

Clinical Tract

Module on

Post exposure prophylaxis of HIV

LEARNING OUTCOMES FOR ALL PARTICIPANTS

After completion of this module the learner should be able to:

- Recognize the transmission risk levels of the different blood borne viruses after exposure: sexual, occupational injuries and human bites
- Do appropriate testing for all parties concerned
- Select appropriate treatment according to risk of exposure
- Manage side effects of ART during prophylaxis

1. INTRODUCTION

Post exposure prophylaxis (PEP) is most commonly used in the context of healthcare worker (HCW) exposure to human immunodeficiency (HIV) contaminated body fluids (occupational exposure). It is however not limited to this group as there are several other circumstances where HIV transmission (or exposure) can occur:

- The HCW: exposure to blood-containing fluids such as needle penetration, blood on mucosal and skin surfaces etc.
- The patient: a few reports of patients being treated by a HIV infected doctor have been reported.
- Sexual exposure: which includes voluntary intercourse, the one night stand or sexual abuse/rape.
- Intravenous drug abusers (IVD): needle sharing, which is the most often form of HIV transmission in European countries and presently in America (IVD is associated with illicit/casual/opportunistic sex which may be a confounder to the mechanism of HIV transmission in this population).
- Blood products: this includes all blood products as well as plasma constituents (this is now rare due to the stringent screening process presently used)
- Pregnancy: most common form HIV transmission in children/neonates.
- Breast-feeding: the second most common form of HIV transmission in children (30-50%) where the mother is HIV positive.

This module will focus predominantly on PEP in the HCW setting, discussing the risks for contracting HIV, risk factors for seroconversion and risk evaluation, PEP evaluation and treatment.

2. EXPOSURE TO HIV IN THE WORKPLACE FOR HEALTHCARE WORKERS

Exposure of the HCW to body fluids from HIV infected individuals is a particularly stress-filled time. The potentially grave consequences of contracting HIV are balanced against the relatively low statistical risk. The HCW is much more likely to be infected through sexual intercourse (occurs more commonly) than through occupational exposure. This has led to the development of policies and procedures to reduce risk of occupational transmission.

Who is at risk?

The concept of HCW exposure is generally taken to imply “the doctor”, however data on HCWs who have seroconverted show that the majority are nurses and laboratory personnel. These studies were done in United States and Western Europe where most phlebotomists are nurses. The laboratory personnel are at high risk due to the high number of blood specimens that are processed.

The type of fluid in significant exposure?

The risk of HIV infection after exposure to body fluids is extremely low. The risk is related to the type of fluid, the presence of blood in the fluid, the amount of blood, the type of injury, possibly the duration of exposure, possibly the patient's viral load and clinical state (how far advanced the disease is), and probably the HCW's immune status.

Documented HIV transmission is defined as seroconversion in a seronegative HCW following exposure in the work place when other sources have been excluded. All documented HIV transmissions to date involved blood or bloody fluid. There have been three exceptions reported and all three were laboratory technicians exposed to HIV viral cultures. There have been no reported transmissions involving urine, stool, sweat, tears or other body fluids. The only fluid where HIV transmission has been reported other than blood or bloody fluid, is saliva. This however was a controversial case and involved inappropriate behavior on the side of the HCW and would not normally be included in the daily duties of the HCW. Exposure to saliva, tears, or non bloody urine or feces does not require PEP (Center for Disease Control (CDC) recommendations). No cases of documented HIV transmission have been reported with cerebrospinal-, synovial-, pericardial-, pleural-, peritoneal- and amniotic fluids. A retrospective case-control study has shown that the larger the quantity or volume of blood exposure the greater the risk for HIV transmission.

What exposure is significant

Table 1. The estimated risk of HIV transmission with a single exposure from a HIV infected source

<u>Exposure</u>	<u>Risk per 10 000 exposures</u>
Needle sharing	67
Percutaneous – occupational exposure	30
Receptive anal intercourse	10 – 30
Receptive vaginal intercourse	8 – 20
Insertive vaginal sex	3 – 9
Insertive anal sex	3
Intravenous blood product	0.015

The type or severity of injury appears to play a role in transmission. The most common form of reported exposure is the needle stick injury. Interestingly in the United States there have been no confirmed reports of seroconversion of surgeons or *suture needle* injuries in HCWs. There is no universal definition of injury severity, and this has conveniently been replaced with terms such as “case-by-case” decisions.

