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Guidance Modules on Antiretroviral Treatments

Module 7

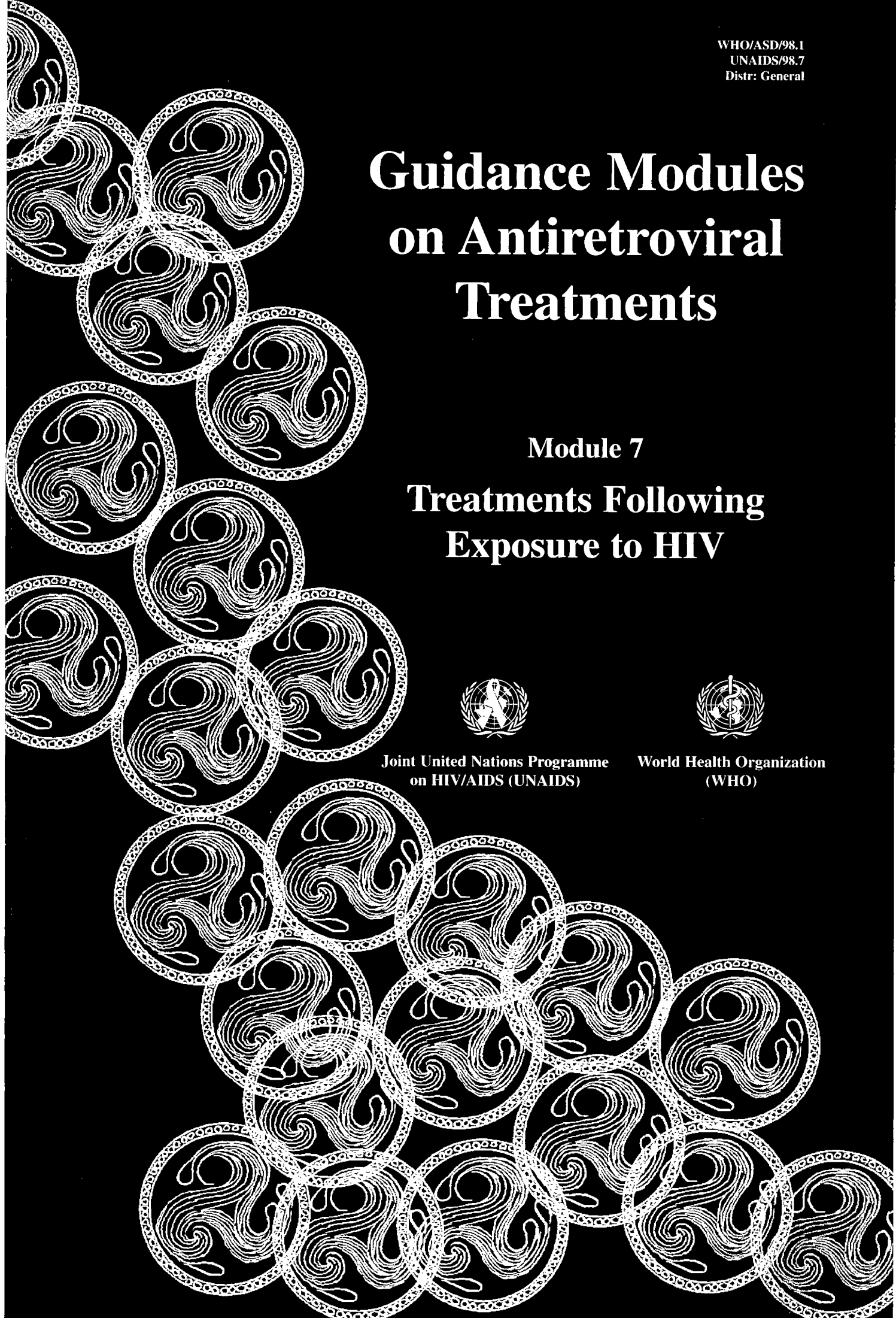
Treatments Following Exposure to HIV



Joint United Nations Programme
on HIV/AIDS (UNAIDS)



World Health Organization
(WHO)



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Module 7

Treatments Following Exposure to HIV

Note on terminology

Accidental exposure to blood (AEB) is defined as any contact with blood or body fluid as a result of injury with a needle or any other sharp instrument, or via mucous membranes (eye, mouth), or contact via damaged skin (eczema, wound).

The term percutaneous exposure (PE) is used when there has been exposure through non-intact skin.

Needle stick injury refers to puncture with a needle or sharp instrument that is contaminated or potentially contaminated with blood.

Blood splash refers to skin visibly contaminated with blood.

Facts and figures

Introduction

Viral transmission due to percutaneous exposure to blood in a hospital occurs in three ways: exposure of health workers to blood of patients; exposure of patients to blood of health workers; exposure of patients to blood of other patients. In practice, the exposure of health workers to blood of patients is the major concern and alone, justifies a specific prevention and surveillance strategy.

The rate of occupational transmission of HIV infection to health workers depends on the prevalence of infection in patients; the frequency of exposures to blood; and the risk of transmission. The **prevalence of HIV infection** varies enormously between different hospital populations (up to 70% of inpatients with tuberculosis in an urban setting in Zambia compared with <0.1% in a geriatric ward in the UK). **Frequency of exposures** is difficult to estimate because of under-reporting of accidents by health personnel and inaccuracies in recall in retrospective studies. It can only be estimated through enquiries undertaken at different points in time or by active surveillance based on sentinel surveys within particular hospitals. Whilst the **risk of transmission** per exposure is low, the risk for a health worker, frequently exposed to the blood of patients in a high prevalence area, may be significant. The risk of transmission is about the same for each percutaneous exposure - around 1-5 per 1000 exposures (0.3%).

Prevention of exposure remains the most effective measure to reduce the risk of HIV transmission to health workers. The priority therefore must be to train health personnel in prevention methods (**universal precautions**) and to provide them with the necessary safe materials and protective equipment. The use of antiretroviral post exposure treatment only

makes sense if universal precautions are widely taught and practised so as to reduce the occurrence of exposures to a minimum.

Frequency of percutaneous exposure (PE)

The reporting and description of accidental exposures of all kinds is an essential first step in prevention. The risk of transmission of HIV from PE has been known since the beginning of the AIDS epidemic. The risk for each exposure is relatively low compared to the risk of transmission of other infectious agents such as hepatitis B and C. Given the prevalence of these viruses in the world, the risk of infection with hepatitis B and C is much higher than with HIV and should not be neglected.

