LITERATURE REVIEW
for the National Guidelines for Post-Exposure Prophylaxis after Non-Occupational and Occupational Exposure to HIV (Revised)

Acknowledgements

Suggested citation:

McAllister J, and the National PEP Guidelines Expert Reference Group. *Literature review for the national guidelines for post-exposure prophylaxis after non-occupational and occupational exposure to HIV (revised)*. Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine. Sydney, NSW, 2016. Available at www.ashm.org.au/pep-guidelines

Contents

Acronyms

3TC	lamivudine
ABC	abacavir
AIDS	acquired immune deficiency syndrome
ART	antiretroviral therapy
ARVs	antiretroviral medication
AZT	zidovudine
CDC	Centers for Disease Control and Prevention
CI	confidence interval
D4T	stavudine
ddI	didanosine
DTG	dolutegravir
EFV	efavirenz
FTC	emtricitabine
GUD	genital ulcer disease
HAART	highly active antiretroviral therapy
HCV	hepatitis C virus
HCW	health care worker
HIV	human immunodeficiency virus
HPC	high prevalence country
HPV	human papilloma virus
HSV	herpes simplex virus
IAI	insertive anal intercourse
IDV	indinavir
IVI	insertive vaginal intercourse
MSM	men who have sex with men
MTCT	mother-to-child-transmission
NFV	nelfinavir
NHMRC	National Health and Medical Research Council
NNRTI	non-nucleoside reverse transcriptase inhibitor
NPEP	non-occupational PEP
NRTI	nucleoside reverse transcriptase inhibitor
NSI	needle stick injury
NtRTI	nucleotide reverse transcriptase inhibitor
NVP	nevirapine
OPEP	occupational PEP
OR	odd ratio
PAR	population attributable risk
PCR	polymerase chain reaction
PEP	post-exposure prophylaxis
PI	protease inhibitor
PoCT	point of care test
PrEP	pre-exposure prophylaxis
PWID	people who inject drugs
RAI	receptive anal intercourse
RAL	raltegravir
RCT	randomised controlled trial
ROI	receptive oral intercourse
RPV	rilpivirine
RVI	receptive vaginal intercourse
SIV	simian immunodeficiency virus
STI	sexually transmissible infection
TDF	tenofovir
Tmax	Amount of time that a drug is present at the maximum concentration in serum
UAI	unprotected anal intercourse
VL	viral load
ZDV	zidovudine

Introduction

At best, condom effectiveness in preventing the sexual transmission of HIV between serodiscordant homosexual and heterosexual couples is 70% and 80% respectively (Smith 2015). Despite safety equipment and protocols and procedures designed to safeguard health care workers, accidents happen and, in many parts of the world, HIV transmission in populations who use intravenous drugs remains endemic (Strathdee 2010). Clearly, additional measures are required to support HIV-negative men and women, at risk of HIV infection, to remain HIV negative. Post-exposure prophylaxis (PEP) is a preventive strategy that aims to prevent an actual or potential exposure to HIV from becoming an infection following non-occupational exposure, e.g. condomless sexual contact, shared injecting equipment in people who inject drugs (PWID) (non-occupational PEP or NPEP), or in health care workers occupationally exposed to HIV (occupational PEP or OPEP). PEP comprises a 28-day course of two or three antiretroviral drugs commenced within 72 hours of exposure. Effective implementation also requires: thorough medical assessment of the exposed individual and source (where possible); an informed estimation of the HIV transmission risk related to the exposure; baseline testing for blood-borne viruses; clinical and laboratory follow-up; and the provision of information, risk reduction counselling and support.

This literature review accompanies the national guidelines for post-exposure prophylaxis after a potential or actual exposure to HIV. This document is built on the literature review for the 2006 and 2013 national guidelines for post-exposure prophylaxis after non-occupational exposure to HIV (ASHM, 2006; Savage and the National PEP Guidelines Reference Group, 2011). Its scope has been broadened to include new information concerning the role of HIV viral load (VL) in sexual exposures to HIV (including condomless anal intercourse) and occupational HIV exposures, and new recommendations around which drug regimens to use in PEP.

The data suggest that PEP may prevent HIV transmission following occupational or non-occupational exposures. However, it will be seen that, in many areas, there remains insufficient evidence on which to make recommendations based on robust empirical evidence, and that policy-makers and clinicians may be required to make assumptions (that are not evidence based) on which to base treatment plans. This document will set out the assumptions made by the National PEP Guidelines Expert Reference Group in this revision and present new evidence supporting the choice of antiretroviral drugs to use in PEP.

PEP is just one preventive measure against HIV. Strategies that prevent exposure to HIV are the most effective interventions.

Methodology

Scope of the review

This literature review revises and expands the 2006 and 2013 reviews (ASHM, 2006; Savage and the National PEP Guidelines Reference Group, 2011). The review considers published reviews and reports from peer-reviewed journals, government, agency and consultant reports. Unpublished data sourced from professionals in the field was sought.

Identification of literature

The main areas for the search were: populations of interest, intervention, intervention review and conditions (that is co-factors, etc.). Key terms applied initially were: HIV exposure, HIV transmission, HIV transmission risk/rate, occupational and non-occupational exposure, male circumcision, MSM, male-to-male sex, anal intercourse, post-exposure prophylaxis, pre-exposure prophylaxis, HIV treatment, mother-to-child-transmission (MTCT) of HIV, PEP, NPEP, OPEP and PrEP.

Only documents published in English were considered.

Databases searched were: the Cochrane Library, EMBASE (Ovid), Medline 1996-(Ovid). Public search engines such as Google were used to locate documents on the management of HIV exposure nationally and internationally.

The formal review process was further informed by searches of the reference lists from publications of interest. Grey literature and citations were reviewed. The grey literature included: conference presentations, project reports, government reports, policies and strategies, and health care organisational agency publications.

Studies in nonhuman primates, systematic reviews and meta-analyses, studies in the role of HIV VL in HIV transmission, and prospective studies of differing PEP regimens in human subjects formed the backbone of the search. Lack of evidence of an intervention's efficacy or the role of co-factors indicates that the evidence has not been found – not that there is no evidence.

Methods of assessment of documents

The classification used for reviewed studies and reports is based on levels of evidence to assess methodological rigour and sources of bias – and thus validity and generalisability. This classification is widely applied (National Health and Medical Research Council's (NHMRC) 2000):
Level 1 - Meta-analysis or systematic reviews of all relevant randomised controlled trials (RCT)
Level 2 - Studies based on well-designed RCTs
Level 3 - Studies based on well-designed cohort or case-control analytical studies
Level 4 - Studies based on opinions of respected authorities, clinical experience, descriptive studies, case reports and expert committees.

Limitations

Due to time limitations, systematic reviews and meta-analyses formed the backbone of the search. Lack of evidence of an intervention's efficacy or the role of co-factors indicates that the evidence has not been found - not that there is no evidence.

Description of presentation of findings

Presentation of the evidence follows the layout of the guidelines in that firstly evidence regarding prescription of a course of PEP is presented (efficacy, initiation and duration of treatment, follow-up during and after the course of PEP); then evidence to assist in the assessment of transmission risk per exposure and finally data on which antiretroviral drug regimens to use is provided.

Results

Prescribing post-exposure prophylaxis

No RCTs have been undertaken in humans to assess the efficacy or finer dosing details of PEP (time to commencement, duration for course, which drugs to use). Guidelines on the management of occupational and non-occupational exposure to HIV in adults have been developed based on data from animal studies, as well as human work on occupational and MTCT, and HIV PrEP.

Animal and nonhuman primate studies

Animal (predominantly nonhuman primate) studies provide information about the pathogenesis of HIV infection, PEP efficacy and the timing and duration of the treatment. These are handicapped by:

- the intrinsic physiological differences between human and nonhuman primates;
- differences between the infecting virus (SIV, SIV/HIV chimera and HIV-2 versus HIV-1);
- the route (intravenous versus mucosal) and controlled size of the inoculum (known inoculating virus titre);
- the route of prophylactic medication administration (antiretroviral PEP is administered subcutaneously in the majority of nonhuman primate studies whereas PEP in humans is universally administered orally); and
- the small sample size of primates available to study.

These factors highlight the need for caution in the interpretation or extrapolation of the conclusions of animal studies to human experience. However, if it is assumed that they accurately reflect human and HIV biology, it is clear that HIV infects genital tissue and draining lymphoid tissue soon after genital exposure thus raising the possibility of a brief opportunity to interrupt initial infection of cervicovaginal and rectal cells and prevent local dissemination to lymph nodes and bloodstream and that prompt administration of antiretroviral drugs can prevent HIV acquisition from becoming an established infection.

❖ Pathogenesis

Nonhuman primate simian immunodeficiency virus (SIV) pathogenesis studies provide models to extrapolate to HIV transmission and prevention in humans.

One study using rhesus macaques inoculated with SIV found that SIV could be detected by polymerase chain reaction (PCR) in cervicovaginal mucosa, lymph nodes and spleen at two days after vaginal inoculation and cultured from lymph nodes at day five (Spira 1996). In contrast, a further study of female macaques (Hu 2000) demonstrated that SIV enters the vaginal mucosa within 60 minutes of vaginal exposure. SIV-infected lymph nodes can be identified 18 hours after the initial exposure. In a further study of HIV pathogenesis, Kaup's group (Kaup 2001) inoculated male rhesus monkeys rectally or intravenously with SIV. They identified SIV-positive cells (immunohistochemically) from rectal biopsies from day three of inoculation.

These pathogenesis studies demonstrate the possibility of a brief opportunity to interrupt initial infection of cervicovaginal and rectal cells and prevent local dissemination to lymph nodes and bloodstream.