The CDC has shown that the following increased the risk of acquiring HIV from a needle stick injury:

- Deep injury (not defined) – odds ratio = 15
- Visible blood contamination – odds ratio = 6.2
- Patient who died of AIDS within two months after exposure - odds ratio = 5.6
- Needle placement in a vein or artery – odds ratio = 4.3

In the largest meta-analysis of HIV seroconversion risk after exposure to bloody fluid showed (before highly active antiretroviral therapy (HAART) was implemented):

- Needle stick injuries: 20 of 6135 exposures (0.33%)
- Mucosal exposure: 1 of 1143 exposures (0.09%)
- Skin exposure: no cases reported (0%)

Risk of infection related to incidence of disease?

The CDC has found a similar frequency for needle stick injuries: (0.36%; 95% confidence interval of 0.2 – 0.5%). It must be noted that all present studies mentioned previously, were done in first world countries where the prevalence of HIV

is substantially lower than that found in South Africa. The exposure rate to HIV-positive patients in the South African workplace is much higher. Studies from Kalafong Hospital (Pretoria) indicate that as many as 60% of the ward patients are HIV-positive at any given time. The majority of these patients have AIDS and most are not on HAART therapy. The viral exposure therefore in our South African community is substantially higher than that for any first world country.

HIV transmission by human bite has only rarely been reported. These HCWs must be evaluated as for other exposures provided there was blood involved, and/or there is broken skin.

Does the patient’s HIV stage of disease impact on transmission?

The stage of the patients’ disease appears to escalate the risk of transmission. There is no direct prospective evidence that has shown that the higher the patients’ viral load the more likely viral transmission. There is however, indirect evidence that substantiates these findings. The first is the CDC findings where transmission was more likely where source patients died within two months after exposure. By inference these patients were more likely to have high viral loads. In studies on transmission in discordant sexual partners the rate of infection positively correlated with the viral load. Thirdly perinatal transmission increases as the viral load increases.

Table 2. Risk of HIV transmission in 415 untreated discordant couples.

<u>Viral Load</u>	<u>Transmissions per 100 person-years</u>
<400 c/ml	0
400 – 3 500 c/ml	4.8
3 500 – 50 000 c/ml	14.0
>50 000 c/ml	23.0

In the United States there have been a further 138 HCWs which have possibly contracted HIV through occupational exposure, however without documented exposure in the workplace.

There are some laboratory data that suggest that PEP should be administered within two to four hours to achieve maximum efficacy. These studies were done in animal models. This may imply that the longer the delay after exposure, the more likely HIV transmission. This has implications on the urgency for PEP administration.

Does the host’s immune status impact on HIV transmission?

The HCW’s immune status may also play a role in HIV transmission as reported in one small study where the majority of HIV exposed HCWs who remained virologically and serologically negative demonstrated transient cellular immune responses to HIV-specific peptides. This can be taken as an indication that there is active viral replication even in non-converters. These people may have effectively cleared HIV at the time of exposure. It is possible that HCWs with poor immune responses may be more prone to HIV transmission.

What should the initial action be following exposure?

The most important concept for PEP is prevention. Proper procedures for working with sharp instruments, disposal of needles, worker protection etc has lead to a decline in needle stick injuries (data from American hospitals). Correct working

procedure must be incorporated into all HCW's daily duties. All health institutions should have a readily available policy for the management of occupational exposure which should be regularly updated.

The initial response should be immediate cleansing of the exposed site. Alcohol is preferred for skin exposures as it is virocidal to HIV, hepatitis B (HBV) and hepatitis C (HCV). Soap is not virocidal although if alcohol preparations are not available, soap should be used. Mucous membrane exposures should be thoroughly irrigated with large amounts of saline or water.

Risk assessment for HIV transmission should follow exposure. The presence of HIV infection should first be confirmed in the source, although it is recommended that this should not delay the institution of PEP therapy. Ideally PEP should be instituted within one to two hours after exposure. Some institutions allow PEP initiation up to one-week post exposure, however efficacy is diminished with delayed therapy.

The risk of HBV and HCV transmission is much higher than HIV, and therefore should also be evaluated from the source using hepatitis B surface antigen and anti-HCV antibody tests (Table 3).

All episodes of exposure should be thoroughly documented with date and time as well as the clinical information of the source. The exposed HCW should be educated on:

- the risk of HIV, HBV and HCV transmission
- the option of PEP
- side effects of antiretroviral medication
- techniques to reduce the risk of HIV transmission to sexual partners or other contacts
- the importance of follow-up
- the need to report any febrile illness to employee

Table 3. Risk of viral transmission with sharps injury from infected source.