Risk of transmission of bloodborne viruses to health care workers following a single exposure	
HIV	
Percutaneous exposure	0.3%
Mucocutaneous exposure	0.03%
Hepatitis B virus (HBV)	
Percutaneous exposure	9-30%
Hepatitis C virus (HCV)	
Percutaneous exposure	1-10%

Most of the current epidemiological data come from developed countries and are based on studies undertaken by the Centers for Disease Control and Prevention (CDC) and EPINet (USA), the Communicable Disease Surveillance Centre (CDSC) in the UK, the Italian Study Group on Occupational Risk of HIV infection and the Groupe d'Etudes sur le Risque d'Exposition au Sang (GERES) in France. Data on the frequency and risk factors for PE to blood in health care systems in developing countries are limited, with the exception of a recent study from Tanzania in nine hospitals in the Mwanza region.

Incidence of AEB and PE reported in the literature*

Study	Incidence of AEB/PE
Nurses in France (Abitboul 1993)	27 AEB/100 nurses/year and 21 PE/100/year**
Nurses in Tanzania (Gumodoka 1997)	487 PE/100 nurses/year
Medical students in USA (Jones 1990)	50 PE/100 students/year
Radiologists in USA (Heald 1990)	50 PE/100 radiologists/year
Doctors in USA (Heald 1990)	60 PE/100 doctors/year
Doctors in Tanzania (Gumodoka 1997)	68 PE/100 doctors/year
Anaesthetists in USA (Heald 1990)	130 PE/100 anaesthetists/year
Senior surgeons in USA (Heald 1990)	38 PE/100 surgeons/year
Surgeons in France (Antona 1993)	1000 AEB/100 surgeons/year
Surgeons in USA (McCormick 1991)	600 AEB/100 surgeons/year
Surgeons in Saudi Arabia (Hussein 1988)	420 AEB/100 surgeons/year
Surgeons in Tanzania (Gumodoka 1997)	1474 PE/100 surgeons/year

* References available from WHO

**In 1991, the incidence was 40 AEB and 32 PE/100 nurses/year

The incidence of AEB/PE varies greatly by type of health care worker (HCW)¹, country and year of study. These differences may be due, in part, to different methods of reporting and different definitions of AEB. In high income countries, prevention measures in health care institutions have contributed to a significant decrease in incidence of PE - nearly 40% in France in two years. In Tanzania, the rate of PE among nursing staff was reported to be 20 times higher than in France, but only 50% percent higher among doctors.

Note also the differences between sites in risks of transmission after a single exposure and the risks of exposure to HIV infected blood. In developing countries with high seroprevalences amongst inpatients, the risk of transmission from all PE will be significantly higher.

Risk factors

General patient care

Most studies show that among health workers, AEB occurs most frequently among nurses in hospital settings. Prospective studies undertaken by GERES estimate 30-40 AEB per 100 nurses/year. In the EPINet study undertaken in nine hospitals in the USA, nurses reported 52% of all AEB whilst doctors and interns reported 9% each. Exposures associated with giving of injections account for most AEB in nurses (75% on average). The rate of AEB is much lower for doctors and nursing auxiliaries (around 10 times lower in the first GERES study for these two groups). In the Tanzanian study 434 health workers were questioned on two occasions at 4 week intervals. It was found that 9.2% of nurses but only 1.3% of doctors had had a needle stick injury in the week preceding the interview. The average incidence of needle stick injury in this study was 9.5% per week or 5 per person per year. However, studies done in the USA and in Denmark found a PE rate higher for doctors than for nurses. Again differences in rates may be due in part to different methods of reporting and different definitions of AEB.

Surgery

Outside general patient care, surgeons in operating theatres are the most at risk for AEB. Various studies have attempted to estimate the incidence of AEB in operating theatres. The rate of exposure per operation varies from 5.6% and 30.1% between studies and for different operations. For surgeons, cutaneous exposure or blood splashes are much more frequent than injection injuries. A study from Grady Memorial Hospital of Atlanta (USA) found that 90% of blood contacts were cutaneous and presented a relatively low or negligible risk: 55% on clothes, 37% on non-protected skin, 8% on hands with torn gloves: whereas 10% were of a moderate/higher risk: 7% were through injections or cuts and 3% were in the eye. In the Tanzanian study, the frequency of needle stick injuries reported by surgeons was low (only 3 needle stick injuries for 488 surgical acts: 0.6%) but examination of surgeons' gloves after the operation showed that in 10% of cases these were pierced after the operation.

¹ Health care worker (HCW) - term used to include all workers in health care situations, including nurses, laboratory staff, physicians, surgeons, traditional medical practitioners etc.

Students are particularly at risk. Medical students have been shown in several studies (USA, France, Zambia and Israel) to have frequent AEB. According to a study undertaken in two faculties of medicine in Paris in 1995, 31% of students in 4-6th year have had an AEB during their clinical training. Although they often have good knowledge about HIV transmission and occupational risks, their inexperience makes them particularly vulnerable. In Zambia medical students report being reluctant to assist with operations or put up drips because of worries about HIV infection. Student nurses are similarly at risk.

In developing countries, there have been few studies of AEB. In Africa, midwives have frequent AEB. Prospective studies in the field are required to investigate the circumstances of accidents in these countries and adapt prevention methods.

High risk procedures

Blood taking

The rate of PE from various procedures varies little from study to study: in general medical care, half of AEB occur during blood taking.

Suturing

Suturing is often reported as a high risk procedure for AEB. In the operating theatre, studies show that most AEB occurs towards the end of the operation, during closure. Suturing is a risky procedure: the suturing needle is responsible for 60% to 80% of percutaneous injuries in surgery. Repair of post-partum tears and episiotomy are high risk events/procedures.

Inadequate disposal of sharps

In general patient care, 30% to 70% of accidents occur when injecting or suturing equipment ("sharps") is thrown away in a container. Other accidents occur during procedures and are therefore dependent on the safety of the instruments themselves. Accidents following procedures are avoidable and indicate poor application of universal precautions. Most sharps injuries occur when needles are recapped or cleaned or when the container for instrument disposal is full, badly made or the opening is too small for the sharps to pass easily. Finally accidents may be caused when used sharps are left on trolleys, beds or other surfaces.

The application of universal precautions should prevent the majority of these accidents.

Risk of HIV transmission following exposure

Prospective studies of health workers exposed to HIV contaminated blood have shown that the rate of transmission after percutaneous exposure is estimated at 0.3% and after cutaneous-mucosal exposure at 0.03%, or 10 times lower. The factors influencing risk of contamination with HIV after accidental exposure to blood are well known.