❖ Efficacy

The efficacy of antiretroviral drugs used to prevent SIV, SIV/HIV chimera or HIV-2 acquisition after exposure was first demonstrated in nonhuman primate models in the early 1990s. Most, although not all, are highly effective, indicate that the timing of the intervention is inversely proportional to efficacy, and demonstrate a trend towards the superiority of newer antiretroviral agents such as tenofovir (TFV) over older agents such as zidovudine (AZT) (Irvine et al. 2015).

In 1995, Tsai et al. (Tsai 1995) treated macaques with subcutaneous TFV (TFV is effective against SIV as well as HIV) either 48 hours before (pre-exposure prophylaxis), or four hours or 24 hours after intravenous SIV inoculation (PEP). The subjects were treated for four weeks and all remained free from infection. All untreated controls became infected.

In a further study, Tsai et al. (Tsai 1998) demonstrated again that macaques treated with 28 days of subcutaneous TFV initiated 24 hours after intravenous inoculation of SIV remained free from infection with SIV but when initiation time was extended to 48 and 72 hours post-exposure, half the animals in both groups were persistently infected.

Also in 1998, van Rompay et al. (van Rompay 1998) inoculated (orally and subcutaneously) newborn macaques with an SIV and an SIV/HIV chimera and immediately dosed them with subcutaneous TFV. This treatment was continued for two weeks. Three of four treated newborn macaques remained infection-free for the trial period. The fourth became persistently viraemic at eight weeks. All untreated controls became infected.

In another macaque model, prophylaxis with subcutaneous TFV following an HIV-2, intravaginal exposure, Otten et al. (Otten 2000) demonstrated that a 28-day course of TFV commencing at 12, 36 and 72 hours post-inoculation was highly effective. One of 12 animals seroconverted at 16 weeks; it was one of four animals that had started

treatment at 72 hours. In comparison with the earlier treatment initiators, this was a statistically significant result (Fisher's exact test P=0.018). Three of four untreated controls seroconverted by week four.

PEP is not always effective. Le Grand's group (Le Grand 2000) evaluated the efficacy of triple therapy (ZDV, lamivudine (3TC) and indinavir (IDV)) given orally via a nasogastric tube for 28 days on groups of macaques inoculated intravenously with an SIV/HIV chimera. They found this combination, active in vitro, did not result in the prevention of infection in any treated cases regardless of treatment initiation at four or 72 hours post-exposure.

More recently, Bourry et al. (Bourry 2010; Sellier 2010) treated macaques with combination ZDV/3TC/IDV (ZDV/3TC subcutaneously and IDV orally) within four hours of intravenous inoculation with SIV. They found that, although SIV production and spread was reduced at day 14, SIV infection was not prevented and recommended greater consideration of the pharmacodynamics of antiretroviral drugs to maximise tissue diffusion.

Finally, in a recent review and meta-analysis of PEP efficacy in nonhuman primates (Irvine 2015), 16 studies were identified which compared 180 treated to 103 untreated controls. The risk of seroconversion was 89% lower among those exposed to PEP, compared to those that did not receive PEP (odds ratio, 0.11 [95% confidence interval (CI), 0.05–.23]). Inoculation was primarily subcutaneous, and prophylaxis was given orally in only 3 (19%) of the studies.

Human studies

❖ **Efficacy and failure**
Evidence about the efficacy of PEP in human studies is hampered by:
- the lack of control subjects;
- the lack of knowledge of variables such as the HIV status of source and, if this is positive, the resistance profiles, HIV viral load and presence of other relevant transmission co-factors; and
- the lack of knowledge of other exposures immediately preceding or following administration of PEP.

HIV PEP has never been the subject of an RCT but has been widely used in occupational and non-occupational settings since the 1990s. Given this almost universal use, a placebo-controlled study to investigate PEP efficacy would raise valid ethical concerns. Furthermore (because of the low numbers of endpoints) very large numbers of participants would be required across differing populations (men versus women versus children, sexual versus shared injecting equipment versus occupational exposure) to demonstrate universal effectiveness and the cost of such studies would be prohibitive. These considerations plus the advent of PrEP which has been the subject of RCTs makes the likelihood of a PEP RCT highly improbable. There are many case reports of occupational and non-occupational failures of post-exposure prophylaxis, emphasising that prevention by PEP is not absolute.

The only empirical evidence supporting the use of PEP comes from a case-control study of percutaneous exposures in health care workers (HCW) (Cardo 1997). Cardo et al. compared HCW occupationally exposed percutaneously to HIV-infected blood who were treated with ZDV PEP to those who were not. The case patients were HCWs who acquired HIV following an occupational exposure and were reported by national surveillance systems in France, Italy, the United Kingdom and the United States. The controls were HCWs in an American prospective surveillance project who were exposed to HIV but did not seroconvert. Although cases and controls came from different populations and times, Cardo demonstrated that, after controlling for other factors associated with the risk of HIV transmission, the odds of HIV infection among HCWs who took ZDV PEP was reduced by approximately 81 percent (OR 0.19; 95% CI 0.06 to 0.52).

Al-Hajjar et al. reported a case of 12-year-old girl who was inadvertently transfused with HIV-infected blood (Al-Hajjar 2014). The VL of the donor was later found to be 9740 copies/ml and was not on antiretroviral therapy. At baseline, her blood test was said to be positive for HIV antibodies but negative for HIV-1 DNA and HIV RNA by PCR and she was commenced on tenofovir (TDF), FTC and ritonavir-boosted darunavir (subsequently changed to lopinavir) and raltegravir for 13 weeks. Her follow-up test showed progressively declining antibodies and at 6 months post-transfusion, the confirmatory testing was negative.

From 57 cases of occupationally acquired HIV infection from 1981 to 2001 in the US, eight cases (14%) had received PEP (Do 2003). Factors possibly related to failure include viral resistance, incomplete course and high viral inoculum.

Jochimsen reported on five failures of ZDV monotherapy OPEP (Jochimsen 1997). The transmission route was percutaneous or intravenous in all cases. Delayed initiation of therapy (one case), high VLs in the source and ZDV resistance were described as possible factors in treatment failure.

Occupational and non-occupational exposures are not directly comparable – particularly because in the occupational setting the source is usually easier to identify, the source HIV status is frequently known or easy to establish and the seriousness of exposure is easier to quantify: these variables are less readily (if ever) defined in the non-occupational setting.

Two interesting human studies provide useful data on variables associated with implementation of NPEP, but do not support or refute arguments about the efficacy of prescribing NPEP or prescribing one regimen over another. They are outlined below.

Schechter et al analysed a cohort of high-risk MSM provided with starter packs of NPEP (ZDV and 3TC) to self-dose after high-risk exposures. This study did not demonstrate a significant difference between the risk of seroconversion for men who did or did not start NPEP (Schechter 2004); however, study design made any conclusions about efficacy difficult.

Roland's group reinforced the difficulties in gathering data in this area and drawing

meaningful conclusions (Roland 2005b). They described 702 patients who were prescribed double nucleoside prophylaxis (ZDV and 3TC or d4T, and 3TC or d4T and ddI after non-occupational exposure. The protease inhibitor (PI) nelfinavir was offered in addition to the double nucleosides if the source had a history of detectable HIV RNA. Sexual intercourse was the predominant exposure mode (94.6%). At 12 weeks, there were 7 HIV infections. No significant difference was found between seroconverters and non-seroconverters who were commenced on AZT and 3TC, or who changed their treatment regimen. Nelfinavir was prescribed for 14 (2%), none seroconverted. All seroconverters were men, with receptive anal intercourse (RAI) as their exposure risk (p=0.03 Fisher's exact test). Four seroconverters knew the source case to be HIV-positive. Of the seven seroconversions, one had plasma RNA detected at baseline (undiagnosed HIV infection at NPEP commencement), three had additional exposures after NPEP completion and before testing, and three rated their adherence to ART as poor. The group concluded that there were three probable 'true' NPEP failures – but that without an untreated comparison group, NPEP efficacy could not be estimated. Further, it concluded that NPEP was less than 100% efficacious, but the three cases of failure did not equate with a 0.4% risk of failure and that this could not be determined without an untreated comparison group. It argued that these seroconversions did not mean that NPEP was not successful (for example, if there were other unknown exposures etc.), but conversely that the small number of seroconversions did not mean that NPEP was effective (given the possible true HIV exposure and per-contact transmission risk).

In a review of 3547 NPEP initiations in a major Canadian cohort of predominantly MSM (Thomas 2015), efficacy was estimated at ~ 99%. Of note, however, there was a high rate (around 16%) of participants who were lost to follow-up before post-PEP HIV testing.

In a multicentre retrospective case review of NPEP failure, Haidari et al. found that only 1 (5%) of the 19 identified PEP failures could likely be attributed to chemo-prophylactic failure and even this failure may have resulted from suboptimal dosing (Haidari 2015).

Ford et al. in a systematic review and meta-analysis, found that of the 37 seroconversions reported in 8007 PEP participants who completed the PEP treatment course, only 3 seroconversions could be ascribed to PEP failure (Ford 2015).

Despite the lack of controlled studies of humans exposed occupationally or non-occupationally, further supporting evidence for the efficacy of PEP can be drawn from studies of MTCT. There are obvious limitations with these studies. The modes of exposure of MTCT studies are quite different from those of non-occupational exposures, and the findings may not be generalisable.

Strategies for reducing MTCT have been extensively investigated. It has been estimated that 15 to 30% of infants will be infected with HIV in utero or during labour, and a further 10 to 15% infected through breastfeeding (Shaffer 1999). The major factor in the success of these regimens relates to reduction of maternal VL in late pregnancy, labour and delivery. Studies of postnatal and perinatal dosing of the infant have also demonstrated the efficacy of ZDV monotherapy during pregnancy and labour.