Source	Risk
Hepatitis B virus (unvaccinated)	
Source HBeAg+	37 – 62%
Source HbeAg-	23 – 37%
Hepatitis C virus	1.8 %
Human immunodeficiency virus	0.3%

What antiretroviral medication should be used?

The ideal drug used for PEP should have high activity against free and cell-associated virus, should have a rapid onset of action with no adverse reactions. No drug presently fulfills these criteria.

There have been no prospective randomized blinded trials with any drug regarding the efficiency of PEP for decreasing HIV transmission. The trials that have been attempted have been hampered by low patient enrolment. Given the low risk for HIV transmission, none of the trials were able to obtain a sufficient sample size. Most trials were therefore abandoned. Presently, the only and best evidence for PEP efficacy is the CDC's case-control study of needle stick injuries. Zidovudine prophylaxis was associated with a substantial decrease for HIV transmission (odds ratio of 0.19). Some authors feel that this study was poorly designed with manipulated statistics and that no reliable conclusions can be drawn regarding the efficacy of zidovudine as PEP.

This has led to the use of animal models to establish efficacy. The available animal models however are not particularly suitable for evaluating efficacy. The trials that have been performed using animal models have not convincingly established decreased HIV transmission with zidovudine (ZDV, AZT).

There is however some indirect evidence from other trials that infer the efficacy of certain PEP drugs for HIV transmission. Mother-infant transmission has been reduced from 25.5% to 8.3% using ZDV (AIDS Clinical Trial Group Protocol 076). More recent data has shown HAART to be more effective in reducing maternal-infant transmission. In conclusion, even in the absence of convincing evidence, the majority of evidence presently available support the recommendation of PEP therapy (see Table 4).

How many antiretroviral drugs should be given for PEP?

The decision on whether PEP should be instituted must be balanced with the following in mind: the risk for transmission, the proven benefit or efficacy of the medication, and the adverse drug reactions. The risk of transmission has been graded by the CDC into class 1 and 2. Class 1 risk assessment includes sources that are asymptomatic or are known to have low viral loads (<1500 RNA c/ml). Class 2-risk assessment includes sources that are symptomatic, have AIDS, acute seroconversion, or are known to have high viral loads. The exposure type has been classified into a) less severe (solid needle and superficial injury) and b) more severe (exposed cuts, deep penetrations, hollow bore needles etc). There recommendations are presented in Table 5.

The present concern is the possibility of HIV transmission with resistant strains. This is due to the ever-increasing number of patients who have access to HAART. If the source is on HAART the chances for resistance is increased, and this may be an indication for an extended PEP regimen.

For HCWs taking PEP, drug toxicity should be monitored using a full blood count, hepatic functions, creatinine concentration at baseline, and two weeks after initiation.

What side effects can the HCW on PEP expect?

Most patients (76 - 85%) experience adverse drug effects from PEP irrespective of regimen. Lamivudine (3TC) reportedly has very few side effects and is tolerated very well. The most common side effects of PEP are nausea (57%), fatigue (38%), headache (18%), vomiting (16%), and diarrhea (14%). Taking the drug with meals can decrease gastrointestinal intolerance to zidovudine. Other less common side effects are dependent on the drug used but may include skin rashes, renal stones, peripheral neuropathy, pancreatitis and anemia. Most of the side effects are controllable with anti-emetics, loperamide and paracetamol. Those who cannot tolerate the side effects must be placed on alternate drug regimens.

Table 4. The CDC recommendations concerning HIV PEP for percutaneous injuries.

Exposure Type	Infection status of source				
	HIV-positive Class 1	HIV-positive Class 2	Source of unknown HIV status	Unknown source	HIV-negative source
Less severe	Basic 2 drug regimen	Expanded 3 drug regimen	No PEP warranted. Consider basic 2 drug regimen for source with HIV risk factors	No PEP warranted. Consider basic 2 drug regimen for setting where exposure to HIV-infected persons is likely,	No PEP warranted
More severe	Expanded 3 drug regimen	Expanded 3 drug regimen	No PEP warranted. Consider basic 2 drug regimen for source with HIV risk factors	No PEP warranted. For setting where exposure to HIV-infected persons is likely consider basic 2 drug regimen	No PEP warranted

Table 5. The 2001 United States Public Health Service recommendations for basic and expanded HIV post exposure prophylaxis regimens.