In a case control study done by the CDC in collaboration with the UK and France, regression analysis revealed that the following factors were independently associated with risk of transmission:

Deep injury	OR 15.0	(95%CL: 6 - 41)
Visible blood on instrument	OR 6.2	(95%CL: 2.2-21)
Procedure involving needle in artery or vein	OR 4.3	(95% CL: 1.7- 12)
Terminal illness in source patient	OR 5.6	(95% CL: 2 -1 6)
Post exposure zidovudine	OR.0.19	(95% CL: 0.06-0.52)

OR: Odds Ratio

CL: Confidence Level

Other risk factors, not identified in this case control study, also probably play a role:

- the time interval between use of needle and the exposure
- the wearing of gloves.

When gloves are worn, it appears that some of the blood contained in the needle is absorbed as it passes through the glove: the reduction in volume of injected blood into the health worker is around 70% or more for a suturing needle but only 35% to 50% for a hollow needle. Wearing gloves may therefore, decrease the risk of transmission after needle stick injury by reducing the viral inoculum injected. Viral load which is related to the clinical status of the source patient, probably accounts for the variability of risk of transmission.

By the end of 1995, 144 cases of HIV infection, assumed to be occupational, and 79 documented seroconversions had been reported in *industrialised* countries. Most seroconversions occurred in nurses (47%). Technicians taking blood in laboratories were the second highest risk group (22%).

Data on post exposure prophylaxis

Effectiveness of antiretrovirals

In 1990, the CDC published recommendations for health workers in case of percutaneous exposure and included the possibility of treatment with zidovudine (ZDV, formerly known as AZT). At that time, the treatment could not be recommended as there were no data in humans on efficacy or safety of ZDV for this indication. However, in many industrialised countries, hospitals dealing with high numbers of cases of HIV infection, had in anticipation of national recommendations, began offering ZDV in 1988.

Today we know that ZDV taken after exposure to HIV can reduce risk of HIV infection post exposure. The CDC study is the only study, so far, to demonstrate effectiveness of ARV treatment as post exposure prophylaxis. The study included 31 cases of seroconversion and 679 controls (exposed people who had not seroconverted); the exposures had occurred between 1988 and 1994. Nine cases (29%) and 246 controls (36%) had taken ZDV. The dose in most cases was 1000 mg ZDV per day for 3 to 4 weeks. Having taken ZDV was a significant factor related to reduction of infection risk (adjusted OR 0.19 - 95% CL:0.06-0.52). The results show that taking into account other factors, the risk of transmission was reduced by 79% (95% CL 43-94%) for those who took ZDV.

The results of this study should be interpreted with some caution. It was not a prospective randomised efficacy study - which would have provided the best answer. However, such a study would not be feasible now given the large number of subjects required and the ethical problems associated with giving a placebo when an effective treatment exists. The study had very few cases which furthermore, came from different sources. However, even though it may be difficult to determine the exact level of protection from this study, it is nevertheless highly probable that the protection conferred is significant.

Analysis of prophylaxis failures in cases of occupational exposure

Among the nine failures in the case control study (patients infected despite treatment), eight resulted from percutaneous exposures and one mucosal exposure. For the eight percutaneous exposures, ZDV was started between 30 minutes and 12 hours following exposure, for the mucosal exposure, on the 8th day. The daily dose varied between 800 and 1200 mg (median 1000 mg) for 8-54 days (median 21). Two cases of early cessation of treatment were due to development of primary infection. Detailed information about the source patient was available in only four cases: in all four cases, the source patient was at an advanced stage of infection (CD4+ <50/mm³ in 3 cases). In the majority of cases, the source patient was known to have taken ZDV prior to the exposure episode and thus resistance to ZDV may have developed. The sensitivity of the HIV strain to ZDV was only known for two cases, and in these cases, it was shown to be reduced.

Five other cases of failure of PEP with ZDV in non-health workers have been reported, all involving larger quantities of blood than in the percutaneous exposures: a case of blood transfusion from an infected donor, an attempted suicide by inoculation with 2-3 ml of blood from an AIDS patient, a prison guard attacked with a syringe containing infected blood, and two accidental inoculations of contaminated blood during nuclear medicine procedures.

Toxicity and side effects

A data base of records of health personnel from many countries who have received PEP exists and provides estimates of the incidence of side effects of treatment. Most of the currently published data describes monotherapy with ZDV. The Italian National Register had recruited 674 health workers by December 1995. 49% reported at least one side effect and 20% stopped the treatment because of these effects. The most frequently reported symptoms were: nausea (74%), vomiting, abdominal pain, headache and fatigue. The symptoms were dose dependent and reversible with cessation of treatment. They were reported most frequently in the first week of treatment.

Minor anomalies of liver function and haematology were also observed in a minority of cases. In 2% of cases, transaminases increased transiently up to 3 times the normal level and in 3% of cases, anaemia grade 1 (Hb 9.5-11 g/dl) was diagnosed. These disorders appeared after an average, respectively, of 26 days (median 21) and 24 days (median 21) of treatment. Patients did not have to stop treatment and the abnormalities disappeared after the end of treatment. Other minor symptoms, such as skin rash and fever, are common (see modules 4&5). The side effects of PEP are, in the short term, generally moderate and reversible with modification of the dose and/or stopping treatment. However, the long term toxicity of ZDV prophylaxis has not been evaluated.

Prevention

Application of universal precautions

The reduction of AEB in general patient care and laboratories consists essentially of decreasing contact with blood. This is the objective of universal precautions (UPs) which apply to all services and patients. The recommendations of UPs are guided by a general principle which considers blood *a priori* to be contaminated, a substance with which one should not have direct physical contact.

Universal precautions

Gloves should be worn for

- any contact with body fluids
- any contact with cutaneous or mucosal lesions
- any contact with contaminated, or potentially contaminated material.

All wounds should be covered

Wash hands

- immediately after any contact with potentially infective fluids
- after every health care procedure.

Wear protective clothing (masks, goggles & aprons) when there is a risk of splashing

- tracheo-bronchial aspiration
- endoscopies
- catheterisation
- surgery
- deliveries.

Care when handling potentially infected sharps

- needles should never be bent back or put back in their original holder
- needles should not be removed by hand from syringes or vacutainers
- needles and other sharps should be disposed of immediately in a special, puncture proof, sealed container (sharps box).

