

# Short-Term Toxicity and Discontinuation of Antiretroviral Post-Exposure Prophylaxis

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## ABSTRACT

**Background:** Side effects and PEP discontinuation were suggested to be more common among individuals on post exposure prophylaxis (PEP) taking PI-regimens and this could affect compliance, resulting in a potential reduction of PEP efficacy. To evaluate short-term toxicity and discontinuation of PEP by regimen, we reviewed data collected in our National Registry.

**Methods:** Individuals were assigned to group A (2 NRTIs), or gr. B (2 NRTIs plus PI), according to their initial regimen. Discontinuation was assumed as < 28 days. Lost to follow up or data not available (57 persons), PEP discontinuation because the source tested HIV negative (n. 340), and subjects who self-withdrew without side effects [38 gr. A (15%); 42 gr. B (10%)], were excluded. Statistical analysis was undertaken with chi-square test.

**Results:** Until 08/01, 216 gr. A (92% ZDV plus 3TC), and 380 gr. B individuals (85% ZDV and 3TC, plus 92% IDV) were included in the analysis. 127 individuals in gr. A (58.8%) and 253 in gr. B (66.6%) experienced at least one side-effect (OR 1.40; 95% CI 0.97-2.00; p = 0.07). The proportion of PEP discontinuation because of side-effects was 21.3% in gr. A (46 subjects, mean PEP duration 10.7 days, median 8, range 1-27) and 27.9% in gr. B (106 subjects, mean 9.3, median 7, range 1-26) (OR 1.43, 95% CI 0.95-2.18; p=0.09). Of the 106 gr. B individuals who discontinued PEP, 18 initially only discontinued the PI (after a mean of 6.4 days, median 4.5, range 1-20), however PEP was completely discontinued because of side effects after a mean of 13.4 additional days on two NRTIs (median 11, range 1-26). Finally, 44 (12%) gr. B individuals discontinued the PI after a mean of 9.4 days (median 7.5, range 1-27), but completed the 4-week course of two NRTIs. Adding these 44 individuals to the discontinuations observed in gr. B, the difference becomes statistically significant (OR 2.41, 95% CI 1.62-3.63, p < 0.001).

**Conclusion:** Although PI including PEP appears associated with a higher risk of side effects and discontinuation, these findings do not justify *per se* the exclusion of PI from the initial regimen. Indeed, our study showed that in most individuals the full-course, 3-drug regimen can be completed. Unless already contraindicated, we suggest beginning PEP with a 3-drug regimen and discontinuing the PI in the case of side effects that are not manageable, in order to prolong and possibly complete the 4 week treatment.

## Background

Several prospective studies have estimated that the risk of acquiring human immunodeficiency virus (HIV) infection after accidental exposures to infected blood or other at-risk materials in the health care setting is less than 0.5%, on average. However, the above reported average risks must be interpreted cautiously because the efficiency of transmission varies widely according to the source as well as the host influencing factors.

Zidovudine, was associated with the reduced risk of HIV infection transmission, when used as a post-exposure prophylactic agent. On the basis of these features, Public Health Agencies in developed countries, including Italy, issued and updated recommendations for the chemoprophylaxis management of exposed health care workers. Moreover, a debate was initiated regarding the opportunity of extending these recommendations to other routes of exposure, for example sexual contact, or injection-drug use. Combination post exposure prophylaxis (PEP) with two nucleoside reverse transcriptase inhibitors (NRTIs) antiretroviral agents for the majority of exposures, plus the addition of a protease inhibitor (PI) for the highest risk exposures, is currently recommended.

In fact, combined three drug antiretroviral therapy is now the recommended standard of care for the treatment of HIV infection in order to reduce the viral burden and replication, as well as to overcome the problem of drug resistance, and to minimize the risk of its development.

Similar objectives of treatment could be of importance also in PEP, and a combination of active drugs at different stages in the viral replication cycle could offer an additional preventive effect in PEP. However, the applicability of these recommendations for persons taking PEP is uncertain, and whether the potential toxicity of a third drug is justified for lower risk exposures has been questioned.

We reviewed the data that was prospectively collected by the Italian Registry of Antiretroviral Post Exposure Prophylaxis.

## The Italian Registry of Antiretroviral Post-Exposure Prophylaxis

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## Methods

In March 1990, the National Commission on AIDS of the Italian Ministry of Health issued a specific protocol to standardize zidovudine prophylaxis, which thereby led to the establishment of the Italian Registry of Antiretroviral Post Exposure Prophylaxis. Data collected on HIV exposed health care workers treated with zidovudine-PEP were previously published. In November 1996, the National Commission on AIDS updated the protocol to include additional antiretroviral drugs in the PEP regimens.