In 1994 Connor et al. demonstrated that maternal and infant administration of ZDV could reduce perinatal transmission of HIV from 25% to 8% (Connor 1994). This intervention was a mixture of treatment as prevention (maternal ZDV), pre-exposure prophylaxis (fetal exposure to ZDV in utero) and PEP (administration of oral ZDV to the neonate/infant).

Shaffer et al. (Shaffer 1999) treated women with placebo or ZDV from 36 weeks into their pregnancy until delivery. The infants were not breastfed. Timing of HIV transmission was defined by the time of the first positive HIV DNA result. There was no statistical difference between infection rates of the treated and placebo groups in utero. However, it was estimated that ZDV had an efficacy of 61.4% in preventing intrapartum infection. Another trial examined the effect of ZDV versus placebo given to pregnant women at 36 weeks of pregnancy (Wiktor 1999) and showed a decline (24.9% placebo, 15.7% ZDV, p=0.07) in MTCT of HIV at three months to predominantly breastfed babies (98%). The mortality rate for the treated group of infants in the first 120 days was significantly reduced (p=0.006).

Sperling looked at the effect of maternal viral burden in women who were treated with ZDV monotherapy antenatally and intrapartum (Sperling 1996). Their infants were given a six-week course of ZDV. There was a wide range of VL and CD4 levels in the treated women. The reduction in maternal VL (either to an absolute level or proportionally) did not entirely explain the decreased transmission to the treated infants. It was hypothesised that ZDV had a post-exposure effect on the neonates to prevent transmission.

The HIVNET 012 randomised trial (Guay 1999) compared NVP with ZDV. There was no placebo arm. Mothers received either NVP or ZDV when labour commenced; their infants received single-dose NVP or one week of ZDV respectively after birth. At 14 to 16 weeks, babies in the NVP arm had 47% lower risk of HIV transmission. At this time, 95.6% of all infants were breastfed. Both drug regimens were equally well tolerated.

Of greater relevance to PEP is a retrospective review of 454 infants born to HIV-infected mothers (Wade 1998). In those babies whose mothers received no antiretroviral therapy during pregnancy or during delivery, initiation of ZDV PEP to the newborn within the first 48 hours of life was associated with a lower risk of HIV acquisition when compared to no ZDV (RR 0.30, 95% CI 0.10 – 0.96, P=<0.05). The rates of HIV acquisition in this group of newborns receiving PEP alone (9.5%) is comparable to the 8% reported by Connor's protocol of maternal and infant ZDV treatment and the 80% risk reduction in Cardo's HCW PEP case-control study. This data further supports the use of PEP in a non-perinatal setting; however, the prevention of perinatal HIV transmission is not analogous to preventing transmission through sexual or needle-sharing events.

The PETRA study (PETRA Study Team 2002) compared combination ZDV/3TC administered to a) the women antenatally, intrapartum and postnatally for one week to both mother and infant, or b) intrapartum and postnatally to both mother and infant, or c) intrapartum alone for one week with d) placebo. Transmission at six weeks was

significantly reduced in arms a) and b). Intrapartum ZDV/3TC alone did not lead to a reduction in transmission. Follow-up at 18 months showed the initial protective effect of therapy in these breastfed infants was markedly reduced.

Another RCT of two regimens compared NVP with combination ZDV/3TC. The mother was given a single dose of NVP or combination treatment at the start of labour and the infant was given a single dose of NVP at birth or ZDV/3TC at birth for one week (respectively). Both regimens were equally efficacious in reducing HIV transmission to ~10%, at eight weeks postpartum (Moodley 2003).

A Cochrane review of antiretrovirals for reducing the risk of MTCT of HIV infection (Brocklehurst 2002) supported the efficacy of short- and longer-term courses of ZDV and NVP for infant and mother to reduce both intrauterine and perinatal HIV transmission. It noted that short antenatal and postnatal courses were less effective in preventing transmission than long antenatal and postnatal treatments or combinations of short or long antenatal with long or short postnatal dosing respectively.

HIV pre-exposure prophylaxis using daily tenofovir disoproxil fumarate/emtricitabine (Truvada™) or tenofovir alone has been widely studied in heterosexual, homosexual and injecting drug populations (Thigpen 2012; Grant 2010; Choopanya 2013). The vast majority have shown high rates of efficacy whereby protection (up to 99%) is highly dependent on daily dosing. While HIV pre and post-exposure prophylaxis are not directly comparable, the high rates of protection against HIV acquisition by the daily use of antiretroviral drugs tested in randomised, placebo-controlled trials lend significant weight to proof of concept for the usefulness and efficacy of PEP.

The use of PEP does not prevent all exposures from becoming infections. Failure of protection may be related to: delayed initiation; poor adherence to both daily dosing and course completion; continued risk behaviour; unknown or undiagnosed primary HIV infection at baseline; suboptimal dosing; and transmission of resistant virus; (Cardo 1997; Roland 2005a; Haidari 2015; Jochimsen 1997).

A survey of the literature on human PEP use shows that time to initiation of PEP may be an important factor in its success. On the other hand, when considering PEP failures, it appears that time to initiation is not the only, and may not be the main factor contributing to an unsuccessful outcome.

Roland et al. (Roland 2005b) examined non-occupational exposure and response to PEP treatment. This group recruited 702 subjects who had been exposed to HIV sexually or through use of injecting drugs. Seroconverters commenced NPEP at a median time of 45.5 hours post-exposure; non-seroconverters started their treatment at a median time of 32.5 hours. There was a non-significant difference between the time to initiation of seroconverters and non-seroconverters (p=0.11).

In Cardo's study (Cardo 1997) 67% of controls (remained HIV negative) and 89% of cases (seroconverted) had commenced PEP within four hours of occupational exposure. This difference was not significant (p=0.28) in a case-control study examining 33 cases and 665 controls. Multivariate analysis did not include time to treatment initiation.

Jochimsen (Jochimsen 1997) looked at failures of AZT PEP. Ten of the 11 cases of treatment failure in health care workers commenced treatment within 12 hours post-exposure; however, in two-thirds of those cases, the source case was receiving AZT, therefore resistance may have contributed to the failure. Of five non-health workers with a PEP failure, four commenced treatment in less than four hours, and the fifth, one week after exposure. Again, this is confounded by source case pre-treatment with AZT and viral inoculum.

The prevalence of drug resistance in newly acquired HIV infections in Victoria and New South Wales is 4.1% for NRTIs, 3.1% for NNRTIs and 1% for PIs (The Kirby Institute 2014). Currently, integrase resistance testing is not performed routinely in Australia.

The work of Wade et al. (Wade 1998) on neonatal regimens of AZT prophylaxis concluded that PEP reduced perinatal transmission when started within 48 hours of birth (adjusted odds ratio (95% CI) is 0.2; no PEP is 1.0). PEP commenced after three days (range 3 to 42 days) was not found to prevent transmission.

In Roland's series (Roland 2005b) 3 of the 7 PEP failures (43%) had their adherence rated as poor or fair, 3 (43%) reported further HIV risk events post-PEP and before follow-up HIV testing.

Haidari's (Haidari 2015) multicentre retrospective case review of NPEP failure (defined as a negative point of care test (PoCT) plus combined 4th generation Ag/Ab laboratory test at the commencement of NPEP with HIV diagnosed during NPEP or in follow-up or acute HIV infection at NPEP initiation with a negative PoCT but subsequent reactive Ag/Ab test once NPEP started) found that of the 19 NPEP failures, 16 (84%) were subsequently confirmed to have HIV once baseline laboratory test results were available and 2 (10%) were found to be seroconverting to HIV at NPEP initiation (Ag/Ab negative but subsequently found to be positive for HIV by PCR on retrospective testing of baseline samples).

Roland et al. (Roland 2005b) also reported undiagnosed primary HIV infection at baseline on one (14%) of the seven reported PEP failures.

Case reports do not shed much further light on this area, mainly because of probable confounding factors of viral resistance and inoculating dose. They tell us that PEP failures occur, but cannot quantify or qualify this.

Fournier described NPEP failure where triple therapy was commenced 70 hours after receptive vaginal intercourse (Fournier 2001). The source case had discontinued treatment two years prior, although resistance studies of the infecting HIV strain did not detect any relevant mutations. Other exposures and non-adherence were denied by the exposed case.

In another case study (Cordes 2004), the exposed case was commenced on NPEP, for four weeks, four hours after uncircumcised, insertive anal intercourse (IAI) with the source case who was on triple therapy (recent VL 20,000 copies/ml). A seroconversion

illness occurred at six weeks post-exposure. Both viruses were drug sensitive. The role of unreported exposures or of the foreskin were postulated as causes for failure.

PEP failure was described after an occupational exposure (Hawkins 2001) where triple therapy was initiated within 95 minutes of exposure. This was changed after approximately six hours when the heavily pre-treated source's therapeutic history was reviewed. Side effects to didanosine (ddI) and nevirapine (NVP) caused adherence to be suboptimal. The exposed case was positive for HIV antibody when tested at three months post-exposure. A resistance assay showed the same mutations as the source, as well as a newly acquired mutation suggesting resistance to non-nucleoside reverse transcriptase inhibitors (NNRTI) class.

Bloch et al. (Bloch 1999) published a case of a woman who was artificially inseminated with fresh seminal ejaculate from a man who was seroconverting to HIV. PEP (triple therapy) was started ten days later. The woman remained HIV-free and delivered a healthy child.

> **Animal and human studies of chemoprophylaxis used to prevent HIV infection support the likely efficacy of PEP.**

Timing of treatment

The evidence supporting early initiation of PEP (within 72 hours of exposure) is a factor in treatment success but is based principally on small animal studies. There is no human evidence that clearly defines the maximal time after exposure that PEP is effective. It would appear that there is a decreasing return associated with delays and the possibility of the development of drug resistance to a PEP drug regimen that was unable to effectively abort an HIV infection. The cost-benefit of this needs to be considered.