Disinfection of surfaces

Soiled instruments and surfaces soiled with blood or other bodily fluids should be disinfected immediately with a fresh 1:10 bleach solution or other effective disinfectant.

Disposal of contaminated material

Contaminated material should be placed in distinctively labelled sealed packaging and then incinerated.

Laboratory settings

The above precautions should take place systematically for all samples; samples should be transported in hermetically sealed tubes or flasks, inside sealed packaging; mouth pipetting is forbidden.

Organisation of work: integration of safety measures

Application of UPs, and provision of a strategy to prevent exposures in general patient care, requires various prevention tools and procedures. AEB prevention depends on good

organisation and appropriate use of safe materials and equipment. All health care institutions should integrate safety measures into all activities and procedures in all hospital services, inpatient, outpatient and laboratory.

The integration of safety measures into hospital procedures must be designed and agreed upon by a cross section of health care workers. They must identify the causes of accidents reported in the institution and take into account the type of procedure involved, and the availability of protective equipment. For example, provision of large containers will not be useful unless procedures are reorganised so that there is always a trolley holding the container next to each patient while taking blood. Likewise there is no point in introducing large sharps containers if the opening of the incinerator is too small to take them.

Analysis of AEB in health workers has allowed manufacturers to design protective equipment to limit the risk of contact with blood, in particular to minimise needle stick injuries. Many medical procedures (such as venepuncture, arterial blood sampling, inserting drips, and intramuscular and subcutaneous injection), can now be performed with minimum risk in industrialised countries where specially designed equipment is available to minimise risks of PE.

Cost is an important constraint in acquiring the new range of products which are not standardised and which are substantially more expensive than the previously available equipment. Furthermore health care workers may need further training if new equipment is introduced, and supply of new equipment must be ensured. For example, using vacutainers to take venous blood samples has been designed to reduce the incidence of needle stick injuries, but supplying these intermittently to a rural African hospital without teaching nursing staff how to use them will be of no benefit.

The policy regarding protective equipment is one of the new aspects of a global strategy of protection of health workers in institutions. It is multidisciplinary and involves doctors, the administration, pharmacists, nurses, paramedics and laboratory staff. An infectious diseases control committee with authority to report incidents and decide on appropriate action for protection against nosocomial infection could be established. This streamlines and focuses activities and allows pooling of resources and expertise, and follow up of activities. The choice and use of protective equipment cannot be made without local evaluation and follow up.

Training of Health Care Workers (HCWs) in universal precautions and prevention of AEB

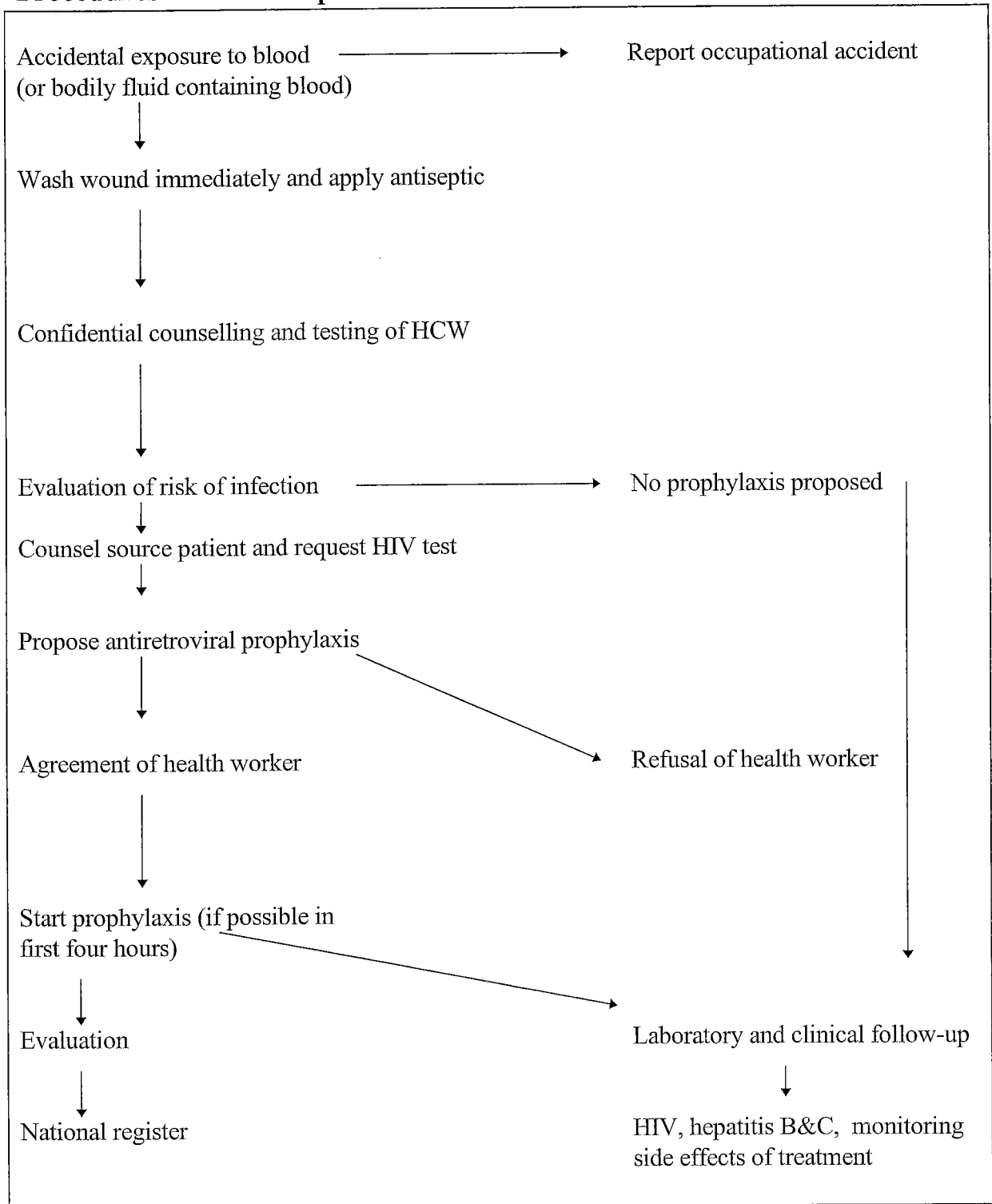
All health workers and professionals at risk of exposure (nurses, doctors, laboratory technicians, nursing auxiliaries and surgeons) must be trained in prevention of AEB during the period of their studies rather than when they have started work. Health care workers (HCWs) at risk should have “refresher” courses to update their knowledge and should regularly review procedures as a team. The training should include organisation of care, analysis of accidents and training in the use of new safety equipment. Different training is needed for different categories of HCWs. In many developing countries although HCWs are aware of UPs they are unable to apply them because of shortages of basic equipment such as gloves and other protective clothing. In a study from Zambia a large urban hospital had few sharps boxes available and

needles were sometimes thrown away with the general hospital waste or in cardboard boxes. HCWs need to find ways to improvise using the available resources. In high prevalence areas, many HCWs may already be anxious about HIV and may have had previous needle stick injuries. These anxieties must be addressed sensitively and counselling should be made available.

