Safety in the Working Environment- The Place of Post Exposure Prophylaxis against HIV Infection.

SUMMARY
Occupational exposure to HIV virus is a possibility to all workers working with patients having the virus. This is particularly more apparent when working within the healthcare setting. HIV post exposure prophylaxis (PEP) is a form of secondary HIV prevention that may reduce the incidence of HIV infection occurring during occupational and non-occupational accidental contact with infectious materials. A lot of studies have shown encouraging evidence of post exposure chemoprophylactic efficacy. It is however not 100% effective in preventing HIV transmission. Apart from the basic universal precautions to minimize occupational exposures to HIV virus, the use of post exposure prophylaxis is important when such exposures do occur.

INTRODUCTION
The growing number of health care workers involved in the management of patients with HIV/AIDS puts them at risk of contacting this infection(1). The rate of occupational transmission from an HIV-positive source is believed to be 0.3% for a percutaneous exposure and 0.09% for a mucous membrane exposure (2,3).

HIV post exposure prophylaxis (PEP) is a form of secondary HIV prevention that may reduce the incidence of HIV infection. Post exposure prophylaxis (PEP) aims to inhibit the replication of the initial inoculum of virus and thereby prevent establishment of chronic HIV infection. Several observational studies have found HIV PEP a very useful tool in combating or preventing occupationally acquired HIV infection. Kiertiburanakul et al found no seroconversion among the 820 episodes with occupational blood or body fluid exposures among health care workers offered HIV PEP during a five year-period in a Thai teaching hospital(4). Also Kowalska JD and co in Poland found no post-exposure HIV infection among 79 exposures in health care workers that were offered HIV PEP (5).

PEP is however not 100% effective in preventing HIV seroconversion. Do and co in there extensive review of occupationally acquired HIV infection in 57 healthcare workers in the U.S with documented occupationally acquired HIV infection, most (86%) were exposed to blood, and most had percutaneous injuries. Eight (14%) of the healthcare workers were infected despite receiving post exposure prophylaxis (PEP) (6).

Although preventing exposures to blood and body fluids is the primary means of preventing
occupationally acquired (HIV) infection, appropriate post–exposure management is an important element of workplace safety.

**Risk for Occupational Transmission of HIV**

In prospective studies of health care workers in the U.S., the average risk of HIV transmission after a percutaneous exposure to HIV–infected blood has been estimated to be approximately 0.3% (7) and after a mucous membrane exposure, approximately 0.09% (8). Although episodes of HIV transmission after non intact skin exposure have been documented (9), the average risk for transmission by this route has not been precisely quantified but is estimated to be less than the risk for mucous membrane exposures (10). The risk for transmission after exposure to fluids or tissues other than HIV–infected blood also has not been quantified but is probably considerably lower than for blood exposures (11).

Epidemiologic and laboratory studies suggest that several factors might affect the risk of HIV transmission after an occupational exposure (12). The risk for HIV infection in health care workers particularly has been found to be increased with exposure to a larger quantity of blood from the source person as indicated by:

a) A device visibly contaminated with the patient’s blood,

b) A procedure that involved a needle being placed directly in a vein or artery, or

c) A deep injury (12).

The risk also was increased for exposure to blood from source persons with terminal illness, possibly reflecting either the higher titer of HIV in blood late in the course of AIDS or other factors such as the presence of syncytia–inducing strains of HIV. A laboratory study that demonstrated that more blood is transferred by deeper injuries and hollow–bore needles lends further support for the observed variation in risk related to blood quantity (13).

Some evidence exists regarding host defenses possibly influencing the risk for HIV infection. A study of HIV–exposed but uninfected health care workers demonstrated an HIV–specific cytotoxic T–lymphocyte (CTL) response when peripheral blood mononuclear cells were stimulated in vitro with HIV–specific antigens (14). Similar CTL responses have been observed in other groups who experienced repeated HIV exposure without resulting infection (15–20). Among several possible explanations for this observation is that the host immune response sometimes might prevent establishment of HIV infection after a percutaneous exposure; another is that the CTL response simply might be a marker for exposure. In a study of 20 health care workers with occupational exposure to HIV, a comparison was made of health care workers treated with zidovudine (ZDV) PEP and those not treated. The findings from this study suggest that ZDV blunted the HIV–specific CTL response and that PEP might inhibit early HIV replication (21).

It is not only workers in the hospital that are prone to occupational exposure to HIV, others are also at risk as noted in the case report of a police officer that got infected after punching a suspect in the mouth while effecting an arrest (22).