Animal studies strongly suggest that the commencement of PEP more than 48 to 72 hours following exposure is associated with increasing rates of PEP failure.

In 1991 (Shih 1991) inoculated SCID-hi mice (SCID-hu mice have implanted human haematolymphoid tissue that elaborates functional cells) intravenously with HIV and treated with ZDV post-exposure The mice that were treated at half, one or two hours post-exposure had virus-free lymph nodes at two weeks. Treatment at eight, 24, 36 and 48 hours resulted in 80%, 40%, 20% and 0% virus-free lymph nodes respectively.

In 1998 Tsai et al. (Tsai 1998) demonstrated that half the macaques treated with subcutaneous TFV > 24 hours after intravenous SIV exposure were persistently infected versus no SIV infections on those treated 24 hours after viral inoculation.

The majority of international guidelines (Roland 2005a) recommend an upper limit of 72 hours; a small proportion recommend 36 (New York, Jamaica) or 48 hours (Botswana). The CDC now also restricts the use of PEP to less than 72 hours (Kuhar et al., 2013).

> **Early initiation of PEP, within 72 hours of exposure, is recommended. PEP should not be offered more than 72 hours after exposure.**

Duration of treatment

There have been no RCTs examining the effect of length of treatment on outcome. As for treatment timing, recommendations for regimen duration have been developed based primarily on nonhuman primate studies.

Tsai's work in 1998 with macaques suggested that a course of PEP that lasted less than 28 days was unlikely to be successful. Sixteen macaques were intravenously inoculated and randomised to 28-day, 10-day, three-day and no treatment groups. Zero percent, 25%, 50% and 100% respectively of those groups became infected (Tsai 1998).

In more recent work, investigating intermittent prophylaxis with Truvada® in macaques following rectal challenges to SIV, Garcia-Lerma et al. (Garcia-Lerma 2006) demonstrated that three of six macaques given two subcutaneous doses of FTC/TFV at 24 and 48 hours after each rectal challenge became infected during the first two challenges (Garcia-Lerma 2010). Efficacy was no greater than in the control macaques (p>0.5). This demonstrates the inability of a short-course PEP regimen (in this case 2 days) to control viral spread after mucosal infection.

In human studies, Cardo's paper (Cardo 1997) found that 66% of control subjects finished at least four weeks of AZT, in contrast to 44% of the cases, this difference was not significant (p = 0.28).

There are also case reports of apparent successes for treatment of varying durations. For example, a case report by Katzenstein et al. (Katzenstein 2000) describes successful PEP initiated within 72 hours of exposure. A 14-year-old girl was commenced on PEP (AZT, 3TC and a protease inhibitor) 50 hours after a transfusion of packed red blood cells) from a donor who was seroconverting (this therefore represented a huge inoculating dose). Treatment was continued for nine months and the patient was HIV seronegative 15 months after exposure.

Based on nonhuman primate studies a 28-day course of PEP is recommended. Careful selection of regimens not associated with high rates of adverse events, a proactive approach to managing side effects and emphasising and supporting adherence can all assist patients to complete their treatment.

Safety, PEP initiation by nonexperts and reduction in cost underlay the common practice of PEP initiation using starter packs (commonly 3-7 days of PEP). In a recent review (fifty-four studies providing data on 11 714 PEP initiations) of the evidence on outcomes associated with starter packs for PEP compared to full prescriptions Ford et al. found that overall, outcomes were better when participants were offered a full 28-day course of PEP at initial presentation. They found fewer refusals (11.4% [95% confidence interval {CI}, 5.3%–17.5%] vs 22% [95% CI, 16.7%–28.1%]) and higher completion rates (70% [95% CI, 56.7%–77.3%] vs 53.2% [95% CI, 44.4%–62.2%]) and that (28% [95% CI, 21.4%–34.5%]) of individuals provided with a PEP starter pack failed to return for their subsequent appointment. This systematic review suggests that,

despite the authors rating of the quality of evidenced as poor, a 28-day PEP prescription at assessment is better than PEP initiation with a starter pack (Ford et al.(b) 2015). For patients presenting to sexual health clinics, HIV clinics or s100 prescriber GPs consideration should be given to prescribed drugs for the entire 28 days. Exceptions might include when source testing is underway and clinical or adherence concerns.

All international guidelines recommend a 28-day course of PEP.

> **A 28-day course of PEP has been accepted as the standard treatment duration.**

Follow-up testing

There is very little in the literature to guide the recommended period for follow-up HIV antibody testing post PEP. Early reviews attempting to define the period of seroconversion and the timing of follow-up testing in the PEP treated cohort lack precision and are based on the use of a range of first-, second- and third-generation antibody tests.

In the study by Jochimsen (1997) analysing PEP failures using AZT monotherapy, eight of 11 HCWs with occupational exposure to HIV seroconverted within 12 weeks, and all seroconverted within six months. Ten of those experienced a seroconversion illness and were symptomatic 13 to 75 days after exposure. There were five additional treatment failures among non-health care professionals. Seroconversion illnesses were experienced in two of five cases at three weeks and three months; seroconversion was confirmed between 15 days and four months post-exposure.

Ciesielski examined the serology of 41 HCWs who seroconverted (Ciesielski 1997Thirty-one (76%) tested positive within six months of their exposure. Of the other ten cases, six were not actually tested between 13 weeks and 6 months. Two of the ten had presumed acute seroconversion illnesses, and were antibody negative at five, and five and a half months. Both tested antibody-positive some months after. Two cases were antibody-negative at 27 weeks and 8 months respectively after exposure, both were positive within 12 months.The second case was co-infected with hepatitis C virus (HCV) and had a prolonged anti-HCV seroconversion. Of the ten cases that allegedly seroconverted after six months, only one was actually confirmed; there is considerable uncertainty with the remainder. In this study, seroconversions for the three to six months after exposure were not examined. The four cases that completed PEP and still seroconverted, did so within six months. The individual who was co-infected with HIV and HCV declined AZT (Ridzon 1997).

Of the 10 seroconversions in a large Canadian prospective cohort of PEP in predominantly MSM, the only participant HIV seroconversion not attributed to ongoing risk behaviour was HIV-negative at week 4 but positive by week 12 (Thomas 2015).

The median (interquartile range) window period for third-generation and fourth-generation HIV tests is 22 days (19-25) and 18 days (16-24) respectively and the probability of a false-negative result for third-generation and fourth-generation HIV tests is 0.01 at 80 days' post-exposure and at 42 days respectively (Taylor 2015). The choice of a diagnostic assay for testing post-PEP is likely to be important however the impact of recent antiretroviral therapy (PEP) on the sensitivity and specificity of a given HIV test is unknown.

All laboratories in Australia now use fourth-generation HIV tests.

There is a balance to be struck in trying to develop a position to ensure that all seroconversions are detected and that the guidelines reflect the reality of the limited proportion of patients who return for follow-up, at 6 months particularly.

Armishaw et al. (Armishaw 2011) reported that follow-up rates for 2396 presentations over approximately four years at a centralised NPEP service in Victoria were 86% at one week, 47% at week 4/6 and 34% at three months. This service provides active follow-up for up to three months only. Work by Poynten et al. (Poynten 2007) found that only 15% (129/859) of subjects returned for the recommended six-month review. It suggested that this reflected the impracticality of the guidelines and that adopting a three-month follow-up period would be more realistic.

The World Health Organization, British HIV Association and American Centers for Disease Control PEP guidelines all recommend final HIV testing at 12 weeks post-exposure (World Health Organization 2014; CDC 2016).

Under Australian conditions, testing for HIV seroconversion at three months after exposure (and two months after the completion of PEP) would be expected to identify the cases of HIV that had been acquired as a result of the notified exposure. The exceptional circumstance to alert the clinician is co-infection with other blood-borne viruses. A three-month follow-up has the additional advantages of decreased client attrition and reduction of the anecdotally reported psychological and emotional cost of an extended wait for the six-month follow-up period.

> **HIV antibody testing is conducted at baseline, at four to six weeks and three months after exposure where HIV is the only blood-borne pathogen to be potentially transmitted. If there is a possibility of co-infection, expert advice should be sought.**

Assessment of the risk of HIV transmission

It is important to gather as much information as possible about the exposure prior to prescribing PEP for possible or known exposure to HIV. This includes:

- knowledge of the exposed individual's HIV status and general health, including the use of prescribed, proscribed, over-the-counter or traditional medications;
- the HIV status of the source and if HIV-positive (and the information is possible to obtain) relevant clinical details concerning source HIV VL and treatment history or results of past HIV resistance testing; and
- a detailed assessment of the risk event.

This will allow accurate risk assessment and tailoring of the antiretroviral drug regimen.

Mathematically, the risk of HIV transmission is the product of the risk of a single, particular exposure and the risk of the source being HIV-positive. Co-factors such as HIV VL, size of inoculum, genital infection, bleeding or trauma may affect transmission risk.

> **Risk of HIV transmission =**
>
> **risk/single exposure   x   risk of source being HIV-positive**

HIV status of the potentially exposed individual

All individuals prescribed PEP must have a baseline HIV test (guided by the current National HIV Testing Guidelines, ASHM 2014). The results of this should be available as soon as possible to allow for modification (cessation of treatment or treatment intensification to a fully suppressive regimen) for individuals who test positive to HIV at baseline.