Antiretrovirals	Advantages	Disadvantages
Basic Regimen: Zidovudine 300 mg bd & Lamivudine 150 mg bd	Best evidence; AZT most experience; Serious toxicity – rare; Side effects are predictable; Safe in pregnancy Can be given as a single tablet bd in the form of COMBIVIR™	Side effects are common Source patient may have resistant HIV due to previous ADV therapy
Alternative Basic Regimens: Lamivudine 150 mg bd & Stavudine 30 or 40 mg bd OR Stavudine 30 or 40 mg bd & Didanosine 400mg/d on empty stomach	Well tolerated Serious toxicity – rare Twice daily dosing Likely to be effective against source patient using AZT & 3TC	Source patient may be resistant to this regimen Ddl is difficult to administer and unpalatable; May interfere with absorption of other drugs Serious toxicity can occur; Side effects are common*
Expanded Regimen: Basic regimen plus one of the following: Indinavir 800 mg tds on empty stomach Nelfinavir 750 mg tds or 1250 bd with meals Efavirenz 600 mg nocte Abacavir 300 mg bd	Potent HIV inhibitor Potent PI inhibitor Twice daily dosing Might be active earlier than other drugs; Once daily regimen Potent HIV inhibitor; Well tolerated	Serious toxicity (e.g. Nephrolithiasis); Hyperbilirubinemia common; Requires acid for absorption; Certain concomitant usage not recommended (e.g. rifampicin) ** Associated with rash; Nervous system side effects; Should not be used in pregnancy ** Severe hypersensitivity reactions may occur
Antiretroviral used only with expert consultation Ritonavir Saquinavir Amprenavir Delavirdine Lopinavir/Ritonavir 400/100 mg 3 caps bd	Potent HIV inhibitor; Well tolerated	Difficult to take; Poor tolerability; Many drug interactions Bioavailability is relatively poor Dosage consists of eight large pill taken bd; Many drug interactions Associated with rash; Many drug interactions Might accelerate clearance of certain drugs **
Antiretroviral agent not recommended for PEP Nevirapine 200 mg/d for two weeks then 200 mg bd		Associated severe hepatotoxicity Associated with rash

Potential for delayed toxicity in the form of oncogenicity/teratogenicity is unknown, except for Nevirapine
 ** Certain concomitant usage not recommended (eg. rifampicin)

Table 6. The CDC recommendations concerning HIV PEP for mucous membrane and non-intact skin exposures.

Exposure type	Status of Source			
	HIV-positive Class 1	HIV-positive Class 2	Source of unknown HIV status	HIV-negative Source
Small volume (drops)	Consider basic 2 drug regimen	2 drug regimen	No PEP warranted. For source with HIV risk factors consider basic 2 drug regimen	No PEP warranted
Large volume (major blood splash)	2 drug regimen	Expanded 3 drug regimen	No PEP warranted. For source with HIV risk factors consider basic 2 drug regimen	No PEP warranted

How effective is PEP?

In the absence of well-controlled studies it is unknown how effective PEP really is. From mother-infant HIV transmission studies it is clear that PEP is not 100% effective. Failure of PEP has been reported in at least 14 HCWs. The same conclusion can be derived from case controlled studies of needle stick injuries of the CDC. According to the latter study PEP is about 80% effective in preventing transmission. With newer regimens and improved antiretroviral drugs this figure should be higher. The efficacy of a regimen is not solely dependent of the medication but also on compliance. It is known that compliance for PEP is poor amongst HCW (53% in some studies), and this may decrease “drug efficacy”.

How long should PEP be administered?

In the absence well-controlled studies the recommendations suggest a four-week course irrespective of the severity of exposure. The optimum treatment period is not known. The duration of PEP is not based on experimental findings but rather on the average duration of time it takes to seroconvert.

How long does it take to seroconvert after exposure?

Most of the documented cases of seroconversion occurred within six months of exposure (96%). Only three cases have been described where seroconversion occurred after six months. These findings have lead to guidelines concerning the time interval for HIV serology testing: at the time of exposure, six weeks after exposure and three and six months after exposure. The likelihood of conversion after this time is minimal and therefore testing is not recommended after six months unless symptoms compatible with seroconversion arise. Most (81%) of HCWs who seroconverted have been found to experience a syndrome compatible with primary HIV infection with a median of 25 days after exposure.