**SCIENTIFIC RATIONALE FOR HIV PEP**

Considerations that influence the rationale and recommendations for PEP include:

- the pathogenesis of HIV infection, particularly the time course of early infection;
- the biological plausibility that infection can be prevented or ameliorated by using antiretroviral drugs;
- direct or indirect evidence of the efficacy of specific agents used for prophylaxis; and
- the risk and benefit of PEP to exposed workers (23).

**Role of Pathogenesis in Considering Antiretroviral Prophylaxis**

Information about primary HIV infection indicates that systemic infection does not occur immediately, leaving a brief window of opportunity during which post exposure antiretroviral intervention might modify or prevent viral replication. In a primate model of simian immunodeficiency virus (SIV) infection, infection of dendritic–like cells occurred at the site of inoculation during the first 24 hours following mucosal exposure to cell–free virus. Over the subsequent 24–48 hours, migration of these cells to regional lymph nodes occurred, and virus was detectable in the peripheral blood within 5 days (24). Theoretically, initiation of antiretroviral PEP soon after exposure might prevent or inhibit systemic infection by limiting the proliferation of virus in the initial target cells or lymph nodes.

**Efficacy of Antiretrovirals for PEP in Animal Studies**

Animal studies have provided encouraging evidence of post exposure chemo prophylactic efficacy (25–27). Studies among primates and in murine and feline animal models have demonstrated that larger viral inocula decrease prophylactic efficacy (28–31). In
addition, delaying initiation, shortening the duration, or decreasing the antiretroviral dose of PEP, individually or in combination, decreased prophylactic efficacy (26,30–38). A study confirmed the efficacy of tenofovir PEP when administered 24 hours after intravenous inoculation of a dose of SIV that uniformly results in infection in untreated macaques. In the same study, protection was incomplete if the tenofovir administration was delayed to 48 or 72 hours postexposure or if the total duration of treatment was curtailed to 3 or 10 days (37).

Efficacy of Antiretrovirals for PEP in Human Studies

Seroconversion is infrequent following an occupational exposure to HIV–infected blood (39). In a retrospective case–control study of exposed health workers (12), after controlling for other risk factors for HIV transmission, use of ZDV as PEP was associated with a reduction in the risk of HIV infection by approximately 81%. Although the results of this study suggest PEP efficacy, its limitations include the small number of cases studied and the use of cases and controls from different cohorts.

In a multicenter trial by Connor et al(40) in which ZDV was administered to HIV–infected pregnant women and their infants, the administration of ZDV during pregnancy, labor, and delivery and to the infant reduced transmission by 67%. Only part of the protective effect of ZDV was explained by reduction of the HIV viral load in the maternal blood, suggesting that ZDV prophylaxis, in part, involves a mechanism other than the reduction of maternal viral burden(41,42). Since 1998, studies have highlighted the importance of PEP for prevention of perinatal HIV transmission. The use of ZDV in combination with lamivudine (3TC) in Africa, decreased perinatal HIV transmission by 50% when administered during pregnancy, labor, and for 1 week postpartum, and by 37% when started at the onset of labor and continued for 1 week postpartum(41). Studies in the United States and Uganda also have demonstrated that rates of perinatal HIV transmission have been reduced with the use of abbreviated PEP regimens started intrapartum or during the first 48–72 hours of life (43–46).

TYPES OF HIV POST EXPOSURE PROPHYLAXIS

HIV PEP is commonly conceived of as 2 types: occupational and non–occupational. Occupational
week) might be considered for exposures that represent an increased risk for transmission. The optimal duration of PEP is unknown. Because 4 weeks of ZDV appeared protective in occupational and animal studies (12,37), PEP is recommended for 4 weeks, if tolerated.

Antiretroviral Agents available for PEP

Antiretroviral agents from three classes of drugs are available for the treatment of HIV infection. These agents include the nucleoside reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs). Only antiretroviral agents that have been approved by FDA for treatment of HIV infection are discussed in these guidelines.

