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AIDS and Trauma

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1. Introduction

Trauma is a significant cause of mortality (10%) worldwide and is responsible for 15% of all disability-adjusted life years (DALYs) (Murray & Lopez, 1997). Seven of the top 30 contributors to the global burden of disease are due to injury, including motor vehicle accidents, falls, war injuries, self-inflicted injuries, violence, drowning and burns. All of these injuries are seen in the trauma setting and places trauma workers at risk of exposure to blood and other body fluids. The relevance of HIV and trauma is increasing as the global prevalence of HIV continues to rise. Sixty million have been infected with HIV since the beginning of the epidemic and 25 million have died of HIV-related causes (UNAIDS, 2009). Of those newly infected, 40% were young people - the group most likely to be involved in trauma.

2. Universal precaution

In general, the risk of transmission of any infectious disease may be minimised in the trauma setting by implementing universal precautions. The World Health Organization (WHO) has developed universal precaution guidelines which are summarised below (WHO, 2007).

- Hand wash after any direct contact with patients
- Safe collection and disposal of sharps
- Gloves for contact with body fluids, non intact skin and mucous membranes
- Wearing a mask, eye protection and a gown if blood or other body fluids might splash
- Covering cuts and abrasions
- Cleaning of spills of blood and other bodily fluids
- Safe system for hospital waste management and disposal

In addition, the WHO advocates Hepatitis B virus (HBV) vaccination of healthcare workers, development of post exposure protocols for those at risk of contact with infected body fluids, adequate provision of personal protective equipment (PPE) with appropriate means of disposal, and monitoring of staff training and use of PPE.

Historically, trauma workers have generally had poor compliance with universal precaution guidelines. In a Jamaican study, where health care workers were interviewed to determine the reason for not adhering to universal precautions, numerous reasons were provided including: (1) increase in workload made adherence difficult, (2) a perceived reduction in dexterity when wearing gloves, (3) insufficient supply of PPE and (4) lack of penalties for

not adhering to universal precautions (Vaz et al., 2010). Other studies in the United States have reached similar conclusions and also highlighted that trauma workers have a poor knowledge of infection risk (Kelen et al. 1990; Kim et al., 1999)

3. Post-exposure prophylaxis

Post-exposure prophylaxis (PEP) is the collection of measures taken after exposure to a pathogen in order to prevent or reduce the risk of transmission. In the case of HIV, such measures should include, but are not limited to, first-aid, appropriate HIV testing, counselling, anti-retroviral (ARV) chemotherapy, and follow-up. The risk of occupational exposure to healthcare workers in the trauma setting depends on the relative prevalence of HIV in the trauma population and the level of exposure. The use of PEP in patients attending the trauma service should also be considered in cases of sexual assault and other forms of acute non-occupational exposure. It is strongly recommended that all trauma services have well established PEP protocols, sufficient resources and necessary training for effective implementation.

The only direct evidence supporting the prophylactic use of ARV chemotherapy (zidovudine) for healthcare associated HIV exposure comes from a single case-control study involving patients from the United States, United Kingdom, France and Italy (Cardo et al., 1997). Healthcare workers were 81% less likely to seroconvert if they received zidovudine after a needlestick injury and the risk of seroconversion was linked to the volume of blood transmitted and the HIV blood titre level. Indirect evidence supporting the prophylactic use of ARVs include reduced rates of vertical transmission in HIV positive mothers who received zidovudine and the success of ARVs in raising CD4⁺ counts, reducing viral titres, and decreasing morbidity and mortality in HIV positive patients (Connor et al., 1996).

3.1 Occupational exposure

The risk of HIV transmission through needlestick injury is 0.3%. The risk of transmission from contact of contaminated fluids with mucous membranes or damaged skin is approximately 0.09%. However, the risk of occupational exposure in trauma may be higher than in other hospital settings. This is because the HIV status of patients is usually unknown, the prevalence of HIV in the trauma population is generally greater than the community, the mechanism of injury is often violent and may increase the level of exposure, and the emergent nature of trauma increases the situational stress and may lead to riskier practice.