Register of AEB

Surveillance of AEB provides the foundation for all other activities - the design and setting up of policies and equipment, the application of universal precautions, and the training undertaken in institutions. Monitoring rates of AEB provides a measure for assessing the effectiveness of the different protective measures that have been introduced. For this it is important that AEB be reported in a standard way allowing observation of trends and evaluation of the impact of the measures taken. A standard surveillance register at national level would be useful and each institution should participate in the formulation of a concerted prevention policy. Confidentiality of HCWs who have been exposed to AEB must always be ensured. In some high prevalence areas, HCWs may be reluctant to disclose occupational exposure because of fear of stigmatisation.

Procedures in case of exposure



After first aid (washing wound and application of appropriate antiseptic), the next step is to provide counselling for the exposed HCW and evaluate the risk. Immediately after the accident, a doctor or other designated HCW should evaluate the severity of the exposure, taking into

account the depth of the wound, the type of instrument involved, the bodily fluid and the serological status of the source patient, if known. The option to use PEP depends on the availability of ARVs. In the majority of industrialised countries, all AEBs, where the source patient is known to be HIV infected or at high risk for HIV infection, are considered for ARV PEP. In some middle income countries, the recommendations apply only to serious accidents. Currently, in many developing countries no ARVs are available for PEP.

If ARVs are available, the next step will include determining the serological status and stage of illness of the source patient. It should be possible to carry out this evaluation (which determines the choice of treatment) 24 hours a day. The emergency services of the institution, therefore, should play an important role in the organisation of these activities.

Following the evaluation, the doctor, or designated HCW, may recommend or propose prophylaxis. The health worker may have considerable anxiety following the AEB and sensitive confidential counselling should be available. The exposed health worker should be informed about any uncertainties relating to the effectiveness of the treatment and the possible side effects. It is up to her/him to accept or reject the prophylaxis.

The indications for prophylaxis according to the severity of the cutaneous-mucosal exposure when the serological status of the source patient is known, are summarised below:

Type of exposure	Source patient HIV seropositive	
	Symptomatic and/or high viral load	Asymptomatic and/or low viral load
<ul style="list-style-type: none"> • Massive • Intermediate • Minimal 	<p>Recommended</p> <p>Recommended</p> <p>Possible</p>	<p>Recommended</p> <p>Possible</p> <p>Possible</p> <p>(but to be discussed)</p>

Essential steps

Identification of the accident: the accidental exposure to blood must be recognised as such by the health worker. This requires training of persons at risk, care and non care providers.

Foresee/prepare arrangements: these should function 24 hours a day: anyone exposed should be able to receive confidential counselling and treatment in the hours following the accident.

Identify resource persons: among the hospital personnel to help the exposed person to take the necessary steps and take care of him/her.

Identify prescriber: to evaluate the risk, decide on treatment to be offered and follow up the patient.

Initial serology: The health worker who has been accidentally exposed should have HIV pre-test counselling and a reference serology within eight days of the accident to check for prior infection (this can be a frequent finding in high prevalence areas). All those initially testing negative should have follow up serology.

Serological follow up: counselling and testing should be offered at three and six months after the accident.

Provision of treatment: the drug treatment, which will comprise 1 or a combination of 2 or 3 ARVs must be available at all times, must not be out of date, and must be prescribed by a professional.

Serological testing of the source patient: when the serological status of the source patient is not known, this person must be informed about the accident in order to obtain consent to test for HIV antibodies. Confidentiality of the results must be the rule. If he/she refuses or consent is not possible (patient unconscious), prophylaxis should be considered if there are indications of possible infection (prevalence of infection among the patients in the institution, suspicion of a risk factor in the source patient).

Note that not all patients with risk factors are infected, and that in high prevalence areas, the concept of risk factors may not be very useful.

Therapeutic protocol after occupational exposure

The therapeutic protocol comprises three important elements:

- Timing of initiation of treatment
- Therapeutic regimen
- Laboratory monitoring.

Timing of initiation of treatment

Animal studies show that prophylaxis after exposure can definitively prevent infection if it is administered in a sufficiently short time (within eight hours with the most powerful drugs in macaques). The maximum delay in initiation of treatment which would block infection is not known in humans. As the objective of post exposure prophylaxis is to prevent infection and not to treat an eventual primary infection, the time between exposure and initiation of treatment should be as short as possible. In most industrialised countries which have made recommendations, the optimal delay is extremely short, 2-4 hours. However, with the exception of Denmark which recommends a maximum delay of 24 hours to start treatment, there is no time limit in most country recommendations. Prophylaxis is sometimes given empirically up to 2 weeks in the case of severe exposure when the delay has been unavoidable.

Therapeutic regimen

The therapeutic regimen will be decided principally on the basis of drugs previously taken by the source patient and known or possible cross resistance to different drugs. It may also be

determined by the seriousness of the exposure and the availability of the various ARVs in that particular setting.

So far, ZDV is the only regimen for which data on efficacy exist. However, double and triple therapy are now being used for PEP on an empirical basis in industrialised countries. The use of ZDV as monotherapy for PEP no longer appears justified in countries where it has been used in patients for 10 years, as its effectiveness may be reduced by the existence of resistant strains.

In most industrialised countries, the latest published recommendations tend towards bitherapy, using ZDV, the only drug that has been shown effective for this purpose, and another nucleoside reverse transcriptase inhibitor (NRTI), usually lamivudine, in order to increase antiretroviral activity and eliminate ZDV-resistant strains. Protease inhibitors (PIs) have not yet been tested for this indication, however, they are included in the therapeutic regimen in certain cases notably when the risk of transmission appears higher (severe exposure and high viral load in source patient). Their high therapeutic efficacy must be weighed against the risk of side effects. Drug interactions may also pose a problem. Some countries systematically propose tritherapy.

