Journal of Hospital Infection 92 (2016) 372–377

Available online at www.sciencedirect.com

Journal of Hospital Infection

journal homepage: www.elsevierhealth.com/journals/jhin

Significant intolerability of efavirenz in HIV occupational postexposure prophylaxis

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ARTICLE INFO

Article history:
Received 24 March 2015
Accepted 11 December 2015
Available online 14 January 2016

Keywords:
Postexposure prophylaxis
Tolerability
Occupational exposure
HIV infection
Efavirenz

SUMMARY

Background: Completion of human immunodeficiency virus (HIV) occupational postexposure prophylaxis (PEP) is important for successful prophylaxis.
Aim: To determine factors associated with failure to complete the four-week HIV PEP.
Methods: A retrospective study was conducted among healthcare workers (HCWs) accidentally exposed to blood or body fluids of patients at the Bamrasnaradura Infectious Diseases Institute, Thailand, between March 1996 and June 2014. Logistic regression analysis was used to determine factors associated with failure to complete the four-week HIV PEP.
Findings: In total, 225 exposure episodes were reported. The mean age of HCWs was 33.1 (standard deviation 9.9) years, and 189 (84%) were female. Nurses (43%) were exposed most frequently. The HIV status of the source was defined in 149 (66%) episodes, and 101 (68%) of these were positive. Of 225 exposures, PEP was prescribed in 155 (69%) cases, with intentional discontinuation in 26 cases. Ninety-one of 129 (71%) HCWs completed the four-week regimen. Multi-variate analysis showed that a regimen of two nucleotide reverse transcriptase inhibitors (NRTI) + efavirenz (EFV) was the only significant factor associated with non-completion of the four-week course (odds ratio 37.8, 95% confidence interval 4.2–342.3; $P < 0.01$). Other factors including age, sex, staff position, status of the source and other PEP regimens were not associated with non-completion of the four-week course ($P > 0.05$). None of the HCWs were documented to have HIV seroconversion.
Conclusion: A regimen of two NRTIs + EFV was significantly associated with premature discontinuation of occupational PEP. This regimen should not be used for HIV prophylaxis following occupational exposure.

Introduction

Healthcare workers (HCWs) are vulnerable to accidental exposure to blood and other body fluids while performing their work duties. There is evidence that postexposure prophylaxis (PEP) with antiretroviral drugs can decrease the risk of human immunodeficiency virus (HIV) infection after occupational

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http://dx.doi.org/10.1016/j.jhin.2015.12.015
0195-6701/

exposure.[1] Although the treatment goals of chronic HIV infection are distinct from those of HIV PEP, prophylaxis by many antiretroviral regimens similar to those used in the treatment of chronic infection is recommended.[2,3] However, a previous study demonstrated that interruption of PEP in HCWs was eight times higher compared with that of treatment with the same regimen in HIV-positive subjects, and that the incidence of adverse events was approximately six times higher.[4] Thus, it may not be possible to extrapolate the tolerability of HIV antiretroviral agents for prophylaxis from the data of HIV-infected patients taking the same regimens.[5] Regimen completion is one of the important factors in successful prophylaxis. Limited data are available on the tolerability of PEP regimens in HCWs, particularly in resource-limited settings. Studies in the developed-world setting and their reported results of adverse events cannot be generalized to the developing world.[6] This study aimed to describe the characteristics of occupational exposure, and sought to determine the factors associated with non-completion of the four-week HIV PEP course.

Methods

A retrospective study was conducted among HCWs who were accidentally exposed to blood or other body fluids of patients at the Bamrasnaradura Infectious Diseases Institute, which is the referral hospital for HIV-infected patients in Thailand, between March 1996 and June 2014. All occupational exposure reports were retrieved from the registry data of the Infection Prevention and Control Unit. The exposure data of HCWs who were willing to disclose and provide written informed consent were collected. The source patients were anonymous in the registry. Data, including age, sex, staff position, time of exposure occurrence, location of exposure occurrence, exposure characteristics (type and circumstances), HIV status of the source patient, HIV status of the HCW at baseline, PEP regimens, duration of PEP, adverse events and outcomes (completion of the four-week regimen and HIV status of the HCW at six weeks, three months and six months after exposure), were extracted from the registry and medical records. The study was reviewed and approved by the Institutional Review Board.