PEP is only indicated in cases where there is a risk of transmission (Table 1) and contraindicated in cases where there is no appreciable benefit (Table 2). For occupational exposure, this includes contact between body fluids at risk of HIV contamination and non-intact skin or mucous membranes. Indirect evidence from animal studies suggest that initiation of PEP after 72 hours following exposure is not effective at reducing rates of seroconversion. PEP should therefore not be offered in such cases and strategies should exist to offer PEP as soon as possible after exposure (Martin et al., 1993). Starter packs are well-suited to the emergency department as they offer quick access to ARVs, may result in less wasted medication if PEP is not continued, requires the patient to attend follow-up to obtain additional ARVs ensuring appropriate testing and counselling, and can easily be placed in small or under-serviced departments. Theoretical risk of HIV resistance may develop if starter packs are inappropriately used or ARV courses are not routinely completed.

Exposure between body fluids suspected of, or confirmed to be, HIV positive and:

- Non-intact skin (needlestick, sharp injury, skin abrasion)
- Mucous membranes (oral cavity, nasal cavity, eyes)
- Sexual contact in cases where a condom was not used, broke or fell off during intercourse
- Oral sex with ejaculation¹

Table 1. Indications for PEP²

- Patient is already HIV positive from previous exposure
- Exposure has been chronic³
- Exposure through intact skin
- Sexual contact with condom use that remains intact
- Exposure to non-infectious body fluids such as saliva, faeces, urine, and sweat
- Exposure to HIV negative body fluids
- Greater than 72 hours have elapsed since exposure

Table 2. Contraindications to PEP²**3.2 Exposure as a result of sexual assault**

The risk of non-occupational exposure depends on the nature of contact with contaminated fluids. In cases of sexual assault, the method of assault, the condition of genital or oral mucosa, the circumcision status, and the level of HIV virulence all play a role. Risk is increased in cases of rape, where there is decreased lubrication and may be associated with violent penetration. Children, especially small children, are also at an increased risk for anatomical reasons. Generalised risk from a single sexual contact depends on the method of exposure. Published estimates of HIV transmission for receptive anal intercourse are 1-30%, insertive anal intercourse 0.1-10%, receptive vaginal intercourse 0.1-10%, and insertive vaginal intercourse 0.1-1% (Boily et al., 2009). Case studies have also reported transmission from oral sex with ejaculation (Lifson et al., 1990; Rozenbaum et al., 1988).

PEP should be offered to all victims of sexual assault attending the trauma service where the act occurred within 72 hours. In many cases, particularly with children, the assault may be on a background of chronic abuse, in which case PEP is not indicated. However, special care should be taken to distinguish between cases of chronic abuse and cases of acute-on-chronic abuse where a different perpetrator is responsible for the most recent assault. In such cases, PEP should be offered.

¹ The risk for oral transmission is considered very low but PEP may be offered in cases where the exposure is in association with significant oral disease such as ulceration or dysplasia

² Adapted from: WHO. Post-exposure prophylaxis to prevent HIV infection: Joint WHO/ILO guidelines on post-exposure prophylaxis (PEP) to prevent HIV infection. *HIV/AIDS Programme: Strengthening health services to fight HIV/AIDS*. 2007

³ Chronic exposure should be distinguished from episodic exposure where PEP may still be effective. This distinction may be challenging.

3.3 Other types of exposure

Routine PEP after community-acquired needlestick injury is controversial and administration should be based on risk assessment. At risk populations include children, security workers and cleaners (Celenza et al., 2011). Children from communities with low prevalence of HIV may not warrant PEP (Makwana & Riordan, 2005). Care should also be taken to ensure exposure was within 72 hours as presentation to the emergency department may be delayed (Johnston & O'Connor, 2005).

The risk associated with needle-sharing is approximately 0.67%. PEP for needle-sharing may also be offered if presented within 72 hours and where exposure is likely to be acute rather than chronic.

