IN-DEPTH REVIEW

Occupational exposure to HIV and post-exposure prophylaxis in healthcare workers

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Healthcare workers are at risk of occupationally acquired HIV infection primarily due to percutaneous exposure to HIV infected blood. The average risk of HIV transmission after such exposure is approximately 0.3%. There is evidence of higher risk for exposures involving an increased volume of blood (deep injury, injury with a device visibly contaminated with source patient's blood and a procedure which involved a needle placed in the source patient's artery or vein) and exposures to source patients with a high viral load.

Triple therapy with two nucleoside analogues (zidovudine, lamivudine) and a protease inhibitor (indinavir) is now widely used for post-exposure prophylaxis following occupational exposure to HIV. Most of the evidence for the efficacy of prophylaxis is based on zidovudine monotherapy. Little is known about the long-term toxicity of these drugs in non-infected individuals. Their use in these circumstances requires careful assessment of possible risks and benefits.

Key words: HIV; needlestick; occupational exposure; post-exposure prophylaxis; review; seroconversion.

OCCUPATIONALLY ACQUIRED HIV INFECTIONS: CURRENT FIGURES

The first case of documented seroconversion after a specific occupational exposure to HIV was reported in 1984.1 Subsequently, national and regional systems for surveillance of occupationally acquired HIV infection have been developed in many industrialized countries. Ninety-five definite and 191 possible cases of occupationally acquired HIV infections were reported worldwide to December 19972 (Table 1).

Cases of occupationally acquired HIV infection are usually classified as 'definite' or 'possible'. A 'definite' case is defined as one for which there is documented evidence of HIV seroconversion associated in time with a specific occupational exposure to an identified source of HIV. The definition of a 'possible' case implies that a healthcare worker was found to be HIV infected and that subsequent investigations revealed no risk factor other than occupational exposure.

The true incidence of occupationally acquired HIV infection is unknown, and is likely to be higher than the total of reported cases even from industrialized countries from which published reports originate. Worldwide, the incidence must be very much higher because reporting of occupational exposures is poor in high prevalence areas where surveillance systems are less well developed.

RISK OF SEROCONVERSION AFTER DIFFERENT TYPES OF OCCUPATIONAL EXPOSURE TO HIV

Percutaneous exposures

The risk of HIV infection after a documented exposure to HIV infected blood has been estimated in prospective studies conducted worldwide. In a Centre for Disease Control and Prevention (CDC) surveillance project in the United States,3 as of June 1992, four of 1103 enrolled workers with percutaneous exposure to HIV-infected blood seroconverted (HIV seroconversion rate, 0.36%; upper limit of the 95% CI, 0.83%). Aggregating data from this and 22 other studies, out of 6202 healthcare workers (HCWs) who were followed prospectively after a percutaneous exposure to HIV infected blood, 20 (0.32%; 95% CI, 0.20–0.50%) became infected.4 The risk estimate of 0.3% represents an average of many types of exposures to blood from patients with various stages of HIV infection. It is therefore likely that there are
subsets of exposures for which the risk is higher or lower than 0.3%.

CDC staff in collaboration with colleagues in France, Italy and the UK conducted a case–control study to identify the risk factors for the transmission of HIV to HCWs after percutaneous exposure to HIV infected blood. Thirty-three HCWs who acquired HIV infection after a documented percutaneous exposure to HIV infected blood were compared with 665 HCWs who did not seroconvert after exposure. Logistic regression identified several potential risk factors. Increased risk was associated with three factors that were probably indirect measures of the quantity of blood transferred in the exposure: deep injury, injury with a device that was visibly contaminated with the source patient’s blood, and a procedure that involved a needle placed in the source patient's vein or artery, which means that the needle probably contained undiluted blood. The risk of HIV transmission was also increased if a HCW was exposed to blood from a source patient in the terminal stage of AIDS. This association is probably due to the higher titre of HIV in the blood of patients late in the course of AIDS.

Mucocutaneous exposures

Mucocutaneous exposures account for approximately 8% (eight out of 95) of HIV infections documented to be due to occupational exposure. The risk associated with mucocutaneous exposures has been difficult to quantify, because transmission by this route is rare. The risk estimated by pooling data from six prospective studies is 0.1% (one infection in 1007 mucosal exposures; 95% CI, 0.006–0.5%). Although this estimate may be biased, because the single episode of transmission was reported before the involved institution contributed data to a multicentre study, it suggests that mucocutaneous exposures to HIV pose a lower risk than percutaneous inoculations.

Transmission of HIV through intact skin has not been documented. In the largest prospective study to evaluate cutaneous exposures, no infections were detected after 2712 instances of exposure of intact skin to HIV (95% CI, 0–0.1%).