Armishaw (2011) reported that of 2396 presentations to an NPEP service by 1864 individuals, over nearly four years, there were 22 patients (1.2%) who tested positive for HIV at the baseline presentation. An earlier Australian study reported that four of 680 cases (0.6%) of individuals commencing NPEP between 1998 and 2002 were HIV-positive at baseline (Zheng 2002). A San Franciscan study detected HIV in three of 401 individuals (0.7%) presenting for NPEP (Kahn 2001). In contrast, findings from a South African study of NPEP after sexual assault conducted over a three-year period reflect the importance of different local HIV epidemiology, since between 14% and 22% of patients/year were HIV-positive on presentation (Wulfsohn 2003).

Pre-test information should be provided to all PEP candidates in keeping with the National HIV Testing Policy (ASHM 2014).

> **All individuals given PEP should have baseline HIV testing performed. Clinical circumstances will dictate the urgency of the results. It is advisable to review them within 24 hours, at the latest.**

HIV status of the source individual

In the non-occupational setting, the HIV status of the source is often unknown, and knowledge of clinical details such as VL or drug-resistance profiles is even less common. A number of studies have outlined the advantages of having this information to manage potential HIV exposures (Greub 2001; Greub 2002; Postma 2002; Grulich 2003). These include: withholding or ceasing PEP if the source is not found to be HIV-positive (or in a testing serological window) with consequent psychological physical, financial and service-related benefits; quantifying the transmission risk based on the route and size of the inoculum; and (if the source is known to be HIV-positive and clinical details are available) tailoring the PEP regimen to maximal efficacy based on the source's VL, treatment history and resistance profile.

In reality, in non-occupational settings, this information is not often available and does not become available for most cases. The clinician is left to recommend NPEP on the basis of local epidemiology and transmission risk from the exposure. **Table 1** provides a summary of HIV seroprevalence rates in selected Australian and overseas populations (Hull 2014; Hull 2015; Lee 2015; Lee 2015a; Lee 2015b; Lee 2015c; NCHECR 2010; Pedrana 2012; UNAIDS 2010). Clinicians using the guidelines are advised to apply local seroprevalence data where this is known. In occupational settings, the HIV status of the index case is more often available, with additional information, such as VL and antiretroviral history, to guide the clinician in their therapeutic choices.

Table 1. HIV seroprevalence in Australian and overseas populations

Community group	HIV seroprevalence (%)
Men who have sex with men (MSM)	
• Sydney	8.5[a]
• Melbourne	9.5[b]
• Queensland	11.2[c]
• Perth	5.7[d]
• Adelaide	7.4[e]
• ACT	8.3[f]
Actual seroprevalence may be higher than reported seroprevalence[g]	
People who inject drugs in Australia[h]	
• MSM	30.0
• all others	0.5
Heterosexuals in Australia[h]	
• blood donors (% donations)	<0.003
• STI clinic attendees	<0.5
Female commercial sex workers (Australia)[h]	<0.1
HIV seroprevalence in selected regions for adults[i]	
• Oceania, West & Central Europe, N Africa, the Middle East, E Asia, New Zealand, N America, S & SE Asia, Central & S America	< 0.5
– Thailand	1.35
– Indonesia	0.2
– Vietnam	0.4
– Papua New Guinea	0.9
• E Europe & Central Asia	0.8
• Caribbean	1.0
• Sub-Saharan Africa	5.0
– Kenya	~6.0
– Mozambique	11.5
– South Africa	17.5
– Botswana	25
– Swaziland	27

a   Gay Community Periodic Survey: Sydney 2015. (Hull et al., 2015)
b   Gay Community Periodic Survey: Melbourne 2015. (Lee et al., 2015b)
c   Gay Community Periodic Survey: Queensland 2014. (Lee et al., 2015a)
d   Gay Community Periodic Survey: Perth 2014. (Lee et al., 2015c)
e   Gay Community Periodic Survey: Adelaide 2014 (Lee et al., 2015)
f   Gay Community Periodic Survey: Canberra 2013. (Hull et al., 2014)
g   Pedrana A, Hellard M, Guy R, Wilson K and Stoove M. The difference in self-reported and biological measured HIV prevalence: Implications for HIV prevention. AIDS Behav. 2012 Jan; 16(6):1454-63
h   HIV, viral hepatitis and sexually transmissible infections in Australia Annual Surveillance Report 2010. (National Centre in HIV Epidemiology and Clinical Research 2010)
i   Highly variable within some regions. For seroprevalence of individual countries go to http://aidsinfo.unaids.org/ select country and epidemiological facts. Selected examples within **Table 2**.

> **Prompt determination of the HIV status of the source case is recommended.**
>
> **If this is unknown, clinicians may be guided by local and national estimates of HIV seroprevalence.**

Transmission risks associated with different exposures

Sexual transmission accounts for the majority of HIV infections globally. In Australia in 2014, the majority of newly acquired (84%) and newly diagnosed (70%) cases of HIV were in men who reported having sex with men (The Kirby Institute 2014). A further 19% of newly diagnosed cases were attributed to heterosexual sex, 5% to sexual contact between men and injecting drug use, and 3% to injecting drug use only.

There is great variability in the sexual transmission of HIV per contact event. Infection depends upon the transmission route and inoculation target (mucous membranes or blood directly); factors related to the source case such as VL (stage of infection, immune activation, treatment, treatment failure, compartmentalisation); factors affecting VL locally (such as cervical ectopy, menstruation, pregnancy, genital ulceration or STIs) and susceptibility of the exposed individual as a result of genetic make-up, circumcision, and the presence of genital inflammation or ulceration (Royce 1997). It has been difficult to control for these variables to determine the risk of infection associated with mode of exposure alone (Anderson 1988).
Occupationally, there are similar variables related to transmission. These include: transmission route (percutaneous or other); inoculation site; superficial or deep wound; skin integrity for non-percutaneous exposures; nature of the sharp injury (intravenous, intramuscular, subcutaneous, hollow bore needle (including gauge), suture needle); whether gloves were worn (if appropriate); volume and type of the inoculum, dwell time of the inoculum, source status and patient VL.

The NHMRC guidelines on reviewing scientific literature (NHMRC 2000) recommend that prospective, epidemiological studies are the most appropriate tools to investigate risk; other methodologies provide lower-quality evidence. There are few prospectively conducted, controlled epidemiological studies investigating transmission risk. Many papers cite figures derived from modelling studies rather than the few primary sources.

Population-based risk estimates such as transmission per act or per contact can only provide a crude estimate of risk because of the heterogeneity in disease transmission, due to factors such as the VL of the source, which are very important determinants of infectivity. Population attributable risk (PAR) of transmission must also be extrapolated

with caution. PAR is obviously derived from particular populations; unmeasured biological, behavioural and environmental factors will contribute to the population risk that may render the findings ungeneralisable to other groups. Kaplan argues that assuming a constant infection probability per partner is simplistic and that transmission is not just related to number of sex acts/partner, that there are other significant factors to be elucidated and considered which will have an impact on infectiousness and susceptibility (Kaplan 1990).

Some studies provide high-quality data on transmission per sexual act. Older studies mostly consider relative risk, odds ratios or transmission rate per sexual partnership, and it has not been possible to derive information on contact probabilities from these. It is now clear that HIV VL is inextricably linked to HIV infectiousness or lack thereof and is discussed fully later in this review. The transmission risks for different exposures to a source known to have HIV infection discussed below do not take into account the positive impact of effectively treated HIV infection on the onward transmission of the virus.

The acts of transfusion with HIV-contaminated blood or blood products, sharing needles and receptive anal intercourse (RAI) are estimated to have the highest per-act/event risk of HIV transmission. Occupational exposures, condomless insertive anal intercourse (IAI), vaginal intercourse (receptive and insertive) and oral sex are all described as having lower per-act risks, although there is some evidence which prescribes a greater risk to the uncircumcised male practising IAI. The transmission risk associated with oral sex is estimated to be so low that it is not measurable. However, the probability of infection is not well described (or generalisable) by assuming constant per-act infectivity (Leynaert 1998; Kaplan 1990) and there is insufficient evidence to provide advice on risk stratification incorporating this variable. Clinicians will possibly do this on a case-by-case basis in discussions with their patients. The theoretical or observed risks or rates of transmission are described in different forms in different papers. This makes the presentation of a summary of the findings and comparison difficult.

❖ Receptive anal intercourse

In Australia, the vast majority of newly diagnosed and acquired cases of HIV are in MSM.

A prospective longitudinal Sydney-based study by Jin (Jin 2010) estimated the per-contact probability of HIV transmission through unprotected anal intercourse (UAI) in MSM. Over a three-and-a-half-year period there were 53 seroconversions in 1472 men. This study considered condomless RAI and IAI, with and without withdrawal before ejaculation and the role of circumcision. The per-contact probability of transmission for RAI was 1.43% [95% CI 0.48–2.85] with ejaculation into the rectum and 0.65% (95% CI 0.15–1.53) if withdrawal from the rectum occurred prior to ejaculation. By contrast, the rates of HIV transmission for IAI were 0.62% (95% CI 0.07–1.68) for uncircumcised men and 0.11% (95% CI 0.02–0.24) for men who were circumcised.

In an earlier study, Vitinghoff et al. (Vitinghoff 1999) assessed the per-contact risk of acquiring HIV through a variety of sexual practices in MSM in a prospective cohort

study in the US. 'Per contact' risk describes risk per act, not per partner. It was chosen over 'per partner' risk because of the assumed larger number and range of source infectivity of the cohort's sex partners (in contrast to studies done with heterosexuals in assumed monogamous sexual relationships). Vitinghoff estimated an average per-contact risk with a high-risk contact, either HIV-positive or unknown, and did not make assumptions about the varying transmissibility rate of the source. When comparing seroconverters with non-seroconverters, there was a significant difference between these groups with an HIV-positive partner (p=0.001) and the groups having RAI with HIV-positive or unknown serostatus partners. When types of sexual contact were analysed, RAI with an HIV-positive partner had an infection risk per-contact of 0.82%. RAI with unknown status partners was 0.27%; no further analysis of this group is available as the proportion of subjects with either an HIV-positive partner or partner with an unknown HIV status is unavailable. Protected RAI with an HIV-positive or unknown status partner still had a per-contact risk of 0.18%; episodes of condom failure were included as protected sexual events, which possibly biased the results.