3.4 PEP regimens

When indicated, the ARV regimen used depends on various factors including national policy, institutional policy, level of resources, toxicity and side-effects, daily pill burden, drug contra-indications and compliance. Although a single drug regimen using zidovudine has shown to be effective, multi-drug regimens are now more commonly used in order to cover drug-resistant HIV clones. The use of two drugs must be weighed against cost, toxicity and availability. A third drug may be considered in cases where the background prevalence of ARV resistance is greater than 15%.

Two drug regimens include fixed-dose dual nucleoside reverse transcriptase inhibitor (NRTI) therapy with combination zidovudine-lamivudine or combination tenofovir-emtricitabine. A protease inhibitor (PI), usually in combination with ritonavir, which increases PI plasma levels, are usually added if a third drug is necessary. Combination ritonavir-lopinavir, -atazanavir, -darunavir have all been used. All PEP regimens are given for 28 days post exposure.

3.5 Testing, follow-up and counselling

Testing of the source patient, in cases where HIV status is unknown, should include rapid-ELISA testing for HIV as well as testing for HBV (surface antigen - HBsAg) and Hepatitis C virus (HCV). In cases where HIV or HCV infection has occurred within the last 2-4 weeks, HIV or HCV RNA PCR may be indicated.

Testing of the exposed patient should be carried out as soon as possible to establish a baseline for follow-up testing. Tests should include a rapid-ELISA for HIV, HBV immunity status (anti-HB antibodies), HBsAg and HCV antibodies. Baseline full blood count, liver enzymes and creatinine should also be obtained to monitor for PEP side-effects and sequelae from hepatitis infection. Screening for other sexually transmitted infections may be warranted in cases of sexual assault or in patients with high risk behaviour.

At the minimum, follow-up testing at 6 months should be performed to document HIV negative status. Seroconversion after 6 months in those receiving PEP has been reported but is extremely rare (Ippolito et al., 1999). More intensive follow-up can include HIV and HCV antibody testing at 4-6 weeks, 3 months, and 6 months. Relevant additional testing should be offered in patients who become symptomatic or experience drug toxicity.

Post-exposure counselling should form an integral part of the PEP protocol. Services should be available to address HIV testing, follow-up testing, ARV treatment, legal issues and compensation claims should they arise. In the event that HIV is contracted, services should be available to address relevant needs. Counselling to address special needs of certain

population sub-groups such as children and victims of sexual assault should also be made available.

4. Management and outcome of HIV positive patients in trauma

The function of a trauma unit is to stabilise and treat life threatening injuries. It has been shown that HIV alone is not responsible for mortality in trauma but rather the patient's ability to mount an immune response (Allard & Meintjies, 2005). It is also unethical to not treat life-threatening conditions based on a patient's HIV status (Smit 2010). In fact, a number of studies have suggested that HIV positive patients have the same mortality rate as non-infected patients, especially if they are in the early stages of the disease (Smit, 2010).

With regard to surgical outcomes, early views were often pessimistic. It was felt that HIV positive patients were prone to poor wound healing, high post-operative complication rates, a prolonged post-operative period and higher mortality rates. This helped trigger a number of studies investigating the morbidity and complication rates among HIV positive patients both in general and orthopaedic surgery.

Many such studies have produced conflicting results. Duane et al conducted a retrospective study comparing outcomes of HIV positive and HIV negative patients over a 5-year period in the trauma unit. They found no difference in infection rates or overall complications based on CD4⁺ count alone (Duane et al., 2008). Conversely, Karpelowsky et al showed that in children who were HIV positive or exposed to HIV had increased rates of poor wound healing and breakdown of reconstruction sites (Karpelowsky et al., 2009). Other post-operative complications cited in the study were likely due to non-HIV related factors. For example, a large proportion of the children studied underwent emergency surgery, which is known to have higher rates of post-operative complications since the children tend to be sicker at presentation. This is true for both HIV positive and HIV negative patients. It was also found that up to 79% of children included in the study were undernourished and 36% had other co-morbid diseases including major respiratory and nutritional problems prior to undergoing surgery.

