; 95%CI, 1.01-1.04), being a sexual assault survivor (OR, .59; 95%CI, .38- .91), having had a previous nPEP treatment (OR, 1.44 95%CI, 1.02-2.02), consultation during daytime (OR, 1.35 95%CI, 1.07-1.70) and benefitting from a health insurance (OR, 2.11 95%CI, 1.58-2.89) were significant independent predictors for adherence to nPEP. Patients whose initial treatment was AZT/3TC/IDV/r had similar adherence than patients on d4T/3TC/LPV/r (OR, 0.898 95%CI, .68-1.20).

Interpretation:

Multiple independent risk factors for nPEP retention into care and adherence are present at treatment initiation and might be targeted by tailored interventions. Sexual assault victims are overexposed to deleterious consequences of the lack of health insurance on compliance.

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ARTICLE TEXT

Introduction

Non-occupational post-exposure prophylaxis (nPEP) is a recommended public health intervention to prevent human immunodeficiency virus (HIV) transmission after a sexual or percutaneous exposure. It takes two to three days for HIV virus to become detectable in regional lymph nodes and around 5 days to disseminate in the blood, this allows a therapeutic window of maximum 72 hours for nPEP initiation after an at risk exposure.¹ Data from animal models suggest that efficacy of nPEP depends on the delay before treatment initiation and on the total treatment duration.² The only case-control study done on occupational PEP showed that zidovudine reduces transmission by 81% in health-care workers exposed to needle stick injuries.³ Subsequent cohort studies with patients receiving a 28-day regimen of antiretroviral therapy tend to confirm the efficacy of nPEP, with most of seroconversions being associated to poor adherence to prescribed nPEP regimen or to ongoing high risk behavior following treatment.⁴⁻⁶ Counseling associated with nPEP can enhance nPEP efficacy by reducing further risk behaviors following the exposure.⁷

Yet several barriers prevent patients from receiving optimal post-exposure care. Unawareness of HIV post-exposure prevention strategies and limited awareness of the source patient serostatus restrict access to nPEP.⁸⁻¹⁰ Moreover completion rates are poor in patients seeking care, around 60%, and multiple factors have been associated with compliance.¹¹ Sexual orientation, presence of a health insurance and medical or psychiatric comorbid conditions have been identified as determinants of compliance to nPEP, with MSM, patients having a health insurance and without any comorbidity showing the highest completion rates.^{11,12} Sexual assault survivors show reduced compliance to the full 28 days treatment course.¹³ Other factors contributing to poor adherence are treatment related side effects, pill burden or stigma related to treatment.^{14,15} Attempts to improve compliance have focused essentially on treatment regimens with conflicting results. Even with newer and better tolerated drugs such as raltegravir + tenofovir-emtricitabine compliance ranged from 57% to 92%.^{16,17} Behavioral interventions such as follow-up support through telephone calls have failed to improve adherence to nPEP.¹⁸ Starter packs were also introduced to improve compliance through additional counseling and a closer toxicity monitoring but have failed to improve adherence.¹⁹ A better identification of patients at risk of low adherence to treatment could allow more tailored interventions. We therefore designed a prospective observational cohort study to determine

independent risk factors for incomplete adherence to nPEP, aiming to identify patients at risk of poor compliance in order to better tailor future interventions aimed to improve completion rates.

Methods

Study design and setting

From January 2011 to December 2015 we prospectively recorded all patients consulting for nPEP from a large academic emergency department (ED) in Brussels. The setting of our study is Centre Hospitalier Universitaire Saint Pierre, an HIV reference hospital located close to the gay community nightlife district in a relatively deprived and high immigration area of the city centre of Belgium capital city. This centre alone prescribes half of all nPEP in Belgium. Patients were evaluated for nPEP after a potential HIV exposure by an ED physician according to national guidelines. Baseline serologies were sampled and a standardized electronic history of the event was recorded. To support the ED physician an Infectious Diseases Physician (IDP) was available 24/7 to help in risk assessment or drug regimen's decision. Patients deemed at risk were provided with a starting pack of ART of 5 days to bridge them to an outpatient consultation with an IDP at our STI clinic. Oral and written instructions were provided to all patients providing information concerning ART for nPEP and their upcoming STI clinic follow-up appointment.

Sexual assault survivors were also evaluated by a dedicated psychologist and provided with additional psychosocial support in the ED and follow-up counselling. During outpatient follow-up consultation with an IDP, exposure risk was re-evaluated, side effects of ART were assessed, counselling for STI was offered, further follow-up testing was planned and a decision to continue or to stop ART was taken.

Follow-up visits were typically performed at 2, 6 and 12 weeks from exposure when HIV screening, STI screening, side effects assessment and continuous HIV risk counselling were offered to patients.