Statistics

Descriptive data are presented as mean [standard deviation (SD)], median (interquartile range) and frequencies (%), as appropriate. Study participants were categorized into two groups based on completion or non-completion of the four-week prophylactic regimen. The mean values of continuous variables with a normal distribution between the two groups were compared using Student's *t*-test. Categorical variables were compared using the Chi-squared test and Fisher's exact test, as appropriate. Logistic regression analyses were used to determine factors associated with non-completion of the four-week HIV PEP course. Variables with $P < 0.20$ on univariate analysis were included in the multiple logistic regression model. All statistical analyses were performed using Statistical Package for the Social Sciences Version 15.0 (IBM Corp., Armonk, NY, USA). $P < 0.05$ was considered to indicate statistical significance.

Table I
Characteristics and description of 225 exposure episodes

	N (%)
Sex	
Male	36 (16.0)
Female	189 (84.0)
Age, years (SD)	33.1 (9.9)
Staff position	
Physician	17 (7.6)
Nurse	97 (43.1)
Patient assistant or nurse assistant	40 (17.8)
Medical technician	34 (15.1)
Housekeeper	16 (7.1)
Nursing or laboratory student	16 (7.1)
Other ancillary	5 (2.2)
Place where exposure occurred, $N = 183$	
Inpatient ward	72 (39.3)
Operating and labour room	33 (18.0)
Laboratory	27 (14.8)
Outpatient department	19 (10.4)
Emergency room	16 (8.8)
Dental room	9 (4.9)
Central supply and medical waste unit	7 (3.8)
Circumstances of exposure	
Delivering medication through venous route	50 (22.2)
Drawing blood or recapping	48 (21.3)
Bedside procedure	22 (9.8)
Operating procedure	30 (13.3)
Performing laboratory test	30 (13.3)
Cleaning of equipment	20 (8.9)
Providing nursing care	13 (5.8)
Other[a]	12 (5.4)
Exposure types	
Percutaneous	163 (72.4)
Mucous membrane	43 (19.1)
Non-intact skin	6 (2.7)
Intact skin	13 (5.8)
Status of source	
HIV positive	101(44.9)
HIV negative	48 (21.3)
Unknown HIV status	46 (20.5)
Unknown source patient	30 (13.3)

HIV, human immunodeficiency virus; SD, standard deviation.
[a] Including talking with patients, gardening and processing medical waste.

Results

In total, 225 exposure episodes were reported: 163 percutaneous injury, 43 mucosal exposure, six non-intact skin exposure and 13 intact skin exposure. The mean age of HCWs was 33.1 (SD 9.9) years, and 189 (84.0%) were female. Nurses were exposed most frequently (43.1%), followed by patient assistants or nurse assistants (17.8%), medical technicians (15.1%) and physicians (7.6%). Of all exposures, 53.3% occurred while performing medical procedures (delivering medication through venous route in 22.2%, drawing blood and recapping in 21.3%, and performing bedside procedures in 9.8%), while 13.3% occurred during operating or birthing procedures. The remaining exposure episodes occurred while performing

laboratory tests (13.3%), cleaning equipment (8.9%), and providing nursing care (5.8%). Exposures occurred most often in inpatient wards (39.3%), operating and labour rooms (18.0%), and the laboratory unit (14.8%). Exposures occurred most often during the day shift (68.8%) (Table I).

The HIV status of the source was defined in 149 (66.2%) episodes, and was positive in 101 (67.7%) cases. Of 225 exposures, PEP was prescribed in 155 (68.8%) cases, yet was subsequently intentionally discontinued in 26 cases (source status was HIV negative in 19 cases, and refusal to continue in seven cases). PEP courses should have been completed in 129 episodes (Figure 1). Of 129 prescribed regimens, 49 (38.0%) were two nucleoside reverse transcriptase inhibitors (NRTIs), 48 (37.2%) were two NRTIs + protease inhibitors (PIs), 16 (12.4%) were zidovudine (ZDV) monotherapy, 11 (8.5%) were two NRTIs + efavirenz (EFV) and five (3.9%) were two NRTIs + raltegravir (RAL) (Table II). Only 91 of 129 (70.5%) HCWs completed the four-week regimen. On univariate analysis, female sex ($P = 0.104$), ZDV monotherapy ($P = 0.147$), two NRTIs + EFV ($P = 0.002$), and two NRTIs + boosted lopinavir (LPV) ($P = 0.167$) were the factors with $P < 0.20$. These factors were considered to be candidates for the multi-variate model. On multi-variate analysis, the two NRTIs + EFV regimen was the only factor significantly associated with non-completion of the four-week course [odds ratio (OR) 37.8, 95% confidence interval (CI) 4.2–342.3; $P = 0.001$] (Table III). Of 11 exposure episodes in which EFV was prescribed, 10 were females. The backbones were ZDV + lamivudine (3TC) in nine cases and tenofovir (TDF) + 3TC in two cases. Only one HCW completed the four-week course; she received ZDV + 3TC + EFV. Of 10 exposure episodes in which EFV was discontinued prematurely, the same backbone was continued until completion of a four-week course in six cases (ZDV + 3TC in five cases and TDF + 3TC in one case), and PIs were substituted for the remaining duration in four cases (boosted LPV in three cases and boosted atazanavir in one case). The reason for premature discontinuation of the regimen of two NRTIs + EFV was severe dizziness in all patients. None of the HCWs were reported to have HIV seroconversion.