Determining which agents and how many to use or when to alter a PEP regimen is largely empiric. Guidelines for the treatment of HIV infection, a condition usually involving a high total body burden of HIV, include recommendations for the use of three drugs (38); however, the applicability of these recommendations to PEP remains unknown. In HIV–infected patients, combination regimens have proved superior to monotherapy regimens in reducing HIV viral load, reducing the incidence of opportunistic infections and death, and delaying onset of drug resistance (39,40). A combination of drugs with activity at different stages in the viral replication cycle (e.g., nucleoside analogues with a PI) theoretically could offer an additional preventive effect in PEP, particularly for occupational exposures that pose an increased risk of transmission. Although the use of a three drug regimen might be justified for exposures that pose an increased risk of transmission, whether the potential added toxicity of a third drug is justified for lower–risk exposures is uncertain. Therefore, guidance for two– and three–drug PEP regimens that are based on the level of risk for HIV transmission represented by the exposure.

NRTI combinations that can be considered for PEP include Zidovudine and lamivudine, lamivudine and stavudine, and didanosine and stavudine. However, recent data suggest that mutations associated with ZDV and 3TC resistance might be common in some areas (41).

Thus, individual clinicians might prefer other NRTIs or combinations based on local knowledge and experience in treating HIV infection and disease. The addition of a third drug for PEP following high–risk exposures is based on demonstrated effectiveness in reducing viral burden in HIV–infected persons. Alluvia®, a combination of lopinavir and ritonavir, are a potent HIV inhibitor that, with expert consultation, may be considered in an expanded PEP regimen.

Recommendations for the Selection of Drugs for HIV PEP

Health–care providers must strive to balance the risk for infection against the potential toxicity of the agent(s) used when selecting a drug regimen for HIV PEP. Because PEP is potentially toxic, its use is not justified for exposures that pose a negligible risk for transmission. Also, insufficient evidence exists to support recommending a three–drug regimen for all HIV exposures.

A “basic” two–drug regimen that should be appropriate for most HIV exposures and an “expanded” three–drug regimen that should be used for exposures that pose an increased risk for transmission. When possible, the regimens should be implemented in consultation with persons who have expertise in antiretroviral treatment and HIV transmission.

Most HIV exposures will warrant a two–drug regimen using two nucleoside analogues (e.g., Zidovudine and lamivudine; or lamivudine and stavudine; or stavudine and didanosine). The addition of a third drug should be considered for exposures that pose an increased risk for transmission. Selection of the PEP regimen should consider the comparative risk represented by the exposure and information about the exposure source, including history of and response to antiretroviral therapy based on clinical response, CD4+ T–cell counts, viral load measurements, and current disease stage. When the source person’s virus is known or suspected to be resistant to one or more of the drugs considered for the PEP regimen, the selection of drugs to which the source person’s virus is unlikely to be resistant is recommended; expert consultation is advised. If this information is not immediately available, initiation of PEP, if indicated, should not be delayed; changes in the PEP regimen can be made after PEP has been started, as appropriate. Reevaluation of the exposed person should be considered within 72 hours post exposure, especially as additional information about the exposure or source person becomes available.

PRESCRIBING PEP FOR OCCUPATIONAL HIV EXPOSURE.

The following recommendations apply to situations when a person has been exposed to a source person with HIV infection or when information suggests the
likelihood that the source person is HIV–infected. These recommendations are based on the risk for HIV infection after different types of exposure and on limited data regarding efficacy and toxicity of PEP. Because most occupational HIV exposures do not result in the transmission of HIV, potential toxicity must be carefully considered when prescribing PEP. To assist with the initial management of an HIV exposure, health–care facilities should have drugs for an initial PEP regimen selected and available for use. When possible, these recommendations should be implemented in consultation with persons who have expertise in antiretroviral therapy and HIV transmission. The table below shows a typical outline in use in most centres.

<table>
<thead>
<tr>
<th>Source Patient</th>
<th>Exposed person</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>Negative</td>
<td>No PEP necessary</td>
</tr>
<tr>
<td>Negative or positive or unknown</td>
<td>Positive</td>
<td>No PEP. Counsel and refer for HIV management</td>
</tr>
<tr>
<td>Positive</td>
<td>Negative</td>
<td>PEP x 4 wks repeat exposed person’s HIV test at 3 months and 6 months, if person seroconverts, arrange for counseling and management</td>
</tr>
<tr>
<td>Unknown</td>
<td>Negative</td>
<td>Assume source patient is positive and proceed accordingly</td>
</tr>
</tbody>
</table>

Recommended HIV PEP for percutaneous injuries varies depending on the severity of the exposure and the HIV status of the source. When the source is HIV–negative, no PEP is warranted. When the HIV status of the source is unknown, generally no PEP is warranted, but basic two–drug PEP should be considered for a source with HIV risk factors or in settings in which exposure to HIV–infected persons is likely.