Two systematic reviews (Boily 2009; Baggaley 2010) estimated the pooled infectivity of condomless RAI at 1.7% (95% CI 0.3–8.9) and 1.4% (95% CI 0.2–2.5) respectively.

Cohort and systematic reviews of risk attached to per act of condomless RAI do not assess the impact of HIV VL on infectiousness.

An older study (de Gruttola 1989) also assumes constant infectivity and models the risk/act of HIV transmission by RAI at 0.5–3.0%.

The European Study Group on Heterosexual Transmission of HIV (1992) reported that the odds ratio (OR) of HIV transmission associated with RAI was 5.1, in contrast to no RAI. Leynaert's probabilistic model (Leynaert 1998), using the same sample, suggests that the infectivity of RAI at any stage of the infected male partner's infection is 0.034, compared with 0.0007 for RVI They suggested that male-to-female infectivity through vaginal sex is relatively low and varies little throughout the course of the disease (although the numbers were small and this may account for any lack of variability seen); in contrast, transmission through anal sex is significantly higher at any stage and most particularly during seroconversion and with advanced disease.

A small study of heterosexual women with HIV-positive partners (de Vincenzi 1994) reported a cumulative incidence of seroconversion of 27.8% for women who had unprotected RAI, against 11.7% of women who did not report unprotected RAI. This difference was not significant (p >0.15). Again, this study may not have had power to detect a significant difference.

A cohort study of 436 seronegative female partners of HIV-positive men showed a relative risk of HIV transmission of 2.1 for couples practising anal sex (Musicco 1994). In a number of other studies on heterosexual transmission of HIV, anal transmission was not (or rarely) reported by subjects or not investigated by researchers; its impact is therefore unquantified (Wawer 2005; Gray 2001; Quinn 2000; Fideli 2001; Fiore 1997). However, there is no suggestion of a gender difference in HIV transmission through RAI.

The modelling study of Varghese et al. (Varghese 2002) calculated that RAI was 100
times riskier than insertive fellatio and five times riskier than RVI.

> **Transmission risk through RAI is estimated at 1.4 –1.7% (1/71–1/59) (with
> ejaculation) and 0.65% (1/154) (with withdrawal prior to ejaculation).**

❖ Receptive vaginal intercourse

A multicentre, randomised controlled trial reported early initiation antiretroviral therapy
(ART) (at CD4 levels ranging from 350–550 cells/mm3). The study was conducted
predominantly in Africa and also in South East Asia, India, South America and the
United States. Treated individuals with low (undetectable) VLs have a greatly reduced
risk (96% reduction) of transmitting HIV to their heterosexual sex partners within a
stable relationship of at least three months, compared with a control group who were
treated later (one seroconversion in the early treatment group compared with 28 in the
delayed treatment group) (Cohen 2011). However, although no per-act estimates of
risk for receptive or insertive vaginal or anal intercourse, or other sexual behaviour
were given, the National PEP Guidelines Expert Reference Group considered that the
reduction of HIV transmission from a partner with undetectable VL can be considered
when calculating transmission risk and consequent need (or not) for PEP.

> **Undetectable viral load is defined in these guidelines as less than 50
> copies/mL, consistent with the Seventh National HIV Strategy (Department of
> Health, 2013).**

Boily's (Boily 2009) meta-analysis of observational studies of the heterosexual risk of
HIV infection estimated that in high-income countries the per-act risk of infection for
RVI was 0.08 % (1/1250), and 0.04% (1/2500) for insertive vaginal intercourse (IVI).

A large prospective study from Africa did not detect gender differences in HIV
transmission in 235 discordant heterosexual couples practising vaginal intercourse
(Wawer 2005). The average rate of transmission was 0.0082/coital act (1/122) soon
after seroconversion, 0.0015/act (1/667) six to 15 months after the index case
seroconverted, 0.0007/act (1/1428) with prevalent HIV-positive partners and 0.0028/act
(1/357) six to 25 months prior to death. No anal sex was reported. Similar findings were
reported in another study (Gray 2001), with overall transmission in either direction
estimated at 0.0011/act (1/909). Partner's VL and genital ulceration influenced the rate
of transmission. The age of the exposed partner was also a factor in transmission.

Studies from Europe and the US indicate a higher probability of HIV transmission from
male-to-female than female-to-male. Mastro et al. (Mastro 1996) aggregated the results
of a number of heterosexual studies and estimated a male-to-female transmission rate
of 10 to 30%. In two studies with male partners with advanced disease, the rates were
50%. There is no comment on the forms of sexual behaviour. They estimated HIV
transmission per act at between 0.001–0.002 (1/500–1/1000). There is confounding
with some variables in these studies, causing their interpretation to be difficult.

Another European study estimated a crude rate of male-to-female transmission of 20%; per-act rates were not given, anal intercourse and partner health status were strongly associated with seroconversion (European Study Group on Heterosexual Transmission of HIV 1992). This group also estimated the risk of HIV transmission at 0.001 contacts (sexual episodes); this increased as the partner's health deteriorated (de Vincenzi 1994).

> **The transmission rate of HIV through RVI is estimated at 0.08% (1/1250). ART has been found to greatly reduce heterosexual transmission.**

❖ Insertive anal or vaginal intercourse

The probability of acquiring HIV by unprotected IAI was estimated by Jin's group looking at MSM. For uncircumcised men it was 0.62% (95% CI 0.07–1.68) (1/161) and 0.11% (95% CI 0.02–0.24) (1/909) for circumcised men. Circumcision was associated with approximately 6 times lower probability of infection (Jin 2010).

Jin's estimates are considerably higher than those from the earlier Vitinghoff study. The per-contact risk of transmission of HIV from Vitinghoff's cohort for unprotected IAI was 0.06% with seropositive or unknown partner and 0.04% for protected IAI (condom use, including condom breakages) (Vitinghoff 1999). It is therefore difficult to separate the risks for contact with an HIV-positive source and contact with a source of unknown HIV status. The conclusions to be cautiously drawn from this are that: a) the transmission risk of HIV by IAI with a known HIV-positive partner may be greater than 0.06% (1/1666) and b) the transmission risk of IAI with a partner of unknown HIV status is probably less than 0.06%. However, they are superseded by the findings of Jin's group in the Sydney study (Jin 2010). Two studies on heterosexual transmission did not detect a significantly increased risk of female-to-male HIV transmission through IAI (European Study Group on Heterosexual Transmission of HIV 1992; Leynaert 1998) after controlling for vaginal transmission.

Findings from another systematic review and meta-analysis of observational studies of 25 different study populations showed pooled female-to-male (0.04% per act [95% CI 0.01–0.14]) and male-to-female (0.08% per act [95% CI 0.06–0.11]) transmission estimates in high-income countries without HAART (Boily 2009). These estimates were higher in low-income countries (excluding the effect of commercial sex work). Estimates for the early and late phases of HIV infection were 9.2 (95% CI 4.5–18.8) and 7.3 (95% CI 4.5–11.9) times larger, respectively, than for the asymptomatic phase. Genital ulcer disease (GUD) in either member increased per-act infectivity 5.3 (95% CI 1.4–19.5) times versus no STI. The estimated risk of infection to uncircumcised men was at least twice that of circumcised men.

A meta-analysis of heterosexual infectivity (Powers 2008) concluded that heterosexual infectivity (through receptive and insertive vaginal and anal intercourse) was heterogeneous and generally underestimated at 0.01% infections per contact, and the impact of co-factors such as GUD, male circumcision and HIV disease stage had to be considered in epidemic modelling, policy development and preventive messages. Again, this contention is supported by Jin's work when considering IAI in men who have sex with men (Jin 2010).

The African studies cited earlier did not detect a gender difference between RVI and IVI (Wawer 2005; Gray 2001). Other European and Asian studies report higher rates of male-to-female transmission vaginally; however, there are methodological differences which make comparison of findings difficult (Mastro 1996). There was an associated increased risk of female-to-male transmission (p=0.04) for IVI during menstruation, compared with never having vaginal intercourse during menstruation (European Study Group on Heterosexual Transmission of HIV 1992). This was the only sexual activity associated with an increased risk of female-to-male transmission.

In text in box below, either use MSM or cut acronym and use full term. Dont need both.

> **The transmission risk through IAI in uncircumcised men who have sex with men was 0.62% (1/161) and 0.11% (1/909) in circumcised men.**
>
> **IVI was estimated to be 0.04% (1/2500), unless the female was menstruating.**
>
> **ART has been found to greatly reduce heterosexual and homosexual transmission risk.**

❖ Needle-sharing of people who inject drugs

Sharing needles when injecting drugs has an estimated high risk of HIV transmission per act (Kaplan 1992). This will be affected by variables such as (viable) VL and inoculating dose and route of injection (intravenous, subcutaneous and intramuscular) (Rich 1998; Abdala 2000). This risk has been estimated by modelling. There have not been any prospective studies examining HIV transmission and needle sharing. The probability of HIV transmission through sharing needles for PWID is 0.0067 or 1/150. Baggaley's systematic review and meta-analysis estimated the risk of infection of PWID was 0.63–2.4% (median 0.8%) (Baggaley 2006).

> **HIV transmission through re-using injecting equipment is estimated at 0.8% per act (1/125).**

Table 2 summarises the transmission risk of infection for higher-risk sexual and injecting exposures.