The combination and the recommended doses, in the absence of known resistance to ZDV or lamivudine in the source patient are:

- ZDV 250-300 mg twice a day
- Lamivudine 150 mg twice a day
- The PI recommended on the basis of its acceptable tolerance and limited drug interactions is indinavir 800 mg 3 times a day.

In developing countries where ARVs are not widely used and the source patients are therefore likely to be ARV naive, ZDV monotherapy for PEP is a valid option.

The recommended duration of treatment is four weeks, based on the results of the CDC case control study. However, the optimal duration has never been evaluated. Certain countries propose minimum treatment of two weeks and maximum four weeks.

Accidental exposure to blood for a health worker who is pregnant poses a particular problem, as data on ZDV tolerance in pregnancy in the first trimester is limited. Lamivudine, alone or in combination with ZDV, has been tested in infected pregnant women, and shows good tolerance and a good placental diffusion with cord concentrations equivalent to maternal blood concentrations. A trial of tritherapy with ZDV/lamivudine/tritonavir as PEP is being developed. These agents present no embryotoxicity nor teratogenicity in animals and pass the placental barrier well. However, when prescribing in late pregnancy there is a theoretical risk in the child of neonatal hyperbilirubinemia and renal stones.

Current recommendations for the pregnant woman are in favour of nucleoside bitherapy if the accident occurs after the second trimester of pregnancy. If the accident occurs during the first trimester, the risk/benefit for the mother and the foetus (risk of treatment against risk of transmission) must be assessed on a case by case basis.

Serological and clinical monitoring

Serological follow up particularly for medico-legal reasons, requires testing for HIV antibodies at the time of the accident. Laboratory tests should include, at the minimum, a second HIV serology done three months after the exposure, when the majority of those who are infected have seroconverted. Beyond this, the risk of contamination by some other mode of transmission is higher and serological follow up no longer makes sense. However, currently published recommendations suggest a third serology, usually done at six months following the exposure, for those who have tested negative.

Initial laboratory tests should include (according to the treatment prescribed), blood count, renal and hepatic function, serology for hepatitis B and C (if these are available) and if necessary a pregnancy test. The minimum laboratory tests for monitoring undesirable side effects must include an FBC and transaminases. The pregnancy test is to take into account complications which may arise if the exposed health worker is pregnant.

The health worker taking PEP should be followed clinically during the treatment, especially to monitor side effects which might make a change in treatment necessary. The health worker must be informed about signs of primary HIV infection, so that he/she will be able to consult the doctor quickly.

Counselling following AEB

Counselling for prevention of transmission (safer sex, no blood donation etc.) whilst waiting for the follow up serology, should be provided to the health worker. The health worker may have anxieties about telling his/her sexual partner about the AEB and recommendations to use safer sex until the follow up test result is known. The health worker may wish to involve his/her partner in the counselling. Although PEP is highly effective and the risk of transmission post exposure is low, long term counselling and support services, possibly including treatment for HIV disease, must be in place for health workers who acquire HIV despite PEP. Whether ARVs will be offered to HCWs who acquire HIV despite PEP will have to be decided. If there is a national or hospital policy for compensation of HCWs for occupational injuries or accidents, accidental exposure to HIV may need to be included in this.

HIV testing of health care workers following AEB in high prevalence areas

In countries with the highest risk of acquiring HIV from AEB the background HIV seroprevalence rates amongst HCWs will also be high, irrespective of any occupational risk. Studies from sub-Saharan Africa have shown similar levels of HIV among health care workers as in the general population. Thus many HCWs will be seropositive at the time of the AEB. In studies among HCW at the University Teaching Hospital in Lusaka, Zambia, the majority of HCWs did not report AEB because they felt that they may already be infected - either by previous AEB or through previous sexual contact. Many said they did not want to know their

HIV status, because if they were found to be seropositive there was little that could be done to help them medically, they feared rejection by their partners and they did not believe that the results would remain confidential. Confidential voluntary counselling and testing services in high prevalence areas need to be established for *all* HCWs. This service must be in place before considering introducing ARV treatment for PEP.

Evaluation

Evaluation of PEP, in particular with respect to acceptability, adherence, tolerance, and effectiveness is important as there is still much uncertainty about the efficacy and safety of PEP with ARVs for this indication. Thus it is important that physicians, and HCWs caring for exposed HCWs keep careful records of this data.

Records must include a detailed description of the accident, date, place, time, circumstances, type of exposure, severity, nature of the bodily fluids and the action taken: advice, risk evaluation, treatment and clinical and laboratory follow up. These data must be collected respecting the confidentiality of the exposed HCW and that of the source patient.

National treatment policies on occupational exposure to HIV

The CDC case control study that showed the efficacy of PEP with ARVs, led public health authorities in several industrialised countries to issue recommendations for policies and procedures following accidental exposure of health workers to HIV.

**Comparison of national recommendations for prevention of infection
after occupational exposure to HIV**

Country	Definition of exposure	Time limit for start of treatment	Therapeutic combinations	Length in weeks	References
Germany	serious exposures	within 2 hours, no upper limit	ZDV/3TC/IDV	2wks min. 4 wks optimum	Epid.Bull. Oct.1996, updated Nov.97
Australia	1) percutaneous exposure 2) high risk or ZDV-resist.	within 2 hrs	1) ZDV,DDI or DDC and 3TC 2)2 nucleosides and PI*	6 wks	ANCA,Bull. No.16, March 96
Canada/ Quebec	1) percutaneous exposure 2) high viral load, patient treated with nucleosides, serious nature	within 2 hrs, no upper limit	1) ZDV/3TC 2) ZDV/3TC/IDV	4 wks	CCDR March 19 97 updated Oct. 97
Denmark	percutaneous exposure	within 24 hrs max.	ZDV/3TC/IDV	4 wks	awaiting publication
Spain	1) percutaneous exposure 2) high risk	a.s.a.p, no upper limit	1) ZDV/3TC 2) ZDV/3TC/IDV	2 or 3 wks	CNS Nov. 96 updated Nov. 97
USA	1) percutaneous exposure 2) serious nature, resistance in source patient	within 2 hrs, no upper limit	1) ZDV/3TC or D4T 2) ZDV/3TC/PI*	4 wks	MMWR 96, updated Oct.97
France	1)percutaneous exposure 2) serious nature, resistance in source patient	within 4 hrs, no upper limit	1) ZDV/3TC 2) ZDV/3TC/IDV	4 wks	BEH Dec. 96
Netherlands	exposure to blood	within 2 wks	ZDV/3TC/IDV	4 wks	LCI June 1997
United Kingdom	percutaneous or mucosal, skin broken with blood or high-risk fluid	a.s.a.p	1) ZDV/3TC 2) ZDV/3TC/IDV	2 wks min. 4wks max.	SFOPH February 1997
Switzerland	1) superficial wound or mucosal 2) percutaneous, HIV+ blood transfusion, accidental injection of contaminated fluid	a.s.a.p	1) ZDV/3TC 2) ZDV/3TC/IDV	2 wks min. 4 wks max.	SFOP February 97