3. WHAT IS THE RISK FOR HIV TRANSMISSION FROM A HCW TO A PATIENT?

Reports are very scarce of HIV transmission from doctor to patient. The most publicized cases were from a Florida dentist to six of his patients. The exact mechanism of transmission has not been determined, although the dentist did practice invasive procedures. None of the above patients were documented to be HIV-negative prior to visiting the dentist and one of the cases developed AIDS two years after visiting the dentist, which makes the dentist as an unlikely source. The likelihood of transmission from a surgeon with unknown HIV status is one case per 21 million hours of surgery, while it is 83 000 hours of surgery for a HIV-positive surgeon. This is the same risk as a fatal accident for a patient on the way to hospital. Multiple studies have failed to document any HIV transmission from HIV-positive doctors to patients. There is one other case presented as a possible transmission. This involved a French orthopedic surgeon who acquired occupational HIV. A retrospective search through 936 of his patients yielded one patient who tested HIV-positive without other risk factors. This however is also not a documented case of HIV transmission. The risk for transmission from doctor to patient is therefore negligibly small.

4. PEP AFTER SEXUAL CONTACT OR ABUSE

There is presently no data to support the use of PEP to prevent HIV transmission following sexual exposure. The assumption is that methods used for occupational and mother to infant transmission can be used for this purpose. There is some South African retrospective data (unpublished) on the use of PEP in post rape victims. These investigators have found no seroconversion in patients on PEP although numbers are limited and are still too small to draw any conclusions from. A research team in San Francisco has found similar results.

The South African guidelines for medical management of rape victims recommend the following:

- Pre-test counseling for a HIV test should be offered.
- An ELISA based HIV test or rapid HIV test should be performed on the exposed.
- Every victim should be informed about PEP.
- If the test is negative and the victim is seen within 72 hours of the sexual assault PEP should be offered.
- The two drug basic regimen should be followed.
- Victims presenting after 72 hours should offered counseling and follow-up for monitoring of seroconversion.
- If the victim tests positive, he or she should receive counseling and referred to HIV-AIDS treatment center.

Rape patients adhere very well to PEP (78%) and have excellent follow-up rates at three months. Although not included in these guidelines if the abuser HIV status and clinical condition is known to be positive it may be warranted to start the extended drug regimen with three drugs.

The protocol currently makes provision for rape victims. The question arises: what about persons who have an unplanned sex or the condoms slipped off? The first question would be whether one of the partners are known HIV positive. If both partners present at the casualty or clinic, both can be offered HIV testing after counselling. If one of the partners are HIV positive and one negative, the negative partner should be offered PEP. Counselling should follow about safe sex practices.

The case of HIV negative people who repeatedly present with a request for prophylaxis, should be handled on an individual basis.

6. PEP AFTER NEEDLE SHARING, CONTACT OR ABUSE

Rape victims

The same regimen is applicable to needle sharing as to rape victims. There are no studies that have shown decreased HIV-transmission in this group of patients. There is, however, substantially more data available for these patients than for rape victims, as their route of exposure is the same as for HCWs.

There are presently no known guidelines regarding post needle sharing exposure, however there should be no difference in the PEP regimen, except that this is a high risk population and there would be substantially more seropositive HIV tests at baseline.

Attack with a needle or sharp object

More and more incidents of people attacked with needles, or objects perceived as needles, are reported to casualties. No research results are available on this issue. In fact, it will be very difficult to gather research data. A safe route to follow, would be to counsel, do baseline HIV testing and offer full PEP and follow-up.

The care giver of an ill patient

The other issue that needs to be addressed, is PEP in the home-based care setting. Sometimes the care givers are coming into contact with bodily fluids. Most of these patients have advanced HIV with high viral loads. There is no policy on this issue currently.

The most important issue would be timely advice to all care givers on the general risk of disease transmission by bodily fluids. A problem is that a significant amount of care givers don't know they nurse an HIV positive person. Each case will have to be evaluated individually.

The doctor or sister doing the evaluation should contact an experienced HIV physician when in doubt. If the care giver has open wounds that were in contact with bodily fluids, a safe route to follow, would be to counsel, do baseline HIV testing and offer full PEP and follow-up.

PEP cover for volunteer workers in clinics and hospitals

Currently there is no official standards to which lay counsellors are measured. Lay counsellors currently receive a stipend and do not have any benefits enjoyed by employees with a contractual agreement. That includes benefits and treatment for injuries on duty.

The counsellors are, however, doing a tremendous job and VCT clinics and ART clinics are dependent on them. It would thus be advisable to give them access to the same prophylaxis that is provided to medical staff. That should happen through the nearest casualty or infection control sister.

7. FURTHER READING

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