Stawicki et al found that HIV positive patients had both longer length of hospital stay as well as longer length of stay in ICU (Stawicki et al., 2005). They noted however, that HIV positive patients had more pulmonary, infectious and renal complications than the control group and suggested that the mortality of HIV positive patients was likely linked to these co-morbid processes. They also found that HIV positive patients needed greater numbers of surgical procedures but failed to state what the indication for these procedures were. Studies by Morrison et al and Horberg et al found similar findings to Stawicki et al, stating that HIV positive patients had higher post-operative complication rates, especially respiratory complications (Horberg et al., 2006; Morrison et al., 2010).

Studies comparing complication rates in orthopaedic surgeries have been small and only tentative conclusions can be drawn. It has been shown that HIV positive patients with an open fracture (depending on the contamination of the wound) have a higher rate of infection, especially deep infection. There is also a higher rate of late sepsis with procedures that need internal instrumentation, but sepsis may have been avoided with improved medical management including prophylactic antibiotic use before invasive procedures as well as early evaluation and treatment of possible infections (Luck Jr, 1994; Van Aardt, 2010).

The overwhelming conclusion in all these studies however, has been that there is not enough evidence to properly evaluate the relationship between HIV and outcomes after trauma. There is a significant deficiency in research in this particular area and often available data is extrapolated from studies determining the effect of HIV on patients undergoing surgical procedures, either emergency or elective. Unfortunately, researchers face an ethical challenge when testing for HIV in the trauma setting and it is unlikely that sufficiently powered studies with adequate controls are possible in the current medical climate.

5. Drug interference between ARVs and commonly used trauma drugs

Currently available ARVs inhibit the reverse transcriptase and protease enzymes of the human immunodeficiency virus. These drugs are associated with many side-effects and close monitoring is mandatory. It is also important in the trauma setting to recognise a patient's HIV status and the possible concurrent use of ARVs since administration of drugs with potential for interaction may lead to adverse outcomes.

First-line treatment of HIV involves the use of 2 NRTIs and a non-nucleoside transcriptase inhibitor (NNRTI). Protease inhibitors are used as second line therapies (Town, 2003). Common side effects of NRTIs include lactic acidosis, hypersensitivity reactions, pancreatitis, peripheral neuropathy and hepatic dysfunction (as most are metabolised in the liver). NNRTIs are known inducers or inhibitors of other drugs due to their effect on the hepatic cytochrome systems, and hypersensitivity reactions are common. Protease inhibitors undergo hepatic cytochrome P450 (CYP450) metabolism and many in this class are potent hepatic inhibitors.

Table 3 outlines the drug interactions between NNRTIs or protease inhibitors and other drugs that are dependent on CYP450 metabolism. Many potential interactions of other commonly used drugs remain unknown and have not been included. It is important to take a drug history to ensure that potential side effects can be avoided or closely monitored. In cases where drugs must be administered, dose adjustment may limit side-effects.

	Drugs	ARV interaction	Clinical Effects	Management
A	Aminophylline	Protease inhibitors	Decreased theophylline effects	Monitor and adjust theophylline levels as indicated
	Amiodarone	NNRTI Protease inhibitors	Increased amiodarone effects (hypotension, bradycardia, cardiac arrhythmias)	Monitor and adjust amiodarone as indicated, with reduction of amiodarone dose as needed Should not be co-administered with PIs