*PI : protease inhibitor

Provision of chemoprophylactic therapy should be considered in countries and institutions where universal precautions have been successfully implemented. A programme of PEP implies that most accidents are avoided and UPs are practised. If protective clothing and “barrier” precautions such as gloves, have been used, the inoculum will have been reduced and PEP will be all the more effective. Furthermore, effective prophylaxis requires efficient organisation and management of AEB. The correct timing of treatment and appropriate choice of drugs are absolute imperatives for efficacy. The efficacy of the prophylaxis is not 100% and it is expensive, difficult to take and requires sophisticated health care facilities. It should therefore be considered in institutions where the other elements of a comprehensive prevention strategy of AEB are in place and functioning efficiently.

It should be noted that PEP with ARVs plays no role in the prevention of infection by hepatitis B or C; and the risk of transmission of these viruses is much higher than for HIV. Vaccination of HCWs against hepatitis B should be strongly recommended.

Therapeutic management of AEBs will also depend on the resources of the country and particularly on access to ARVs. There are strong ethical arguments for reserving part of this stock of ARVs for health workers in case of accidental exposure. In caring for HIV-infected patients, health workers are exposing themselves to risk over and above that faced by the general population. Making PEP available to them would contribute to making work in care units where HIV prevalence is high and safety measures less than optimal, more acceptable. However, the provision of counselling and testing services must be assured.

In countries where universal precautions are widely used and ARVs are available, it is imperative to set up a system in all hospitals allowing all workers to benefit from ARV treatment as rapidly as possible if the risk of transmission is considered significant. This would bring procedures into line with legislation on the obligations of employers to ensure the safety of employees at work and to compensate them for the consequences of work accidents.

The regimen offered could be bitherapy if resources permit or monotherapy with ZDV if it has not yet been widely prescribed in the country. It is recommended that the duration of treatment with bitherapy should be at least two weeks and four weeks with ZDV monotherapy. A register of exposed and treated health workers in large institutions in high prevalence areas would provide data for the evaluation of the management of accidental exposures to blood.

Cost estimates

The estimation of the costs of PEP should include:

- drug costs
- HIV testing costs (of exposed person & source patient)
- counselling costs (of exposed person & source patient)
- clinical monitoring, including follow up and treatment of adverse effects
- serological follow up over 3-6 month

Clinical care and time spent on counselling and testing and clinic visits by the exposed health care worker should be considered as well. Counselling services for health care workers may need to be set up.

Cost effectiveness estimations for PEP have been made in industrialised country settings². These show the cost per case of HIV averted in the US is very high. However there are very strong arguments, beyond the economic ones, for offering protection to health care workers (see Module 9 on ethical and societal issues relating to ARV treatment for detailed discussion)

Cost effectiveness has been estimated based on the **total numbers** of PE with HIV contaminated blood. No distinction has been made between “massive” “intermediate” or “minimal” exposures. If all PE with HIV contaminated blood are treated with PEP it must be noted that 997 people out of 1000 will receive ARVs unnecessarily. If a more selective analysis of PE is made and only “massive” and “intermediate” PEs receive ARVs this will cut down the costs of the service and the numbers of people receiving ARVs unnecessarily. However their may be a very small minority of people in the “minimal” group for whom ARVs would have prevented transmission.

It is also important to emphasise that “cost effectiveness” estimations are only one of the considerations to be examined when setting priorities for ARV PEP. Ethical and individual considerations will often be of at least equal importance.

Prophylaxis after non-occupational exposure to HIV

ARV prophylaxis after non-occupational exposure to HIV is of concern to those who have had a sexual or parenteral exposure through sharing drug injecting equipment to HIV. This subject has only recently received attention, following new understanding of the pathophysiology of HIV infection, therapeutic advances with ARVs and evidence that ZDV is effective in PEP. Public demands have been made for PEP following non-occupational exposure. Although there are no consensus guidelines some practitioners in industrialised countries are prescribing ARV prophylaxis treatment after non-occupational exposure.

There are a number of **scientific arguments** to support prophylaxis following non-occupational exposure to HIV:

- Parallel immunological mechanisms exist for percutaneous and mucosal exposure;
- Similar rates of infectivity by each contact for the different type of exposure: percutaneous, mucosal or parenteral;
- Positive results of ARV trials in animals in cases of parenteral or mucosal inoculation as well as results of prophylaxis in pregnant women and health personnel;
- Availability of more powerful treatments than ZDV monotherapy.

Only the city of San Francisco (USA) and France have set up mechanisms to provide ARVs for non-occupational exposures. The treatment for non-occupational PEP draws on the protocol for

² Pinkerton S Cost effectiveness of chemoprophylaxis after occupational exposure to HIV Arch Intern Med 157 1972-80 (1997)

health workers, with the difference that an upper limit on initiation of treatment is put at 48 to 72 hours.

The implementation of such a programme presupposes a certain number of conditions such as high prevalence of preventive behaviours; organisation of care and counselling allowing urgent treatment of accidental exposure, the risk of which can be correctly evaluated, as well as follow up of patients; wide access to testing; availability of ARVs and proper evaluation of the programme.

Such a programme has only been implemented in industrialised countries with relatively low HIV seroprevalence rates. In such settings the number of "accidents" is low and the cost of treatment affordable. In a high prevalence country like Zambia (HIV seroprevalence amongst sexually active adults: 30%; number of condoms sold per annum approximately: 5 million; 1% breakage; 50,000 accidents) PEP following such "accidents" would be unaffordable. Clearly, for most countries in the world, treatment of non-occupational exposures cannot be considered a public health priority.

Rape

Whether people who have been raped should have access to ARV prophylaxis as a priority over those who believe they may have been exposed to HIV in consensual sex, either because of condom breakage or because of a failure to employ condoms during sexual intercourse, is a matter of debate. Those who claim that no distinction should be made between such individuals and rape victims wish to avoid the implication that the former are "guilty" while the latter are innocent. But proponents of treating rape victims preferentially make two arguments: First, the special claim of rape victims stems from the trauma to which they have been subjected. It may be argued that those placed at risk by consensual sex must assume responsibility for such risk (such as condom breakage) which any consenting adult assumes today in his or her sexual relations. Secondly, there is a fear that treating ARV prophylaxis as a "morning after" intervention may subvert prevention messages that stress the importance of practicing safer sex and the avoidance of unprotected sexual intercourse with those whose HIV status is unknown (See Module 9 on ethical and societal issues relating to antiretroviral treatments).