Exposure to other body fluids

Although HIV has been detected in a variety of body fluids, occupational transmission to HCWs has been documented only for blood and visibly bloody fluids. There are insufficient data to estimate precisely the risk of HIV infection after occupational exposure to HIV containing body fluids other than blood. The risk following occupational exposure to secretions and excretions not containing visible blood, if present at all, is likely to be extremely low. In a questionnaire survey, employees at a US healthcare institution reported 2856 skin exposures to fluids other than blood (804 sputum, 912 urine, 300 faeces and 840 to other fluids) from HIV infected patients; none resulted in HIV transmission. In addition, HIV transmission via saliva and respiratory secretions has not been demonstrated in epidemiological studies among household contacts of persons with HIV infection or in a relatively small number of HCWs after exposure to saliva of infected patients.

Two cases of HIV transmission from bites have been reported; both were ascribed to blood contact. In one case the biter died of AIDS 13 days after the bite, suggesting that he had a high viral load.

POST-EXPOSURE PROPHYLAXIS

Post-exposure chemoprophylaxis is now recommended for HCWs who experience certain kinds of exposure to HIV in the workplace. Substantial information has emerged over the past few years that supports, but does not prove, the efficacy of antiretroviral agents in preventing HIV infection after occupational exposure.

Efficacy of antiretroviral chemoprophylaxis

Assessing the efficacy of post-exposure prophylaxis has proved quite difficult. Information has emerged over the years from animal and human studies.

Animal studies In the 1990s animal studies provided convincing evidence that, despite earlier scepticism, antiretroviral agents can prevent retroviral infection. Tsai et al. administered the antiretroviral agent PMEA (9[2-phosphonylmethoxyethyl]adenine) to macaques that had been infected intravenously with simian immunodeficiency virus (SIV). All untreated control animals were infected, whereas no signs of SIV infection could be detected in any of the treated animals. In a similar model, the same author addressed the influence of timing and duration of antiretroviral treatment on the risk of infection. For example, only half the animals treated for 10 days and none of the animals treated for as few as 3 days were protected from SIV, while all the animals treated for 24 days remained uninfected. Delay in treatment was also found to be a substantial risk factor for infection in this model. Only half the animals that received the first dose of post-exposure prophylaxis 48 h after inoculation and only one-fourth of the animals that did not receive the first dose until 72 h after infection were protected from SIV, whereas almost all the animals treated within 24 h of infection were protected. These two studies, together with other similar research in animals, provide encouraging support for the use of these agents as post-exposure prophylaxis in humans.

<table>
<thead>
<tr>
<th>Area of the world</th>
<th>Definite cases</th>
<th>Possible cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td>52</td>
<td>114</td>
</tr>
<tr>
<td>Europe (excluding UK)</td>
<td>28</td>
<td>56</td>
</tr>
<tr>
<td>UK</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Rest of world</td>
<td>11</td>
<td>13</td>
</tr>
<tr>
<td>Total</td>
<td>95</td>
<td>191</td>
</tr>
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Table 1. Occupational transmission of HIV infection, to December 1997
They cannot, however, prove the efficacy of post-exposure prophylaxis in humans.

**Human studies** As early as 1988, the manufacturer of zidovudine attempted to conduct a placebo-controlled efficacy trial of zidovudine chemoprophylaxis for occupational HIV exposure. For a number of reasons, including the relatively low risk for occupational infection associated with a single exposure, the large number of participants required for the study, and the reluctance of HCWs who had such exposures to enter a placebo-controlled clinical trial, the study was discontinued due to lack of accrual. Since then two types of studies in humans have contributed relevant evidence that favours the use of antiretroviral chemoprophylaxis for occupational exposure to HIV. The first of these are studies of antiretroviral treatment of mothers and neonates to attempt to prevent vertical transmission of HIV. In the AIDS Clinical Trials Group Protocol 076 zidovudine was administered to mothers before birth and during labour and delivery. It was also administered to the newborns 6 weeks after birth. This regimen reduced the risk of vertical transmission of HIV by two-thirds. More recently, Wade and colleagues demonstrated the efficacy of zidovudine prophylaxis in preventing perinatal transmission of HIV. They demonstrated that even abbreviated courses of antiretrovirals begun either intrapartum or in the first 48 h of life (true post-exposure prophylaxis) reduced the risk for perinatal HIV transmission. In view of these results, one could argue that the best chance for ablation of infection might well be at the time of exposure, when very small numbers of viral particles are present.