Table 2. Transmission risk/act for sexual exposure and PWID

Type of exposure with known HIV+ source	Estimated risk of HIV transmission/exposure[a]
Receptive anal intercourse • ejaculation • withdrawal	1.4–1.7% (1/71–1/59) 0.65% (1/154)
Insertive anal intercourse • uncircumcised • circumcised	0.62% (1/161) 0.11% (1/909)
Receptive vaginal intercourse	0.08% (1/1250)
Insertive vaginal intercourse	0.04% (1/2500)

Receptive or insertive oral intercourse	< 1 in 10,000 (low)
Re-using or sharing needles and other injecting equipment	0.8% (1/125)
Needlestick injury (NSI) or other sharps exposure	1/440
Mucous membrane and non-intact skin exposure[b]	< 1/1000

a These estimates are based on prospective studies, not cross-sectional data or figures derived from modelling.
b Exposures such as biting are extremely low risk.

❖ Oral sex

Case reports and a small number of cohort studies provide evidence that HIV can be transmitted through oral sex, both receptive – with and without ejaculation – and insertive fellatio and cunnilingus (Rothenburg 1998). The transmission risk per act is generally agreed to be low, but the impact of unquantified or unreported variables such as ejaculation, genital jewellery, oral lesions and other forms of sexual contact, other biases and the lack of prospective controlled data has made precise assessments difficult (Baggaley 2008). Additionally, the small number of studies may not have had sufficient power to demonstrate small, but significant risk (Working Group of the UK Chief Medical Officer's Expert Advisory Group on AIDS 2000). Data is available on men who have sex with men, women who have sex with women, and heterosexual discordant couples. Most often, conventionally ascribed higher-risk behaviour (such as anal or vaginal intercourse) has occurred within the study period, making it hard to control for the effect of such variables and possibly masking the role of oral sex in transmission.

Animal studies have demonstrated that exposure to SIV by oral inoculation can rapidly lead to infection (Stahl-Hennig 1999). HIV is present in saliva, pre-ejaculate, semen, and cervical and vaginal secretions. In vivo work with human keratinocytes incubated with HIV and other co-factors present in saliva and sperm have shown the biological plausibility of infection via the oral route (Acheampong 2005). Other STIs (e.g. gonorrhoea, chlamydia, herpes simplex virus (HSV), syphilis etc.) are well known to be transmitted through oro-genital contact.

❖ Receptive fellatio (with or without ejaculation)

No HIV transmissions were reported in a study of discordant heterosexual couples who practised protected genital and anal sex, but unprotected oral sex (de Vincenzi 1994) over a median two-year period (no data on ejaculation).

A cross-sectional study reported the per-contact risk of HIV transmission (Vitinghoff 1999) of receptive oral intercourse (ROI) with ejaculation with an HIV-positive partner or those with unknown status. This was 0.06%, compared with 0.82% for unprotected RAI with an HIV-positive partner, and 0.27% with an HIV-positive or unknown partner. Since the HIV status of the sources was mixed, and the proportions were not described, it is impossible to calculate a transmission risk for ROI with an HIV-positive partner. No information is provided on the condition of the recipients' oral mucosa. In reporting these risks, the study did not control for other sexual exposures as it states that there were no seroconversions among men reporting unprotected ROI as their only exposure.

❖ **Insertive fellatio**

Insertive fellatio with an HIV-positive female partner was not associated with an
increased risk of HIV transmission (European Study Group on Heterosexual
Transmission of HIV 1992).

❖ **Cunnilingus**

In a study following discordant heterosexual couples for two years, there were no
seroconversions in men performing oral sex on their HIV-positive female partners
(n=12) or HIV-positive men performing oral sex on their seronegative female partners
(n=98) and otherwise practising protected vaginal/anal sex (del Romero 2002). No data
is provided the men's oral health. Nineteen seronegative women had an unspecified
vaginal infection when cunnilingus was performed on them.

Breaches in oral mucosa may lead to an increase in transmission risk; such cases
should be assessed individually.

> **The estimated risk of HIV transmission/act of receptive and insertive oral sex
> is so low as to be unmeasurable. Non-intact oral or genital mucosa present a
> potentially greater risk that should be assessed on a case-by-case basis.**

❖ **Community-acquired needle-stick injury**

There have been no documented cases of HIV seroconversion after a community
needle-stick injury from a publicly discarded needle. These injuries involve small-bore
needles containing extremely small amounts of blood. This will not usually be injected –
that is, the needle pierces the skin but the needle contents are not injected into the
wound and the syringe is empty, further reducing potential exposure. Virus viability has
been assessed in the occupational setting and controlled environments, measuring a
range of variables such as blood volume, temperature and duration of storage (Rich
1998, Abdala 2000). In both these settings, it has been found to be very low.

Such injuries can generate considerable individual anxiety and public interest that is
out of proportion to the estimated risk of HIV transmission and the potential risks
associated with taking a course of PEP.

> **The risk of HIV infection resulting from a community-acquired needle-stick
> injury is estimated to be very, very low – although biologically plausible.**

❖ **Non-occupational exposure of intact mucous membranes and skin**

Non-occupational exposure of intact mucous membrane and skin has not been studied.
While it is biologically plausible, the risk is considered to be so low that it is not
measurable. Non-intact oral mucosa and skin present a potentially greater risk that
should be assessed on a case-by-case basis.

> **The risk of HIV transmission after non-occupational exposure through intact
> mucous membranes and skin is so low as to be unmeasurable.**

❖ Bites and other bloody trauma

Bites and other blood-contaminated trauma can potentially lead to HIV transmission. This has been reported very infrequently. In cases of individuals who have been bitten by HIV-infected people, there has been one documented seroconversion (Vidmar 1996; Richman 1993). The exposed individual was bitten by a man with advanced HIV disease who was having a fit and had evidence of having bitten his own tongue. The bitten man tested HIV-negative at the time of the bite and seroconverted six weeks later. He had no other risk factors and his wife (his only sex partner) was HIV-negative. A small number of case reports retrospectively ascribe the transmission of HIV infection to biting (Anonymous 1987; Wahn 1986). However, there may have been other risk factors.

HIV can be transmitted by an HIV-positive person biting another person, or theoretically by a seronegative person biting an HIV-positive individual. HIV has been demonstrated at low levels in cell-free saliva and can be present in oral secretions contaminated with blood, again at low levels. The presence of oral disease – infections, ulcers, inflammation for example, in an HIV-positive person may also increase oral HIV viral shedding (Richman 1993). The VL and severity of injury are other factors that may affect exposure, and hence, transmission. The risk of HIV transmission through human bites is generally considered very low if saliva is not contaminated with blood; blood-stained saliva is a potentially greater risk (CDC 2016).

> **The risk of HIV transmission through human bites is generally considered very low if saliva is not contaminated with blood; blood-stained saliva presents a potentially greater risk that should be assessed on a case-by-case basis.**

❖ Occupational exposure

In a descriptive epidemiological study conducted (1 July 2000vto 30 June 2003) in a tertiary teaching hospital (1000 beds and 3200 full-time-equivalent HCWs) in Adelaide, Peng et al (Peng 2008) reported that there were at least 4.1 potential blood-borne pathogen (BBP) exposure incidents per week. Ten per cent of possible BBP exposures were to HCV (HCV antibody positive), followed by HBV (3% HBV surface antigen positive), and HIV (2% HIV positive). Exposures were managed with HBV immunisation in non-immune staff, while staff exposed to HIV were provided with post-HIV exposure prophylaxis. Across the study period, 93% of individuals reporting a blood or sharps exposure were followed up for serology testing for HBV and HIV, and 94% of individuals were followed up for testing for HCV. There were no seroconversions to HIV, HBV or HCV.

An occupational exposure that may put a HCW at risk of HIV infection is described in the CDC guidelines as 'a percutaneous injury (e.g., a needlestick or cut with a sharp object) or contact of mucous membrane or nonintact skin (e.g., exposed skin that is chapped, abraded, or afflicted with dermatitis) with blood, tissue, or other body fluids that are potentially infectious' (CDC 2013).

In addition to blood and visibly bloody body fluids, the following also are considered potentially infectious:

- cerebrospinal fluid;
- synovial fluid;
- pleural fluid;
- peritoneal fluid;
- pericardial fluid; and
- amniotic fluid.

The risk for transmission of HIV infection from these fluids is unknown.

Faeces, nasal secretions, saliva, sputum, sweat, tears, urine and vomitus are not considered potentially infectious unless they are visibly bloody (CDC 2013).

Cardo's case control (Cardo 1997) study showed that significant risk factors for HIV infection were:
- a deep injury (odds ratio (OR) = 15, 95% CI: 6.0-41);
- injury with a device that was visibly contaminated with the source patient's blood (OR = 6.2, 95% CI: 2.2-21);
- a procedure involving a needle placed in the source patient's artery or vein (OR = 4.3, 95% CI: 1.7-12); and
- exposure to a source patient who died of the acquired immunodeficiency syndrome within two months afterward (OR=5.6; 95 %CI: 2.0-16).

Prospective study of HCWs helps to quantify occupational risk to HIV infection.

More than 20 longitudinal studies provide data to estimate the transmission risk associated with discrete occupational exposures to blood from patients infected with HIV (Ippolito 1997; Henderson 1990; Henderson 2009; Bell 1997). In these studies, HCWs who had occupational HIV exposures were tested for HIV antibody at or near the time of exposure and then periodically to detect serological evidence of infection. The combined data from these studies provide an estimate of the average risk of HIV transmission associated with percutaneous exposures of 0.32% to blood from HIV-infected individuals (or approximately 1 infection for every 325 documented exposures) and acquisition following 0.09% (or approximately 1 infection for every 1000 documented exposures) for mucous membrane exposure.