Conclusion

The availability of post exposure prophylaxis for occupational exposure does not replace traditional methods of prevention. It must be an integral part of primary prevention. It is justified only in situations where the wide application of prevention measures already reduces exposure to HIV. PEP should be viewed as an option when preventive measures have failed.

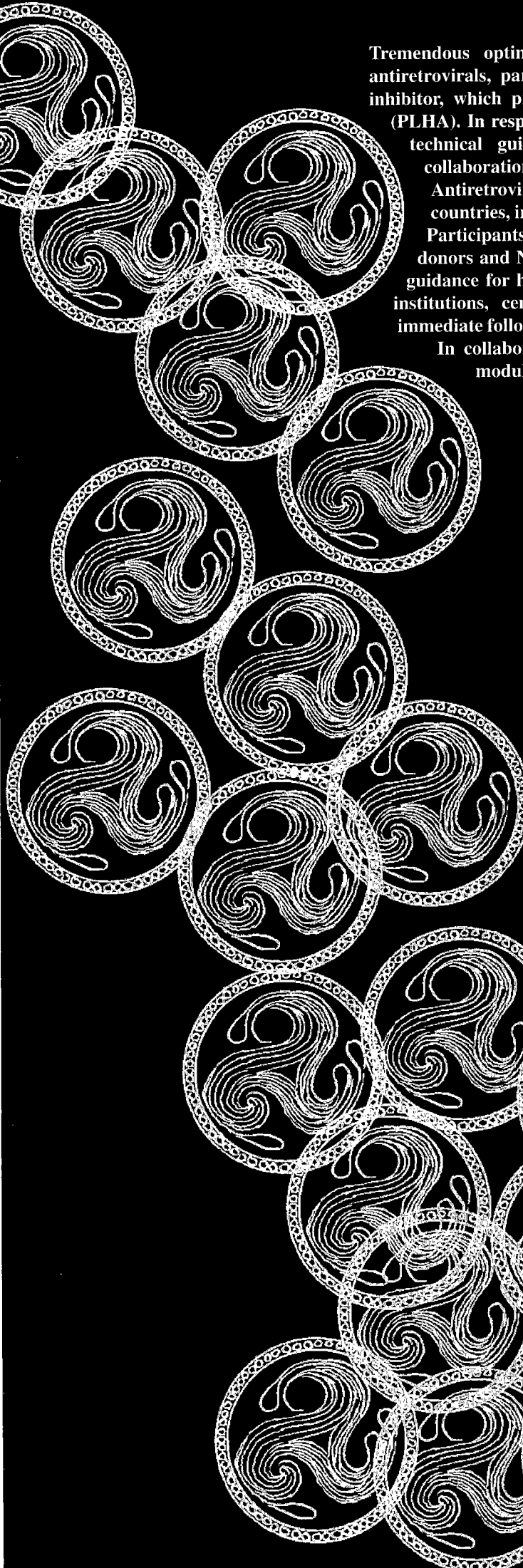
The average risk of infection after exposure to HIV is very low, compared to other infectious agents, such as hepatitis B and C. The average level of risk for a percutaneous exposure is around 3 per 1000. This low risk of transmission per exposure means that treatment is only useful for a minority of individuals exposed. This implies as accurate as possible an assessment of risk following the exposure, in order to avoid exposing individuals unnecessarily to a treatment, the toxicity of which is not yet known in healthy subjects.

Results from a case control study in humans and several animal trials indicate the efficacy of nucleoside monotherapy. This treatment has been shown to be effective when initiated rapidly after exposure but there are limited data on PEP given after 24 hours. In animals, efficacy decreases significantly with time. Efficacy is related to dose and duration of treatment. Currently published recommendations for treatment following exposure in humans are those established for health workers. Usually no time limit is placed on initiation of treatment, although it is strongly recommended to start treatment in the first hours following exposure and to continue for four weeks.

Trials in animals combining several drugs, testing different timing of initiation, and durations of treatment less than four weeks, allowing better adherence and limiting secondary effects, are ongoing. Although short term side effects of treatment are very frequent, they are generally moderate, and reversible after stopping treatment. Exposure of a large number of healthy people are likely to reveal toxicities that are not yet known. So long term monitoring will be important. In industrialised countries where source patients are likely to be taking ARVs, bi- or tritherapy as PEP is usually indicated, whereas in developing countries where source patients are usually ARV naive, zidovudine monotherapy (ZDV) is recommended.

Treatment of HCWs after exposure to blood is appropriate in countries where training, prevention and surveillance of accidents in health care institutions are well organized. It is not a priority in countries where there are many avoidable AEBs as a result of inadequate protective material and equipment and insufficient training in prevention measures. Adequate training of HCWs and provision of HIV education and counselling to all HCWs must precede the introduction of ARV PEP services.





Tremendous optimism has been generated by the recent development of new antiretrovirals, particularly the triple combination therapies including one protease inhibitor, which promise a longer and better life for people living with HIV/AIDS (PLHA). In response to requests for the treatments from PLHA, and for policy and technical guidance from health professionals and governments, WHO, in collaboration with UNAIDS, held an Informal Consultation on the Implications of Antiretroviral Treatments with particular reference to low and middle income countries, in April 1997.

Participants at the consultation, ministries of health, health professionals, PLHA donors and NGOs working in HIV/AIDS have all called for technical and policy guidance for health planners and policy makers, and decision makers in training institutions, central and district hospitals on antiretroviral treatments, as immediate follow up to the consultation.

In collaboration with UNAIDS, WHO has produced a set of nine guidance modules on the following aspects of antiretroviral treatments:

1. Introduction to antiretroviral treatments
2. Introducing antiretroviral treatments into national health systems: economic considerations
3. ARV treatments: planning and integration into health services
4. Safe and effective use of antiretrovirals
5. Laboratory requirements for the safe and effective use of antiretrovirals
6. The use of antiretroviral drugs to reduce mother to child transmission of HIV
7. Treatments following exposure to HIV
8. Antiretrovirals: regulation, distribution and control
9. Ethical and societal issues relating to antiretroviral treatments

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