**Efficacy of post-exposure prophylaxis after occupational exposure to HIV** There is limited evidence to date on the efficiency of post-exposure prophylaxis with zidovudine following occupational exposure to HIV. The CDC conducted a retrospective case–control study of occupational HIV infections in healthcare professionals. The study matched 33 cases of occupational HIV infection reported from the US, Italy, France and England with 665 controls from the CDC’s prospective study of HCWs exposed to HIV in the workplace. The administration of zidovudine chemoprophylaxis was associated with an 80% reduction in the risk for occupational HIV infection. Because it is difficult to control for known and unknown factors that contribute to HIV transmission, a retrospective case–control study is not the optimal design for assessing the efficacy of zidovudine; a placebo-controlled trial, however, has not so far been possible.

**CLINICAL MANAGEMENT OF OCCUPATIONAL EXPOSURE TO HIV**

**Drug regimens**

Although compliance with infection control recommendations on handling sharps is the mainstay of prevention, additional prevention strategies now include post-exposure prophylaxis with antiretroviral therapy. This has become widely used since the early 1990s, despite lack of clear evidence of benefit. Most of the evidence for prophylaxis is based on zidovudine monotherapy. Triple therapy is now advocated because of the superior efficacy of combination therapy in established infection and the potent antiviral efficacy of the new protease inhibitors. There are increasing reports of viral resistance to zidovudine and at least 11 cases where post-exposure zidovudine failed to prevent HIV infection. Recommendations for the use of post-exposure prophylaxis were issued by the US Public Health Service, the International AIDS Society, and the Italian Ministry of Health in 1996, and the UK Department of Health in July 1997. These guidelines recommend a 4-week course of zidovudine in combination with lamivudine for most parenteral exposures. The International AIDS Society and the British guidelines suggest adding a protease inhibitor for all significant exposures while the US guidelines advocate it only for particularly high-risk exposures or when resistance is suspected.

The choice of lamivudine and the protease inhibitor indinavir as the companion drug to zidovudine is to some extent arbitrary, and newer drugs such as the non-nucleoside reverse transcriptase inhibitors may soon provide more choices. Lamivudine proved safe in early treatment trials and combined with zidovudine acts against zidovudine-resistant virus; indinavir is similarly active and appears to be the most active protease inhibitor available.

**Side effects**

Little is known about the long-term toxicity of these drugs in non-infected individuals, although life-threatening side effects have not been reported. Substantial subjective toxic effects are reported in almost every study evaluating HCWs exposed to HIV who have elected to take post-exposure chemoprophylaxis. While there is evidence that triple therapy is tolerated better than high-dose zidovudine monotherapy, side effects remain. The most common reported side effects to combination therapy are nausea and abdominal pain. In the cases we have treated, vomiting, lethargy and headache, often resulting in sickness absence, are also common. Adverse effects were almost always reversible within a few days of lowering the dose or interrupting the treatment. In some instances, dose reductions or specific treatment of symptoms (e.g. nausea) were highly effective in facilitating compliance.

**When to test and when to treat**

Deciding when to recommend prophylaxis after occupational exposure should take into consideration the risk associated with the specific incident. Factors that increase the risk of seroconversion include exposures to a large inoculum of infected blood and a source patient with terminal HIV infection. Therefore, initial risk assessment should include details of exposure as well as...
information about CD4 count, viral load and antiretroviral history of the source patient.

Potential problems arise when the source patient’s HIV status is not known. The General Medical Council has produced guidance on ethical procedures for testing of source patients. Where the patient refuses testing or is unable to consider giving consent (because of mental illness or disability, decreased level of consciousness for 48 h) testing should not be arranged except in exceptional circumstances. For example, where there is good reason to think that the patient may be HIV positive. In such cases existing blood samples may be tested but there must be good justification for this decision. Where the source patient’s status remains unknown, Department of Health guidance states that ‘PEP should only be recommended if the health care worker has been exposed to blood or other high risk body fluids or tissue known to be, or strongly suspected to be, infected with HIV’.21

Incident reporting

Institutions and occupational health departments need to publicize the importance of reporting all exposures and provide a confidential and user-friendly mechanism for doing so. Exposed HCWs need to be fully informed of the risks, the rationale for treatment, and side effects so that whenever possible the decision about prophylaxis rests in their hands. Expert advice from HIV specialists should be taken where the exposed worker is pregnant or breast feeding; has concurrent medical conditions or drug therapy; has developed side effects to treatment; when drug resistance is suspected; and where the occupational health physician has limited experience with triple therapy.

The lack of clinical follow-up data on the effectiveness, tolerability, and safety of post-exposure prophylaxis requires a systematic approach to data collection. In the UK, the Public Health Laboratory Service (PHLS) Communicable Disease Surveillance Centre (CDSC) has set up a national surveillance scheme for occupational exposures to HIV.21 This should provide useful data for reviewing current treatment regimes, especially as new generations of antiretroviral drugs become available.

The Department of Health Expert Advisory Group on AIDS (EAGA)21 is currently revising its guidelines on PEP. The new guidelines are likely to be published in the year 2000.

REFERENCES