First line drug regimen for starter packs consisted of d4T/3TC/LPV/r. Since January 2015 sexual assault survivors were provided a different drug regimen based on fixed dose single tablet EVG/COBI/FTC/TDF and first line starter packs changed into AZT/3TC/IDV/r. National guidelines did not offer any recommendation in term of drug regimen for nPEP. Our drug regimen choice was an attempt to balance budgetary restrictions against short term side effects, in order to keep nPEP accessible free of cost to everyone. Any antiretroviral treatment associated with nPEP was completely free of charge irrespective of the health insurance status of the patient. Meanwhile,

any cost related to ED consultation or IDS follow-up was at charge of the patient and reimbursed according to his insurance status.

This prospective observational cohort study was approved by the Ethical Board of Centre Hospitalier Universitaire Saint Pierre. All participants were older than 18 years and were deemed candidates for nPEP according to national guidelines and IDP advice.

Outcomes measures

The primary outcome of this study was the documented completion of a 28-day course of nPEP. Documented completion of nPEP was defined as patients self-reporting having completed the full treatment course during a follow-up visit more than 4 weeks after exposure, and was retrospectively evaluated through chart review. In addition pharmacy charts were also reviewed and completion status of nPEP was refined in patient receiving 28 days of treatment. Patients interrupting nPEP before completion following IDP advice were excluded from the analysis. Patient that self-declared that they would have follow-up elsewhere were also excluded from the analysis. The secondary outcome of the study was attendance to the first follow-up appointment at the STI clinic after the ED consultation.

Data collection and analysis

Clinical and demographic data were extracted from digitalized medical records by a statistician not involved in the study and all data were anonymized. A manual review of medical charts was performed in cases of ambiguous data. Information concerning demographic data of patients, sexual orientation, health insurance status, geographical origin, type of exposure, HIV status of the source patient were gathered and evaluated as risk factors for failing to complete a 28 days regimen of nPEP. Time of consultation at the ED (regular work hours [8AM to 5PM] vs. off hours [5PM to 8AM]), day of consultation of the ED (week days [Monday to Friday] vs. week-ends [Saturday and Sunday]) were extracted from medical charts. Number of previous nPEP treatments were also collected as well as type of treatment regimen received. Chi square test was used to compare adherence rates for categorical variables while Student T test was used for continuous variables. The same process was successfully applied to identify risk factors for failing to consult at the first STI clinic appointment after an ED consultation. Given that we hypothesized a correlation between different risk factors, we performed a multivariate analysis that

allowed us to determine the independent contribution of each of the factors. We fitted a multivariate logistic regression and performed Allen-Cady modified backward selection with HIV status of the source, gender and sexual orientation included by default in all models.²⁰ We used a cut-off of $p \geq .20$ for termination of variables during the backward selection procedure. We evaluated whether having a health insurance modifies the relationship between the type of exposure, gender, sexual orientation and compliance to treatment, by including interaction terms in a separate multivariate regression model. Significance tests were two sided with significance set at $p \leq .05$. Results of the multivariate regression were presented as adjusted ORs and 95% confidence intervals. Only available data were analysed. All statistical analysis were performed using Stata software 14.0 (Stata Corp., College Station, Texas, USA).

Results

Summary statistics and bivariate analysis

During the 5 year study period 2663 patients consulted for nPEP and 1881 received treatment (70.6%), representing the study population. The remaining 782 patients did not receive treatment either because consulting beyond 72 hours after exposure, because HIV serology of the partner was negative, because they refused indicated treatment or because their exposure was deemed at very low risk according to Belgian Guidelines.²¹

The median age of the study population was 30 years (IQR 25 – 37 years). Sexual exposures represented the large majority of cases (98.6%) with non-sexual exposures such as mucous membrane contacts, exposure to abandoned needles and needle sharing practices, accounting for the remaining 27 exposures (1.4%). Among sexual exposures, 15.0% were sexual assault survivors; 90.8% of whom were female. Male represented 74.6% of the study population. Sexual orientation was 44.3% MSM, 49.4% heterosexual and 6.2% bisexual. Half of the population was native Belgian (50.7%) and the remaining half were immigrants; 84.5% of patients had a health insurance while 15.5% faced self-payment of follow-up consultations in the STI clinic. 152 patients initially put on ART had their treatment interrupted during follow-up with an IDP according to low risk exposure or undetectable viral load in source patient.²² Out of the remaining 1729 only 1148 (66.4%) completed the prescribed treatment regimen. Within patients not adherent to the full course of nPEP 41.1% failed to attend their initial follow-up appointment.