Discussion

Only 71% of HCWs in this study completed the four-week HIV prophylactic course. The HIV status of the source did not influence the completion of PEP, whereas the choice of antiretroviral regimen did influence the completion of PEP. Antiretroviral prophylaxis with an EFV-based regimen was significantly associated with non-completion of PEP. Female sex and ZDV monotherapy had a trend towards premature interruption. However, HIV seroconversion was not found among any of the HCWs.

The exposure characteristics found in this study were consistent with other studies of occupational exposure to HIV.[7–9] The most common type of exposure was percutaneous. Such exposures occurred more often when performing medical procedures in the inpatient wards than during surgical procedures in the operating rooms. This may be due to heightened awareness of exposure to blood or body fluid of patients in surgical situations. Standard precautions should be applied in all settings of patient care. The PEP discontinuation rate was

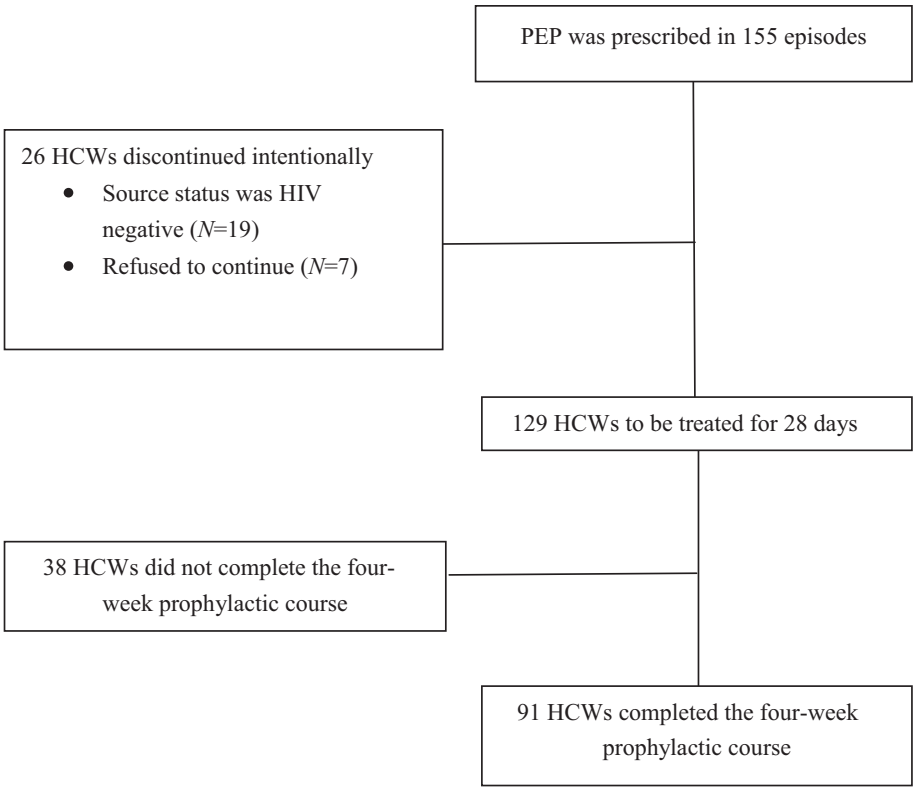

Figure 1. Postexposure prophylaxis disposition. HCWs, healthcare workers; HIV, human immunodeficiency virus; PEP, postexposure prophylaxis.

Table II
Characteristics of 129 episodes that were intended to be treated with the complete four-week prophylactic course

