Suspected unexpected and other adverse reactions to antiretroviral drugs used as post-exposure prophylaxis of HIV infection – five-year experience from clinical practice

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Abstract

Introduction: With increased use of antiretroviral drugs (ARVs) in HIV uninfected persons, proper reporting on suspected unexpected serious adverse reactions (SUSARs) and continued insight into adverse drug reactions (ADRs) are needed for adequate information on safety of ARVs in such populations.
Material and methods: Medical documentation of persons receiving ARVs after non-occupational HIV exposure (non-occupational post-exposure prophylaxis – nPEP) during 5 successive years (2009–2013) was evaluated by two HIV physicians. Adverse drug reactions s and SUSARs were defined according to international standards. In statistical analyses Cox proportional hazard models were used to identify independent predictors of developing a first ADR.
Results: In total 375 persons received nPEP with the following indications: needle stick (43%), unprotected sexual intercourse (17%), rape (10%) and first aid (10%). In 84 (22%) cases the source patient was HIV positive or an active injecting drug user. In total 170 ADRs were reported. One hundred thirty-nine persons had only 1 ADR. The most frequent first ADRs were gastrointestinal disorders (22%), followed by general symptoms (9%), hypersensitivity reactions (1.6%) and CNS symptoms (1.3%). The remaining events represented less than 1% of all patients. Eight (2.1%) patients developed a SUSAR. In multivariate analyses only age at first visit to the clinic was an independent predictor of developing an ADR (HR = 1.17, 95% CI: 1.03–1.34; p = 0.02).
Conclusions: In our observations ADRs in reaction to nPEP were frequent yet usually mild events, mostly occurring in the first 2 weeks and rarely causing discontinuation. The only significant factor increasing the risk of ADR was age. SUSARs were rare, transient and clinically insignificant.

Key words: HIV prophylaxis, post-exposure prophylaxis, adverse drug reaction, suspected unexpected serious adverse reactions.

Introduction

With the increasing use of antiretroviral drugs (ARVs) in HIV uninfected persons exposed to HIV infection there is an emerging need for adequate information on drug toxicity and tolerability in this popula-

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tion of patients [1–8]. Until now, information on ARV safety has mostly been translated from the observations on its toxicity in HIV-infected individuals. In concordance with such an approach, current guidelines recommend starting pre-exposure prophylaxis (PEP) regimens considered to be well tolerated and effective in HIV-positive individuals [9]. At the same time, data available from both observational and randomized clinical trials indicate that ARV tolerability is poorer in HIV uninfected individuals, leading to premature PEP discontinuation [10]. Factors related to this difference are not fully identified. Post-exposure prophylaxis is considered effective prevention of HIV infection only under the assumption that adherence is optimal and ARVs are used continuously in a defined period of time [11, 12]. Therefore investigation of ARV toxicity observed in such settings remains crucial for any future prevention programs. This area of research is especially lacking in Poland, with only a few published papers and none of them evaluating risk factors for adverse drug reactions [13–16].

Recently several national and international guidelines have adopted the approach of pre-exposure prophylaxis (PrEP) of HIV infection, and many local programs are considering applying it in clinical practice [17–20]. This will expand the conventional use of ARVs, which was limited to post-exposure prescription [2, 21, 22].

Both retrospective and prospective observational studies remain the most relevant approach in investigation of adverse drug reactions (ADRs) and suspected unexpected adverse reactions (SUSARs) of antiretroviral drugs prescribed for HIV uninfected individuals in clinical practice. Therefore we investigated the prevalence and factors related to adverse reactions to ARVs in persons consulted for post-exposure prophylaxis at the HIV Out-Patient Clinic, Hospital for Infectious Diseases in Warsaw.

Material and methods

Medical documentation of persons receiving ARVs after non-occupational HIV exposure (non-occupational post-exposure prophylaxis – nPEP) during 5 consecutive years (2009–2013) was evaluated. Adverse drug reactions and SUSARs were evaluated by two HIV physicians. Adverse drug reactions was defined as any undesirable, suspected reaction associated with the use of an antiretroviral drug in an HIV uninfected patient. SUSAR was defined as an adverse reaction that is both unexpected (not consistent with the applicable product information) and meets the definition of an adverse reaction.

The general characteristic indications for starting nPEP were grouped into three categories: sexual risk (men who have sex with men (MSM) oral intercourse, MSM anal intercourse, heterosexual vaginal intercourse and rape), physical contact with blood on injured skin (including human bite, being involved in a fight or attack, giving first aid) and incidental needle stick not related to occupational activities.