Copies of the updated national protocol were sent to all centres licensed to dispense antiretroviral drugs. Moreover, the updated protocol was published on two widely distributed national medical journals.

Data were collected prospectively using a standardized form, which included, among others, the dosage and nature of the administered antiretroviral agents, reported side-effects with date of occurrence and duration, and reasons for premature interruption of PEP, if any.

All individuals consenting to prophylaxis received appropriate follow up at 10 day-two week intervals during the treatment and two weeks after its completion. The follow-up visit included physical examination, history taking, and laboratory testing according to toxicity profiles of the drugs included in the combination. All drugs were prescribed at the standard dose.

Individuals were assigned to group A (2 NRTIs), or gr. B (2 NRTIs plus PI), according to their initial regimen. Discontinuation was assumed as < 28 days. Lost to follow up or data not available (63 persons), PEP discontinuation because the source tested HIV negative (n. 387), and subjects who self-withdrew without side effects [43 gr. A; 59 gr. B], were excluded.

Statistical analysis was done with chi-square test, using the EPI-INFO version 6 statistical package.

## Results

Until December, 2001, 1260 individuals on combination PEP were enrolled into the study. Figure 1 shows the distribution of PEP by route of exposure. Among them, 708 fulfilled inclusion criteria: 247 received 2 NRTIs, mostly (92%) zidovudine plus lamivudine, for an overall total of 6,570 days, and 461 individuals were given two NRTIs plus a PI for an overall total of 1,986 days (mean 26, median 30, range 1-60), and 11,064 days (mean 24, median 29, range 1-60), respectively. Most subjects received zidovudine, lamivudine (85%), and indinavir (90%). Table 1 shows individuals who experienced side-effects, and Table 2 those who discontinued PEP, in the 2 groups.

Figure 2 and 3 show the main constitutional and laboratory adverse effects reported in the two groups. Type and incidence of specific adverse effects were similar to those reported in the literature.

**Table 1**

	Total	Side effects (%)	Mean (days)	Median (days)	Range (days)	OR	95% CI	p
Gr A	247	136 (55)	26.6	30	1-51	1		
Gr B	461	297 (64)	25.9	30	1-60	1.48	1.06-2.05	0.01

**Table 2**

	Discontinued (%)	Mean (days)	Median (days)	Range (days)	OR	95% CI	p	
Gr A	48 (35)	10.4	8	1-27	1			
Gr B	114 (38)	NRTI	10.5	8	1-27	1.36	0.92-2.04	0.1
		PI	9.5	7.5	1-26			

Of those 114 in group B who discontinued PEP, 20 individuals initially discontinued only the PI (after a mean of 8 days, median 6 d, range 1-20), but side-effects persisted and then PEP was completely discontinued after a mean of 8.2 additional days on two NRTIs (median 6 days, range 1-24 days).

Moreover, 52 (11%) additional individuals in gr. B discontinued only the PI, but completed the 4-week course of two NRTIs.

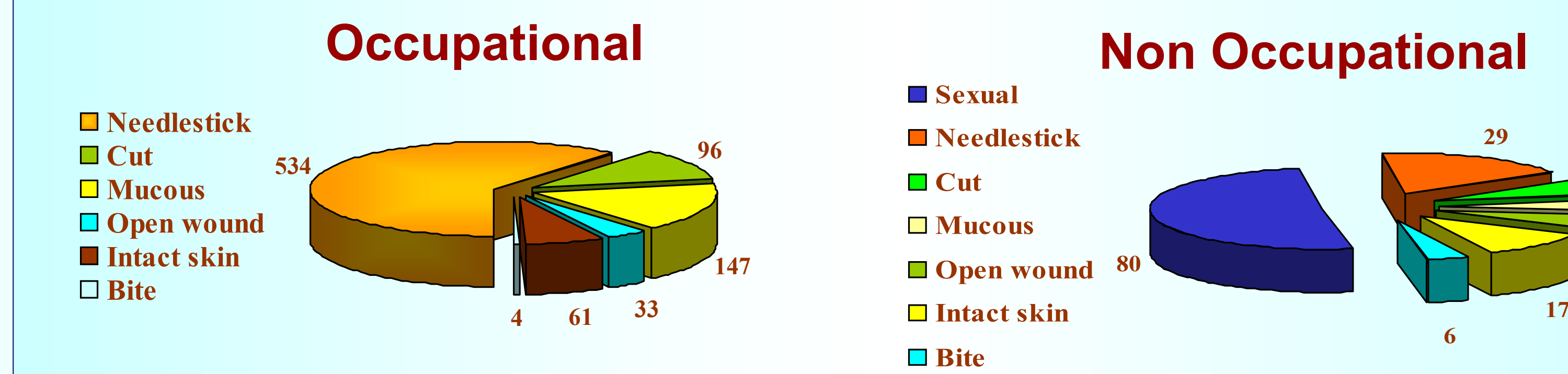
If we add these 52 individuals to the 114 discontinuations observed in the gr. B, the difference becomes statistically significant