	All ($N = 129$)	Completed ($N = 91$)	Not completed ($N = 38$)	*P*-value
Sex, *n* (%)				0.086
Male	17 (13.2)	15 (16.5)	2 (5.3)	
Female	112 (86.8)	76 (83.5)	36 (94.7)	
Age, years (SD)	33.1 (9.7)	32.9 (9.7)	33.5 (9.7)	0.728
Staff position, *N* (%)				0.313
Physician	12 (9.3)	9 (9.9)	3 (7.9)	
Nurse	63 (48.8)	43 (47.2)	20 (52.6)	
Patient assistant or nurse assistant	22 (17.1)	14 (15.4)	8 (21.1)	
Medical technician	20 (15.5)	18 (19.8)	2 (5.3)	
Housekeeper	8 (6.2)	5 (5.5)	3 (7.9)	
Nursing or laboratory student	3 (2.3)	2 (2.2)	1 (2.6)	
Other ancillary	1 (0.8)	0	1 (2.6)	
Source patient status, *N* (%)				0.674
HIV positive	84 (65.1)	62 (68.1)	22 (57.9)	
HIV negative	6 (4.7)	4 (4.4)	2 (5.3)	
Unknown HIV status	23 (17.8)	14 (15.4)	9 (23.7)	
Unknown source patient	16 (12.4)	11 (12.1)	5 (13.1)	
PEP regimen, *N* (%)				
One drug: mono ZDV	16 (12.4)	9 (9.9)	7 (18.4)	0.240
Two drugs				0.427
ZDV/3TC	43 (33.3)	32 (35.2)	11 (29.0)	
ZDV/ddI	2 (1.6)	1 (1.1)	1 (2.6)	
d4T/3TC	2 (1.6)	2 (2.2)	0	
TDF/3TC or FTC	2 (1.6)	2 (2.2)	0	
Three drugs				<0.001
Two NRTIs + EFV	11 (8.5)	1 (1.1)	10 (26.3)	
Two NRTIs + LPV/r	21 (16.2)	19 (20.8)	2 (5.3)	
Two NRTIs + IDV	15 (11.6)	10 (11.0)	5 (13.2)	
Two NRTIs + NFV	7 (5.4)	6 (6.6)	1 (2.6)	
Two NRTIs + ATV/r or DRV/r	5 (3.9)	4 (4.4)	1 (2.6)	
Two NRTIs + RAL	5 (3.9)	5 (5.5)	0	

3TC, lamivudine; ATV/r, boosted atazanavir; d4T, stavudine; ddI, didanosine; DRV/r, boosted darunavir; EFV, efavirenz; FTC, emtricitabine; HIV, human immunodeficiency virus; IDV, indinavir; LPV/r, boosted lopinavir; NFV, nelfinavir; NRTIs, nucleoside reverse transcriptase inhibitors; PEP, postexposure prophylaxis; PIs, protease inhibitors; RAL, raltegravir; TDF, tenofovir; ZDV, zidovudine.

high in this study, in agreement with the results of a previous systematic review.[10] Exposure prevention and better safety habits among HCWs are still essential.

This retrospective study included cases of exposure between 1996 and 2014. Before 2014, the authors' institute followed the US Public Health Service guidelines for the management of occupational exposures to HIV and recommendations for postexposure prophylaxis 2001 and 2005.[11,12] Two- or three-drug PEP regimens were considered by transmission risk, and EFV was recommended as an alternative third drug in the expanded regimen. PEP regimens were selected on an individual basis based on the above guidelines. As such, variation in PEP regimens occurred, which may explain the continued use of EFV. However, due to the retrospective nature of this study, the reasons for EFV selection are not known.

Antiretroviral treatment with EFV-containing regimens has substantial adverse events, particularly on the central nervous system; these resolve or improve in a few days in HIV-infected patients.[13] Nevertheless, Quirino *et al.* showed that antiretroviral treatment for prophylaxis of HIV-negative subjects had much higher treatment interruption compared with that of treatment of HIV-positive patients with the same regimen, and that the incidence of adverse events was also higher.[4] This may explain why only one of the 11 HCWs who took the EFV-based regimen completed the four-week prophylactic course, while the other HCWs were intolerant. Each female HCW was asked about their last menstrual period before receiving PEP. If the menstrual period was not in a regular cycle, a urinary pregnancy test was performed. They were also advised to use condoms for transmission prevention and birth control if they had sexual intercourse. Moreover, side-effects of the EFV-based regimen were documented to be the only cause of interrupted prophylaxis. Hence, concerns related to pregnancy are not thought to be the cause of EFV-containing PEP discontinuation. Although ZDV or other antiretrovirals were possible causes of dizziness, EFV was likely to be the offending drug from the data of the two NRTIs + EFV cohort. Completion of a four-week regimen has proven to be critical in animal studies.[14,15] Thus, two NRTIs + EFV should not be used or recommended in HIV PEP. In addition, this study found no difference in non-completion of PEP between regimens of two NRTIs and two NRTIs + PIs. This finding was similar to previous reports.[16,17] Interestingly, all of the HCWs taking two NRTIs + RAL completed the four-week course. Despite the fact