A risk categorization HIV–positive source can be divided into 2.

**Class 1**, are defined as those with asymptomatic HIV infection or known low viral load (< 1,500 ribonucleic acid copies/mL).

**Class 2** risk, have symptomatic HIV infection, AIDS, acute seroconversion, or known high viral load.

However, for practical clinical purposes this is usually divided into low risk and high risk contact.

**Low risk contact include**
- Solid needle, superficial exposure on intact skin.
- Small volume (drops of blood) on mucous membranes or non–intact skin exposures
- Source is asymptomatic

**High risk contact include:**
- Large bore needle, deep injury, visible blood on device, needle in patient artery/vein
- Large volume (major blood splash on mucous membrane or non–intact skin exposures)

Source patient is symptomatic, acute seroconversion.

Recommended schedule of investigations before HIV PEP. Exposed workers to HIV should be evaluated within hours (rather than days) after their exposure and should be tested for HIV at baseline (to establish infection status at the time of exposure). If the source person is seronegative for HIV, baseline testing or further follow–up of the exposed person normally is not necessary. Serologic testing should be made available to all workers who are concerned that they might have been occupationally infected with HIV. For purposes of considering HIV PEP, the evaluation also should include:
- Information about medications the exposed person might be taking and any current or underlying medical conditions or circumstances (i.e., pregnancy, breast feeding, or renal or hepatic disease) that might influence drug selection.

This includes baseline investigations such as HIV screening, full blood count (FBC), liver function tests (LFTs), and renal function tests.

After two weeks a repeat of these tests are recommended again.

After 3 months a repeat HIV screening and also after six months.

Use of PEP When HIV Infection Status of Source Person is Unknown.

If the source person’s HIV infection status is unknown at the time of exposure, use of PEP should be decided on a case–by–case basis, after considering the type of exposure and the clinical and/or epidemiologic likelihood of HIV infection in the source. If these considerations suggest a possibility for HIV transmission and HIV testing of the source person is pending, initiating a two–drug PEP regimen until laboratory results have been obtained and later modifying or discontinuing the regimen accordingly is reasonable.

The following are recommendations regarding HIV post exposure prophylaxis:
- If indicated, start PEP as soon as possible after an exposure.
- Reevaluation of the exposed person should be considered within 72 hours postexposure, especially
as additional information about the exposure or source person becomes available.
• Administer PEP for 4 weeks, if tolerated.
• If a source person is determined to be HIV–negative, PEP should be discontinued.

PEP for Pregnant workers
If the exposed worker is pregnant, the evaluation of risk of infection and need for PEP should be approached as with any other person who has had an HIV exposure. However, the decision to use any antiretroviral drug during pregnancy should involve discussions regarding the potential benefits and risks to the mother and her fetus.

Certain drugs should be avoided in pregnant women. Because teratogenic effects were observed in primate studies, Efavirenz is not recommended during pregnancy. Reports of fatal lactic acidosis in pregnant women treated with a combination of stavudine and didanosine have prompted warnings about these drugs during pregnancy. Because of the risk of hyperbilirubinemia in newborns, indinavir should not be administered to pregnant women shortly before delivery.

SIDE EFFECTS OF HIV PEP

The majority (50%) of persons on HIV PEP experience adverse symptoms (e.g., nausea, malaise, headache, anorexia, and headache) while taking PEP and that approximately 33% stop taking PEP because of adverse signs and symptoms (51–54). Some studies have demonstrated that side effects and discontinuation of PEP are more common among those taking three–drug combination regimens for PEP compared with those taking two–drug combination regimens (51,54). Serious side effects, including nephrolithiasis, hepatitis, and pancytopenia have been reported with the use of combination drugs for PEP (51,52,55,56). One case of NVP associated fulminant liver failure requiring liver transplantation and one case of hypersensitivity syndrome have been reported in those prescribed NVP for HIV PEP(57).

The commonest reported side effect of HIV PEP is nausea and vomiting. This has been found to be most pronounced in those with occupational exposure. Other side effects include skin rashes notably Steven Johnson syndrome in patients especially on a nevirapine based regimen.

Monitoring and Management of PEP Toxicity
If PEP is used, exposed workers should ideally be monitored for drug toxicity by testing at baseline and again 2 weeks after starting PEP. This scope of testing should be based on medical conditions in the exposed person and the toxicity of drugs included in the PEP regimen. Laboratory monitoring for toxicity should include a complete blood count and renal and hepatic function tests. Monitoring for evidence of hyperglycemia should be included for exposed workers whose regimens include any Protease inhibitor; if the exposed worker is receiving indinavir, monitoring for crystalluria, hematuria, hemolytic anemia, and hepatitis also should be included. If toxicity is noted, modification of the regimen should be considered after expert consultation; further diagnostic studies may be indicated.