The study was approved by the Bioethical Committee at the Medical University of Warsaw (No. AKBE 133/16).

Statistical analysis

In statistical analyses χ^2 and Kruskal-Wallis tests were used as appropriate. Kaplan Meier survival analysis was used to estimate the probability of ADR and Cox proportional hazard models to identify independent predictors of developing ADR. The time was censored at the day of first ADR occurrence. The variables tested in univariable analyses were chosen based on clinical relevance and center experience. They included gender, age, calendar year, indication for nPEP (exposure risk defined as sexual, needle stick or other), HIV status of source patient (known HIV added to injecting drug use or unknown), ARVs used (zidovudine/lamivudine – AZT/3TC or tenofovir/emtricitabine – TDF/FTC) and regimen used (two or three drugs). A multivariable model included all named variables. Only the first ADR was included in the analyses. A confidence interval (CI) of 95% was applied. All analyses were performed with SAS version 9.3 (SAS Institute, Cary, NC).

Results

During 5 years of observation 375 persons received antiretroviral treatment as prevention of non-occupational exposure to HIV infection. The mean age at the first visit in the clinic was 34.1 (standard deviation (SD) ± 11.8) years and 55% of patients were male.

The most common reason for initiating nPEP was needle stick (43%) followed by physical contact (30%), unprotected sexual intercourse (17%) and rape (10%). In 84 (22%) cases the source patient was either known to be HIV positive or within a high-risk group, namely an active injecting drug user. In 3 cases the source patient was tested for HIV and found to be negative. In the remaining cases the source person remained of unknown HIV status.

The nucleos(t)ide reverse transcriptase inhibitors used for nPEP were AZT/3TC (91.7%) and TDF/FTC (8.3%). A three-drug regimen was used in 136 (36.7%) patients. The third drug used was a protease inhibitor, with the majority (131 persons, 96.3%) of patients receiving lopinavir boosted with ritonavir. Sixty-four (17.1%) patients

discontinued nPEP drugs before 28 days, but only 22 (5.9%) as a consequence of experiencing ADR. Nineteen (5.1%) patients required sick leave from work.

Adverse drug reactions

One hundred thirty-nine (37%) persons experienced at least one adverse drug reaction to nPEP. In this group 29 (8%) persons experienced two and 2 (0.5%) persons experienced three ADRs. In total 170 ADRs were reported.

The most frequent first ADRs were gastrointestinal disorders, followed by general symptoms, hypersensitivity reactions and CNS symptoms. The remaining events were laboratory abnormalities, other and unknown, each contributing to less than 1% of all patients, as shown in Table I.

The comparison of baseline characteristics between patients experiencing and not experiencing ADRs is presented in Table II.

The median time to first ADR was 8 (IQR: 2–14) days. In general the majority of ADRs, namely 125 (89.9%) events, occurred within the first 15 days of nPEP. Figure 1 presents the Kaplan-Meier plot of time to first ADR and the numbers of events occurring at a given time point.

Table III presents the univariate and multivariate Cox proportional hazard models for the risk of developing a first ADR. In multivariate analyses only the age at first visit to the clinic was an independent predictor of developing ADR (HR = 1.17, 95% CI: 1.03–1.34; p = 0.02).

Suspected unexpected adverse reactions

Eight (2.1%) patients developed an adverse reaction recognized by the study doctor as a SUSAR. The events were bradycardia, vivid dreams, lymphadenopathy of the neck, increase in platelet count, swelling of and painful large joints, swelling of lower limbs after statins were stopped, peripheral edema, and loss of concentration. Each patient experienced one event.

Discussion

Our study showed that adverse reactions to antiretroviral drugs used as part of nPEP were frequent events and more than one in three patients experienced at least one ADR. However, most of these events were of no clinical consequence, and they led to nPEP discontinuation in only 5.9% of cases. These results are well in line with other studies [10, 23–26].

In our multivariate analyses the only factor significantly increasing the risk of ADR was age, with a 17% increase in the risk for each ten years older. Factors associated with the risk of developing ADRs identified by other studies were gender, sexuality and the ARV regimen used for prophylaxis, with AZT being the most frequent cause of ADRs [10, 27, 28]. We did not observe such effects. However, a limitation of our study might be the low number of patients in the comparative TDF/FTC group. This could explain why we did not observe increased risk of ADRs with AZT-containing regimens. For that reason we were also unable to further analyze any single ARV-related effects.