Table III
Logistic regression analyses of factors associated with non-completion of the four-week regimens in 129 episodes that were intended to be treated with the complete prophylactic course

Factors	Crude OR (95% CI)	*P*-value	Adjusted OR (95% CI)	*P*-value
Sex				
Male	1			
Female	3.55 (0.77–16.37)	0.104	5.59 (0.93–33.46)	0.060
Age	1.01 (0.97–1.05)	0.725		
Staff position				
Physician	1			
Nurse	1.39 (0.34–5.72)	0.643		
Patient assistant or nurse assistant	1.71 (0.36–8.23)	0.501		
Medical technician	0.33 (0.05–2.37)	0.272		
Housekeeper	1.80 (0.26–12.50)	0.552		
Nursing or laboratory student	1.50 (0.10–23.07)	0.771		
Status of source				
Unknown source patient	1			
HIV positive	0.78 (0.24–2.50)	0.677		
HIV negative	1.10 (0.15–8.13)	0.926		
Unknown HIV status	1.41 (0.38–5.45)	0.614		
PEP regimen				
Mono ZDV	2.40 (0.74–7.83)	0.147	3.19 (0.98–10.42)	0.054
Two NRTIs	1			
Two NRTIs + EFV	30.83(3.57–266.37)	0.002	37.77 (4.17–342.25)	0.001
Two NRTIs + LPV/r	0.33 (0.07–1.60)	0.167	0.33 (0.07–1.55)	0.160
Two NRTIs + IDV	1.54 (0.44–5.41)	0.499		
Two NRTIs + NFV	0.51 (0.06–4.71)	0.556		
Two NRTIs + ATV/r or DRV/r	0.77 (0.08–7.58)	0.823		
Two NRTIs + RAL	<0.01 (NA)	0.999		

3TC, lamivudine; ATV/r, boosted atazanavir; CI, confidence interval; d4T, stavudine; ddI, didanosine; DRV/r, boosted darunavir; EFV, efavirenz; FTC, emtricitabine; HIV, human immunodeficiency virus; IDV, indinavir; LPV/r, boosted lopinavir; NA, not applicable; NFV, nelfinavir; NRTIs, nucleoside reverse transcriptse inhibitors; OR, odds ratio; PEP, postexposure prophylaxis; PIs, protease inhibitors; RAL, raltegravir; TDF, tenofovir; ZDV, zidovudine.

that the present sample size was too small, recent studies have demonstrated good tolerability of the RAL-based prophylactic regimen for non-occupational exposure.[18,19] The current US Public Health Service and UK guidelines[2,20] recommend tenofovir + emtricitabine + RAL as the preferred HIV PEP regimen. However, lack of availability or accessibility to RAL may be difficult in resource-limited settings. Several alternative regimens in the recommendation could be used instead, but the use of EFV as an alternative should be reviewed. Likewise, the use of two NRTIs + EFV as an alternative regimen for HIV PEP in the World Health Organization's guideline[21] should also be reconsidered.

ZDV chemoprophylaxis alone tended to be associated with non-completion of the four-week course compared with two NRTIs. This can be explained by the high dose of ZDV that was prescribed. In the early HIV era, HCWs who took ZDV prophylaxis received a dose of approximately 1000 mg/day. Female sex also had a tendency towards early discontinuation. This finding is comparable with previous studies,[5,22] but the reason is not known. Several reports in HIV-infected individuals have suggested that females achieve higher plasma antiretroviral drug concentrations than males at the same dose.[23–25] High plasma drug levels may increase the risk of drug toxicities. Gervasoni *et al.* found that low body weight in females could increase antiretroviral-drug-related adverse events.[26] This may explain why women who took a fixed dose of antiretroviral prophylaxis had higher intolerability.

This study has several limitations. First, because of the retrospective study design, some data about the exact duration of antiretrovirals in HCWs who discontinued PEP prematurely and adverse events were missing. Second, selection bias may have occurred because this study required voluntary disclosure of exposure data. Third, the small number of subjects may have limited the ability of this study to detect the significance of some factors. However, the obligation of the study institute was to minimize this number to prevent and control infection. Lastly, the efficacy of PEP could not be evaluated due to the small number of participants. Such an evaluation would require a very large sample size due to the low risk of seroconversion.

In conclusion, a regimen of two NRTIs + EFV was significantly associated with premature discontinuation of occupational PEP. This regimen should not be used for HIV prophylaxis following occupational exposure, particularly in resource-limited settings. Although prophylaxis with two NRTIs + integrase inhibitors or late-generation PIs should be evaluated further, exposure prevention and better safety habits among HCWs are still essential.

Conflict of interest statement
None declared.

Funding sources
None.

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