Male were more likely to complete nPEP (OR, 2.28; 95%CI, 1.83 -2.85; $p < 0.0001$). MSM showed better compliance than heterosexuals (OR, 1.98; 95%CI, 1.60 -2.44; $p < 0.0001$). We compared compliance between

MSM and bisexuals and found that MSM had non-significant higher compliance than bisexuals (OR 1.31; 95%CI, 0.86 – 2.02; $p=0.20$). Patients covered by a health insurance were more likely to complete nPEP (OR, 2.43; 95%CI, 1.87 -3.17; $p<0.0001$). Sexual assault survivors showed reduced compliance to the full 28 days regimen of nPEP (OR 0.34; 95%CI, 0.26 -0.45; $p<0.0001$).

Compliance to treatment was significantly different according to different geographical origins ($p<0.0001$). We further classified patients into three groups we considered relevant for further discussion (i.e. Native Belgians, Europeans and rest of the World) and found that both Europeans (OR 0.66; 95%CI, 0.50 -0.85) and all other immigrants (OR 0.50; 95%CI, 0.40 -0.63) had a lower compliance compared to native Belgians. The whole risk factors are shown in Table 1.

We observed, within all nPEP receivers, one episode of seroconversion at 4 months post-exposure in a MSM patient having received a complete nPEP regimen following an unprotected receptive anal intercourse with a HIV positive source and not reporting any subsequent at risk behaviors. This episode was therefore a probable PEP failure.

Multivariate analysis

We constructed a multivariate logistic regression model, through an Allen-Cady modified, backward selection procedure, to identify independent predictors of adherence to a complete regimen of nPEP (Table 2, Model 1). Types of exposure were excluded during this procedure as they never reached the cut off threshold of .20. Being a victim of a sexual assault (OR, 0.59; 95%CI, .38- .91) was significantly associated with a reduced adherence to treatment. Older age (OR 1.02; 95%CI, 1.01-1.04), benefiting from a health insurance (OR, 2.11 95%CI, 1.58-2.89), being MSM (OR 1.41; 95% CI, 1.04-1.90) and being native Belgian (OR 1.50; 95%CI, 1.18-1.90) were independent characteristics associated with a better adherence to the full 28 days treatment. HIV status of the source patient and gender of the patient were not associated with better adherence to treatment. Interestingly having already received a previous nPEP treatment was associated with a better compliance (OR, 1.44 95%CI, 1.02-2.02) as well as consultation during daytime hours (OR, 1.35 95%CI, 1.07-1.70). Patients receiving a starter pack based on AZT/3TC/IDV/r were as compliant (OR, .90 95%CI, .68-1.20) as patients receiving d4T/3TC/LPV/r as a starter pack. Finally, we found a significant positive effect of the interaction between being a survivor of a sexual assault and health insurance (OR, 2.33 ; 95% CI, 1.03-5.30 ; Table 2, Model 2) with health insurance significantly reducing the negative effect of sexual assault on adherence to treatment. Health insurance

did not significantly modify the relationship of other covariates and adherence to treatment and separate results are thus not reported.

We performed a second multivariate analysis in order to determine independent predictors for failing to attend an initial STI clinic appointment (Table 3). Patients having a health insurance (OR 3.36; 95%CI, 2.33-4.86) and patients having already received a previous nPEP treatment (OR 2.36; 95%CI, 1.27-4.39) were more likely to attend their first STI appointment. Sexual assault survivors were less likely to attend their first follow-up visit (OR 0.39; 95%CI, 0.23-0.67). Consultation during daytime hours was associated with a subsequent better linkage to care with increased rates of patients attending their STI Clinic appointment (OR 1.50; 95%CI, 1.09-2.07).

Discussion

Post-exposure prophylaxis for non-occupational exposures is an effective public health measure to reduce transmission of HIV.^{4,5} Although HIV is relatively inefficiently transmitted, nPEP can effectively reduce HIV acquisition after exposure.^{4,23} Protection offered by nPEP is highly dependent on adherence of patients to the prescribed regimen. Moreover follow-up consultations during an nPEP episode can offer benefits beyond monitoring drug related side-effects and improving compliance. Follow-up is a unique opportunity for HIV and STI risk counselling. Therefore linkage to care is of paramount importance as it is the key not only to a good adherence to treatment for the current nPEP episode but allows counselling on subsequent risk behaviours. Furthermore follow-up visit are an opportunity to discuss PrEP which might be the best treatment option for a subgroup of patients consulting for nPEP.