	Discontinued PI only(%)	Mean	Median	Range	OR	95% CI	p
Gr. B	52 (17.5)	9	7	2-27	2.33	1.59-3.45	<0.001

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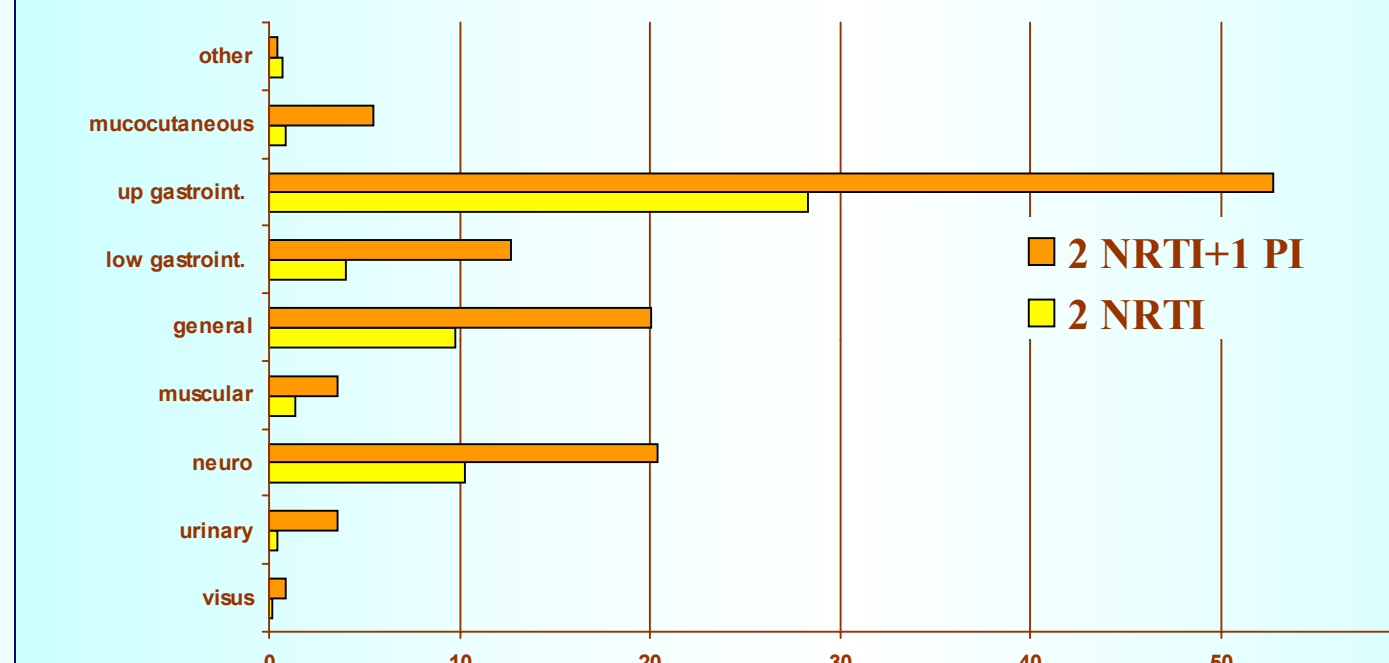
## Route of exposure