Over 2% of patients developed an adverse reaction that was unexpected and not consistent with the applicable product information, therefore fulfilling the definition of SUSAR. Data on the prevalence of these specific adverse reactions are not reported, and therefore the knowledge in this field is very limited. Studies investigating the toxicity of ARVs used as part of PEP are rare, mostly retrospective with a low number of participants.

Whereas it is easier to identify ADRs, even retrospectively, SUSARs are rare events and require a long time or large groups to be observed. In addition, a qualified, trained personnel needs to evaluate and confirm the event as a SUSAR.

Table I. Frequency of first adverse drug reactions

Adverse drug reaction	Frequency	Percentage of all patients	Percentage of all ADRs
Gastrointestinal disorders	83	22.1	59.7
General symptoms	34	9.1	24.5
Hypersensitivity reactions	6	1.6	4.3
CNS symptoms	5	1.3	3.6
Hematological disorders	3	0.8	2.2
Liver enzymes elevation	2	0.5	1.4
Increase of serum creatinine	2	0.5	1.4
Unspecified	2	0.5	1.4
Other not classifiable as any above	2	0.5	1.4

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Table II. Baseline characteristics for patients experiencing adverse drug reactions (ADRs) and not experiencing them (no ADR)

Parameter	All (*n* = 375)	Patients with ADRs (*n* = 139)	Patients without ADRs (*n* = 236)	*P*-value
Age, mean ± SD [years]	34.1 ±11.8	32.7 ±10.7	25.6 ±6.0	0.02
Days of nPEP completed, *n* (%):				0.16
28 days of ARV	311	114	197	
14–27	43	16	27	
< 14	21	9	12	
Male gender	206 (54.9)	74 (53.2)	132 (55.9)	0.67
Calendar year, *n* (%):				0.20
2009	139 (37.1)	50 (36.0)	89 (37.7)	
2010	66 (17.6)	19 (13.7)	47 (19.9)	
2011	47 (12.5)	15 (10.8)	32 (13.6)	
2012	66 (17.6)	28 (20.1)	38 (16.1)	
2013	57 (15.2)	27 (19.4)	30 (12.7)	
Type of exposure, *n* (%):				0.34
Sexual contact (MSM anal)	5 (1.3)	3 (2.2)	2 (0.8)	
Sexual contact (MSM oral)	32 (8.5)	12 (8.6)	20 (8.5)	
Sexual contact (vaginal)	28 (9.3)	13 (9.3)	15 (6.4)	
Sexual contact (rape)	38 (10.1)	11 (7.9)	27 (11.4)	
Physical contact	112 (29.9)	35 (25.2)	77 (32.6)	
Incidental needle stick	160 (42.7)	65 (46.8)	95 (40.2)	
Source patient HIV-positive or active injecting drug use	84 (22.4)	28 (20.1)	111 (79.9)	0.44
Days of nPEP completed, *n* (%) [days of ARVs]:				0.16
28	311 (82.9)	114 (82.0)	197 (83.5)	
14–27	43 (11.5)	16 (11.5)	27 (11.4)	
< 14	21 (5.6)	9 (6.5)	12 (5.1)	
Use of three ARVs, *n* (%)*	136 (36.7)	58 (41.7)	81 (58.3)	0.10
Use of NRTIs, *n* (%)**:				0.85
AZT/3TC	344 (91.7)	128 (92.1)	216 (91.5)	
TDF/FTC	31 (8.3)	11 (7.9)	20 (8.5)	

*Antiretroviral drugs, **nucleo(t)side reverse transcriptase inhibitors.*

Data from national and European drug safety reports for PEP are not available [12]. The ideal approach is the one taken for newly registered ARVs planned for PrEP due to its favorable pharmacokinetics. However, still most published PrEP randomized controlled trial studies are not reporting SUSARs [29–31]. Currently, several randomized controlled clinical trials have been published and others are ongoing to investigate the efficacy and safety of ARVs used in HIV uninfected individuals for PrEP [11, 29–32]. However, such studies are planned for short term use and on young and healthy individuals.

Antiretroviral drugs side effects contribute to substantial risk of treatment interruption or non-adherence, limiting the efficacy of the whole PEP [12]. Numerous studies have presented the tolerability and safety profile of drugs as two crucial factors for the choice of antiretroviral agents in nPEP [5, 13, 27, 30, 33].