	Drugs	ARV interaction	Clinical Effects	Management
B	Bactrim	Lamivudine	Increased Lamivudine levels?	Unknown at present but no dose adjustment necessary for either drug
	Beta- Blockers	Protease inhibitors	Increased effects of Beta-blockers	Use with caution
D	Diazepam	Zidovudine, Protease inhibitors, Efavirenz	Increased diazepam levels (increased sedation, respiratory depression)	Do not co-administer Alternative agents: Lorazepam, oxazepam, temazepam
	Digoxin	Protease inhibitor	Increased digoxin levels	Monitor digoxin levels closely
	Diltiazem	Efavirenz	Decreased diltiazem effects	Titrate diltiazem to clinical effect
F	Fentanyl	NNRTI Protease inhibitors	Increased effects of Fentanyl	Close monitoring necessary
	Flagyl	Protease Inhibitors	Disulfiram-like reaction	Do not co-administer
	Furosemide	NNRTI Protease inhibitors Lamivudine	Increased effects of ARVS?	Use with caution
H	Haloperidol	NNRTIs PIs	Increased haloperidol effects	Monitor and adjust dosage as indicated
I	Ipecac	All	Decreased effects of ARVs if recently ingested due to induced vomiting	Avoid concurrent use
K	Ketamine	NNRTIs	Reduced effects of ketamine	Monitor and adjust dose as necessary
L	Lidocaine	Protease Inhibitors	Increased lidocaine levels	Monitor and adjust lidocaine dose
M	Methyl-prednisone	NNRTIs Protease Inhibitors	Possibly increased methylprednisone effects	Monitor while using
	Midazolam	NNRTI Protease inhibitors	Increased midazolam effects (increased sedation, confusion, respiratory depression)	Single dose IV midazolam may be used; chronic midazolam administration should be avoided

	Drugs	ARV interaction	Clinical Effects	Management
	Morphine	Protease inhibitors	Increased morphine levels (increased sedation and respiratory depression)	Monitor closely when using together
N	Nitroglycerine	Protease inhibitors	Possible increase in effects of nitroglycerine	Not known- but monitor for hypotension
P	Phenergan	NNRTIs Protease inhibitors	Unknown	Monitor closely in used concurrently for side effects
	Phenobarbitol	NNRTIs, Protease inhibitors	Decreased NNRTI and PI levels	Avoid combination if possible
	Phenytoin	NNRTIs Protease inhibitors	Decreased NNRTI and PI levels	Avoid combination if possible
	Prednisone	NNRTIs Protease Inhibitors	Possibly increased prednisone effects	Close monitoring
S	Succinylcholine	NNRTI Protease inhibitors	Possible prolongation of effects of succinylcholine	Use with caution

Table 3. Commonly used drugs in the trauma unit and possible complications (McNicholl 2011; University of Cape Town 2003; University of Liverpool 2010)

6. Conclusion

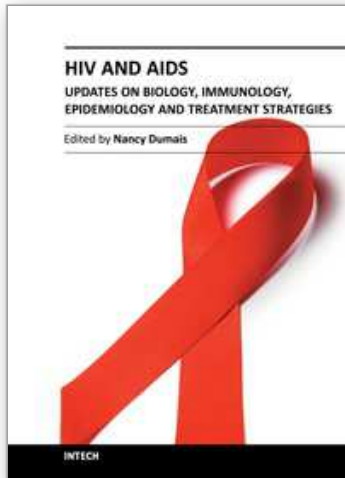
It is likely that trauma units will see an increasing number of HIV positive patients in the years to come. In an area still lacking adequate research, trauma workers need to be diligent to approach the HIV positive patient in the context of their presentation. They must also stay vigilant to protect themselves against transmission. It is hoped that as HIV prevention and treatment improve, HIV patients will no longer represent a unique cohort and their management, and most importantly, their outcomes, will be as good as those without HIV.

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The continuing AIDS pandemic reminds us that despite the unrelenting quest for knowledge since the early 1980s, we have much to learn about HIV and AIDS. This terrible syndrome represents one of the greatest challenges for science and medicine. The purpose of this book is to aid clinicians, provide a source of inspiration for researchers, and serve as a guide for graduate students in their continued search for a cure of HIV. The first part of this book, “From the laboratory to the clinic,” and the second part, “From the clinic to the patients,” represent the unique but intertwined mission of this work: to provide basic and clinical knowledge on HIV/AIDS.

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