Numerous risk factors for poor completion rates have been previously identified in the literature. To our knowledge this is the first study assessing adherence to nPEP as a primary outcome through a multivariate analysis. We acknowledge one relatively small study investigating the issue of completion of nPEP follow-up at 16 weeks as a primary outcome through a multivariate study which does not correspond to treatment completion.²⁴ Our study demonstrates that having a health care insurance is an independent factor associated with improvement in adherence with an OR of 2.11. Patients who do not have to face self-payment of follow-up visits are twice as likely to complete their treatment, a finding also seen in a recent study highlighting patient attrition between ED and HIV Clinic.¹² Clinics, local, regional and national health systems should be aware of this risk and consider offering free of charge follow-up to patients without medical insurance as a measure to improve compliance. Adherence to treatment was higher in both national patients and MSM with odd ratios being respectively 1.50

and 1-41. These results should be interpreted with caution. These findings might highlight a better awareness of the risks associated with HIV exposure and the importance of nPEP within the MSM community compared to heterosexuals and in native Belgians compared to immigrant populations. Besides correlation between being native Belgian and being MSM hinders any strong conclusion about causality. Moreover educational level and health literacy which were not measured might be correlated with both these variables. Increasing age was associated with improved adherence in our cohort, with an OR 1.02 per year gain, suggesting better understanding of nPEP, increased awareness or increased risk aversion in the older population. Sexual assault survivors were strongly identified as an independent risk category for reduced adherence with an OR of 0.59, highlighting them as a fragile population needing tailored interventions. Although a South African RCT involving sexual assault survivors showed no significant benefit for telephone follow-up in terms of treatment completion rates, a subsequent study showed benefit of enhanced counselling in high risk exposures suggesting a possible benefit of tailored interventions to support adherence in victims of sexual assault receiving nPEP.^{18,25} Our findings suggest that the beneficial effects from having a health care insurance on treatment compliance are even larger for victims of sexual assaults than for patients with other types of sexual exposures. This result further call for free of charge follow-up visits and laboratory analysis for this vulnerable group of patients. Patients consulting during daytime hours, independent of the week day, showed a better compliance and a higher linkage to care than patient consulting during night hours. Interestingly the results on the time of exposure and ED visits during week-ends do not significantly affect treatment compliance, suggesting that results could be driven by prescriber fatigue. A better patient – prescriber relationship, a longer visit and a better communication are expected during daytime hours and could explain our result.²⁶ Although causality cannot be inferred, as results might be driven by multiple non-measured factors, this factor should be kept in mind when balancing the advantages of a 24/7 service with better accessibility against the risk of lower compliance when treatment is prescribed during night hours.

Finally patient receiving a AZT/3TC/IDV/r based starter pack showed a similar compliance compared to d4T/3TC/LPV/r based starter pack. The very few patients treated with EVG/COBI/FTC/TDF in our cohort impeded any safe interpretation of compliance results associated with this combination. The choice of AZT/3TC/IDV/r and d4T/3TC/LPV/r as starter packs lies outside most of national guidelines. This was a pondered choice between short term side effects and long term sustainability of our nPEP program given the very limited budget allocated per patient by our Social Security fund.

Results of the second multivariate analysis shows similar results, except for age, sexual orientation and geographic origin, as determinants for linkage to further care. Age, sexual orientation and geographic origin may be therefore

considered solely as associated with a better retention into care. Contrarily to previous results in the literature individuals with exposure to a known HIV positive individual did not show neither improved compliance to prescribed treatment nor better rate of attendance to their first follow-up.¹²

Altogether these results highlight different independent factors for both linkage and retention into care that can be tackled and taken into account when designing or optimizing nPEP programs.

Our study has both strengths and weaknesses. Its main strength is the wide number of patients included and the representation of diverse groups consulting for nPEP. This large cohort allows for precise multivariate analysis and accurate determination of the different determinants of compliance to nPEP. One of his weaknesses is the absence of socio-economic and education data as these might correlate with the observed determinants of compliance to treatment and represent the actual causal determinant of different behaviors. Another weakness is the monocentric design of our study which might hinders the extrapolation of our results to other contexts.

Generalisability as previously mentioned might be affected by the monocentric design of our study. Nevertheless our results are generated within a healthcare frame that shares major similarities with all other nPEP systems from developed countries.

Future works should take these covariates into account and investigate targeted interventions tailored to pre-identified groups at risk of low linkage and retention into care.

Conclusion

Success of an nPEP program relies both on efficacy of the treatment and compliance to it. This study identifies multiple observable characteristics of nPEP users independently associated with linkage and retention into care. Patients' characteristics can be used to early identify patients at risk of low compliance to treatment and to design targeted interventions in order to bridge gaps in care. Time of consultancy for nPEP influences further compliance to treatment and should be taken into account when implementing an nPEP program in order to balance all aspects of a 24/7 delivery system. Finally our study shows how starter packs for nPEP based on AZT/3TC/IDV/r are associated with a similar compliance when compared to d4T/3TC/LPV/r.

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Declaration of interest

Stefano Malinverni states no conflict of interest

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