In one comparative U.S. study, 90% of physicians prescribing nPEP and 68% of those who never prescribed nPEP reported delivering nPEP as feasible in their practice [4]. In light of new policies, which are encouraging health care providers to offer and deliver nPEP, and providers' readiness to do so, better understanding of the safety profile for the non-HIV population is vital [1–8, 17].

Currently, most recommendations for the selection of HIV PEP components are based on experience with their use in the HIV infected population. For example, the recommendation for the use of three- versus two-drug PEP reflects reports from studies presenting superior effectiveness of such treatment in reducing the viral burden in HIV-infected persons [34, 35]. However, published case reports and analyses of retrospective data indicate that some unexpected or unexplained adverse reactions to PEP components may occur [36, 37]. Randomized controlled trials are not able to capture rare events or reactions occurring in patients with chronic morbidities, who are usually excluded per protocol. In addition, most post-exposure trials are not designed to actively follow up on adverse events, and trials using al-
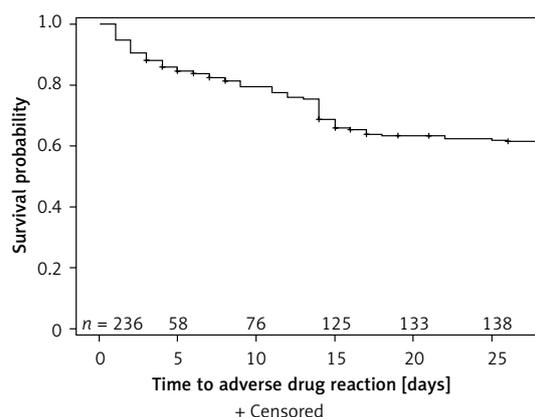
Figure 1. The Kaplan-Meier plot of time to first adverse drug reaction with the numbers of events occurring at a given time point

ready registered substances with an off-label indication do not focus on collecting SUSARs. From this perspective, data from both prospective and retrospective, observational studies are valuable and important, but there is an increasing need for structured and systematic pharmacovigilance of the use of ARVs in the population of HIV non-infected persons.

Table III. Cox proportional hazard models for the risk of developing ADR

Parameter		Univariate			Multivariate		
		Hazard ratio	95% CI	*P*-value	Hazard ratio	95% CI	*P*-value
Gender	Female	1.00	–	–	1.00	–	–
	Male	0.9	0.64–1.26	0.53	1.05	0.73–1.50	0.81
Calendar year	2009	1.00	–	–	1.00	–	–
	2010	0.79	0.47–1.34	0.38	0.76	0.44–1.31	0.33
	2011	0.90	0.51–1.60	0.72	0.86	0.47–1.56	0.62
	2012	1.24	0.78–1.97	0.36	1.11	0.67–1.84	0.68
	2013	1.52	0.95–2.43	0.08	1.17	0.63–2.16	0.62
Age	With each 5-year increase	1.02	1.00–1.03	0.01	1.08	1.01–1.16	0.02
	With each 10-year increase	1.18	1.04–1.35	0.01	1.17	1.03–1.34	0.02
NRTI	AZT/3TC	1.00	–	–	1.00	–	–
	TDF/FTC	0.95	0.51–1.76	0.87	0.91	0.46–1.81	0.79
Regimen	2 ARVs	1.00	–	–	1.00	–	–
	3 ARVs	1.33	0.95–1.86	0.10	1.22	0.75–1.99	0.41
Exposure risk	Sexual	1.00	–	–	1.00	–	–
	Needle stick	1.10	0.74–1.63	0.64	0.98	0.62–1.54	0.92
	Other	0.82	0.52–1.29	0.38	0.80	0.49–1.32	0.39
Source patient HIV status	Unknown	1.00	–	–	1.00	–	–
	HIV infected or high risk	0.85	0.56–1.29	0.45	0.83	0.51–1.33	0.44

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In conclusion, although in our observation ADRs to nPEP were usually mild events, the risk of their occurrence significantly increased with age. This should be taken into account when assessing the risk of HIV transmission through non-occupational exposure, as older patients would have a lower net benefit from prevention with ARVs than younger ones. Older patients should be informed of the higher risk of ADRs and properly explained what this means.

Acknowledgments

Conflict of interest

The authors declare no conflict of interest.

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