**Figure 1**

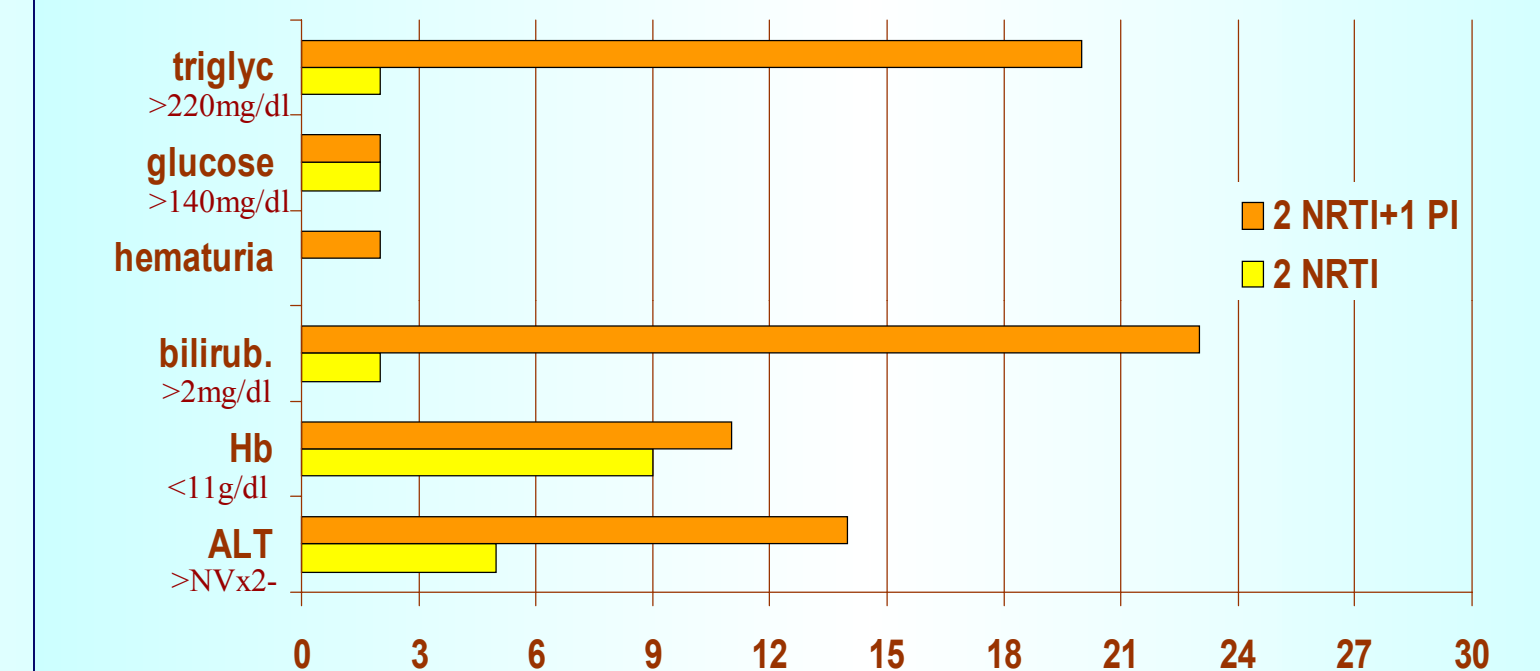
(in some cases more than one route of exposure)

## Main constitutional adverse reactions during PEP (%)



**Figure 2**

## Lab Side effects (cases)



**Figure 3**

## Discussion

Current CDC guidelines for the management of occupational exposures to HIV and recommendations for post-exposure prophylaxis state that a basic regimen consisting of two NRTIs should be used, adding a PI only in the highest risk exposure. These recommendations could apply also to non occupational PEP.

However, the definition of higher risk is not easily standardized, and risk assessment must be performed on a case-by-case basis taking into consideration the route of exposure, the materials involved in the exposure, and the amount of inoculum.

Moreover, a careful acquisition of data necessary for specific risk assessment is often difficult to obtain. In health care settings a clinical and epidemiological evaluation of the source patient involved in an occupational exposure should include a review of medical records, consultation with the physicians caring for the patient, and possibly a confidential interview with the patient. Determination of the viral load for HIV infected source patients should now be routinely available, adding new and important information for risk assessment. However, often the source patient has never been tested, or is unknown, and the risk factors are not always easy to be assessed. These difficulties could be present, and likely enhanced, also in the assessment of the risk in case of non occupational exposure.

Some studies seem to suggest that side effects and discontinuation of PEP are more common among individuals taking three-drug regimens for PEP, compared with those taking two drugs; patients' compliance could be affected by this higher rate of side effects, resulting in a potential reduction of PEP efficacy.

## Conclusions

Our study seems to demonstrate that the difference in the proportion of individuals developing side-effects and discontinuing PEP is not very significant, among the two regimens.

Although the incremental benefit of a regimen of three versus two drugs is speculative at present, combination PEP is recommended for its higher antiretroviral activity and for overcoming resistance. Although the use of regimens proven to be well tolerated is obviously recommended, we believe that the rate of discontinuation because of protease inhibitor side-effects does not justify *per se* the initial use of a less potent regimen. Unless already contraindicated, we suggest beginning PEP with a three-drug regimen and discontinuing the PI in the case of adverse effects that are not manageable by modification of the regimen (i.e. modifying the dose intervals), and by medications that target the specific symptoms.