Exposed workers who choose to take PEP should be advised of the importance of completing the prescribed regimen. Information should be provided about potential drug interactions and the drugs that should not be taken with PEP, the side effects of the drugs that have been prescribed, measures to minimize these effects, and the methods of clinical monitoring for toxicity during the follow–up period.

Counseling and Education
Although HIV infection following an occupational exposure occurs infrequently, the emotional effect of an exposure often is substantial (58–60). HIV–exposed workers should be advised to use the following measures to prevent secondary transmission during the follow–up period, especially the first 6–12 weeks after the exposure when most HIV–infected persons are expected to seroconvert: exercise, sexual abstinence or use condoms to prevent sexual transmission and to avoid pregnancy; and refrain from donating blood, plasma, organs, tissue, or semen. If an exposed woman is breast feeding, she should be counseled about the risk of HIV transmission through breast milk, and discontinuation of breast feeding should be considered, especially for high–risk exposures. Additionally, NRTIs are known to pass into breast milk, as well as Nevirapine too; whether this also is true for the other approved antiretroviral drugs is unknown.

The patient–care responsibilities of an exposed health care worker do not need to be modified based solely on an HIV exposure, to prevent transmission to patients. If HIV seroconversion is detected, the person should be evaluated according to published recommendations for infected workers (61).

Exposed workers should be advised to seek medical evaluation for any acute illness that occurs during the follow–up period. Such an illness, particularly if characterized by fever, rash, myalgia, fatigue, malaise, or lymphadenopathy, might be indicative of
acute HIV infection but also might be indicative of a drug reaction or another medical condition.

For exposures for which PEP is considered appropriate, exposed workers should be informed that a) knowledge about the efficacy of drugs used for PEP is limited; b) experts recommend combination drug regimens because of increased potency and concerns about drug resistant virus; c) data regarding toxicity of antiretroviral drugs in persons without HIV infection or in pregnant women are limited; d) although the short–term toxicity of antiretroviral drugs is usually limited, serious adverse events have occurred in persons taking PEP; and e) any or all drugs for PEP may be declined or stopped by the exposed person.

Exposed workers who experience HIV occupational exposures for which PEP is not recommended should be informed that the potential side effects and toxicity of taking PEP outweigh the negligible risk of transmission posed by the type of exposure.

Follow–up of Exposed workers

Post exposure Testing

Workers with occupational exposure to HIV should receive follow up counseling, post exposure testing, and medical evaluation, regardless of whether they receive PEP. HIV–antibody testing should be performed for at least 6 months post exposure (e.g., at 6 weeks, 12 weeks, and 6 months). HIV testing should be performed on any exposed person who has an illness that is compatible with an acute retroviral syndrome, regardless of the interval since exposure. When HIV infection is identified, the person should be referred to a specialist knowledgeable in the area of HIV treatment and counseling for medical management.

LIMITATIONS OF HIV PEP

Failure of PEP to prevent HIV infection in HCP has been reported in at least 21 instances (8,61–68). In 16 of the cases, ZDV was used alone as a single agent; in two cases, ZDV and didanosine (ddI) were used in combination (61–67); and in three cases, >3 drugs were used for PEP(66–68). Thirteen of the source persons were known to have been treated with antiretroviral therapy before the exposure. Antiretroviral resistance testing of the virus from the source person was performed in seven instances, and in four, the HIV infection transmitted was found to have decreased sensitivity to ZDV and/or other drugs used for PEP. In addition to possible exposure to an antiretroviral–resistant strain of HIV, other factors that might have contributed to these apparent failures might include a high titer and/or large inoculum exposure, delayed initiation and/or short duration of PEP, and possible factors related to the host (e.g., cellular immune system responsiveness) and/or to the source person’s virus (e.g., presence of syncytia–forming strains) (61).

CONCLUSIONS

The risk of occupational infection with HIV, although alarming, has never reached the scale of hepatitis B. However, most countries, especially those with a high population prevalence of HIV infection like Nigeria, have never instituted surveillance systems that would capture data on such cases. In the absence of these sorts of data, HIV PEP is an integral part of care of health care workers exposed occupationally to this infection.

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