For example, in 1990, Henderson et al. reported on 346 mucous membrane exposures, 2712 exposures of intact skin and 179 percutaneous exposures. There were no cases of HIV transmission after exposure of mucous membranes or intact skin. In this cohort, one case of seroconversion was reported after a deep percutaneous injury with a bloody sharp; the source case had been hospitalised with AIDS and died soon after this accident. They concluded that HIV transmission risk 'with a percutaneous exposure to blood from an HIV-1-infected patient is approximately 0.3% per exposure (95% CI, 0.13% to 0.70%); the risks associated with occupational mucous membrane and cutaneous exposures are likely to be substantially smaller'.

In the United States, health departments report to the Centers for Disease Control and Prevention (CDC) data on cases of AIDS and cases of suspected occupationally acquired HIV infection. In 1997 Bell found that of the approximate 500,000 annual

HCW percutaneous blood exposures approximately 5000 involved exposures to blood known to be HIV infected and that the average risk of HIV transmission after percutaneous exposure to HIV-infected blood was 0.3%. Ultimately, there has only been one confirmed case of occupational HIV transmission in the United States since 1999 (Joyce 2015).

Ippolito's group (Italian Multicenter Study 1993) followed a cohort of health care workers. There were exposures to body fluids and tissues by 930 needle-stick injuries and 122 cuts, and exposures of mucous membrane and non-intact skin 178 and 362 times respectively. There was no transmission of HIV infection through non-intact skin. There was a seroconversion after percutaneous exposure to a patient who was HIV antibody negative, HIV p24 antigen positive (that is, in the window period). The estimated seroconversion rate was 0.10% (1/1003; 95% CI, 0.006% to 0.55%). This single case is an example of an exposure to a high HIV VL through a needle-stick injury. A single seroconversion after a mucous membrane and skin exposure was reported. In this case, a nurse was exposed to a high volume (not specified) of blood from an asymptomatic HIV-positive patient in intensive care when she was unblocking an arterial line. Transmission risk from this was described as 1/158, also with a very wide CI (95% CI, 0.018%–3.47%). This study has been the only one to document a seroconversion after such an exposure. The authors pooled results from other studies to estimate the overall risk at 0.09% (CI = 0.006%–0.5%) or 1:1000 after mucous membrane exposure. However, they concluded that this may overstate the risk of transmission by this route because of the effect of their single case. There is concern about overestimated risk through exposure to mucous membranes occupationally from this study which has been echoed in other guidelines (BASHH 2015).

Although episodes of HIV transmission after non-intact skin exposure have been documented, 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 (CDC 2013). 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 that for blood exposures (CDC 2013).

Assessment of occupational risk takes into account multiple factors such as the type of exposure and its severity. The factors that may increase the risks are:
1. related to the injury and increased blood volume:
    a. device that is visibly contaminated with blood or has a hollow bore (blood volume)
    b. procedure which involves devices inserted directly into a vein or artery
    c. deep injury
2. related to the source case:
    a. high VL
    b. viral strain (e.g., syncytial-producing strains).

The impact of these factors on transmission risk per exposure has not been estimated. British and US guidelines (BASHH 2015; CDC 2013) include a graduated approach to the classification of injuries of different severity and consequent recommendations for PEP.

Table 3. Percutaneous and mucous membrane occupational exposures and HIV transmission risk/exposure (after Baggaley 2006)

Exposure	Transmission risk
Contaminated medical injection (e.g.intramuscular injection)	0.24–0.65% (1/417–1/154)
Contaminated blood transfusion	88.3–100% (1/1.1–1/1.0)
Needle-stick and other sharps exposure	0.00–2.38% (0–1/42)(weighted mean 0.23% –1/440)
Mucous membrane exposure (probable overestimate –see text)	0.09% (1/1111)

Occupational exposure of intact and compromised mucous membrane and skin HIV transmission has been reported after mucocutaneous exposure. Prospective occupational studies provide evidence of the risk of HIV transmission that is low, but not negligible. This risk needs to be qualified further as workplace exposures vary greatly in the infectiousness of the source and the susceptibility of the exposed individual.

> **The aggregated risk of transmission of HIV after percutaneous exposure to blood is estimated at 0.23% (0.00–2.38%) or 1/440) per exposure.**
>
> **This risk will be modified by the severity of the injury and the viral load (through exposure type and extent, blood volume or source infectivity).**

Co-factors for infection

Transmission, and thus prevention, of HIV infection are governed by many variables. These include:

- viral factors such as viral resistance patterns and viral 'vigour';
- transmission factors such as inoculating dose (HIV VL in the source), mode of exposure, co-existing sexually transmissible infections (STIs) (of the exposed and/or source individual), presence of blood, a deep needle-stick injury with a large hollow bore needle straight from a vein or artery; and
- exposed case factors such as mucosal integrity, male circumcision, the timing of initiation of and adherence to PEP regimen, route of administration for NPEP, other potential HIV exposures before, during and after the course of PEP.

In estimating exposure risk, for the purposes of determining the indications for PEP, the focus is on host (source and exposed) and pathogen-related co-factors. The likelihood of infection from some sexual transmission routes appears to be less than through some other means of exposure (transfusion, MTCT, IDU) (Royce 1997). There is a wide variability of transmission, related to source factors such as VL and inoculating dose, and on host factors (for the exposed individual) such as genetic expression (Royce 1997), presence of sexually transmissible or reproductive tract infections, cervical ectopy, male circumcision, menstruation and pregnancy. Pathogen-related

factors include the variability in transmission of different sub-types of HIV. For example, it has been suggested that subtype E, which is predominant in Thailand, has a far greater tropism for Langerhans cells than subtype B which is predominant in Australia and the US (Hu 1996). This tropism may explain the rapidity of the heterosexual epidemic in Thailand, although the data to support this is not strong. Phenotypic differences found in seminal and blood isolates and genotypic differences with vaginal and blood isolates may confer transmission variability (Zhu 1996).

HIV transmission may be affected by altering an individual's susceptibility to infection or by altering the infectiousness of the condition.

❖ HIV infectiousness

Infectiousness is increased when the viral concentration of blood or genital secretions increases or with the presence of a more infectious viral strain. VL in the blood is affected by, for example, stage of disease, intercurrent infection (malaria, tuberculosis, HSV-2 and other STIs) and ART (Ghys 1997; Fleming 1999; Galvin 2004). Usually the VL in the blood is mirrored in the genital concentrations; however, there have been reports of patients with very low or undetectable blood VLs but with HIV recoverable from semen or female genital secretions (Vernazza 2000; Galvin 2004).

HIV VL is inextricably linked to HIV infectiousness or lack thereof. In a landmark study, the HPTN 052 study group found a 96% reduction in HIV transmission due to early initiation of ART, compared with delayed treatment in 1171 sexually active serodiscordant heterosexual partnerships, of whom 5% and 6% of HIV-infected and HIV-uninfected participants respectively reported condomless sex in the preceding week. (Cohen 2011; Safran et al., 2015). No transmissions occurred over the whole study period from HIV-positive partners who were on ART with undetectable VL. Therefore the transmission risk for vaginal intercourse with an HIV-positive partner with an undetectable VL may be estimated to be decreased by a factor of 20.

This is consistent with Attia's systematic review and meta-analysis (Attia 2009) of serodiscordant heterosexual couples which did not identify any HIV transmissions in individuals on ART who had VLs below 400 copies/mL.

In anal sex (of most relevance for MSM), preliminary data from the Partners and Opposites Attract studies (Rodger 2016, Grulich 2015) report that no HIV transmissions have occurred within male-male sexual partnerships, from a partner with an undetectable HIV VL. The Partners study (which includes 340 MSM couples) report zero HIV infections when the HIV VL in the infected partner was undetectable in 1238 couple years of follow-up (CYFU). The MSM couples in this study reported around 22,000 acts of condomless sex. Opposites Attract also reports no HIV infections with an undetectable VL in 98.0 CYFU of 153 MSM couples reporting 5905 acts of condomless anal sex.

The likelihood of the sexual transmission of HIV when the virus is fully suppressed in plasma is strikingly small but protection may not be absolute. Using sensitive assays, plasma HIV RNA has been detected in a significant majority of patients labelled as 'undetectable' (Maldarelli 2007). Although the majority of studies show that this virus

does not evolve, it can be shown to be replicative competent in culture, and single genome studies indicate that only a single virus produces clinical infection (Doyle 2012, Keele 2008).

In 2008, Sturmer et al (Sturmer 2008) retrospectively (5 or so years) reported a case of possible sexual transmission of HIV (phylogenetically linked) within a serodiscordant MSM couple despite ART. The relationship started in August 2000 a month after the positive partner (the source) had begun treatment. His first measured undetectable VL occurred in November 2000. HIV was diagnosed in the initially HIV-negative partner (the index) on 12 July 2004. His last negative test was reported to be in 2002, but was done anonymously with no written report. Adherence to ART (poor adherence to ART can cause VL rises) in the HIV-positive partner was by self-report, VL was measured at approximately 3 monthly intervals and was <50 copies/mL at each time point. Both the source patient and the treating doctor independently confirmed the absence of any STIs. The retrospective nature of this report, the temporal relationships between ART initiation, the start of the relationship and the first post-treatment initiation measurement of VL, self-reported ART adherence in the source plus the degree of uncertainty around the previous HIV negative result in the index all confound the validity of this report.

Attia (2209) in his systematic review noted that his data was compatible with one transmission per 79 person-years.

A possible explanation for the sexual transmission of HIV despite fully suppressive ART is the compartmentalisation of HIV whereby HIV RNA can be found in seminal or vaginal fluids despite there being no plasma viraemia (Lorello 2009, Cu-Uvin 2010). Also, Kolodkin-Gal et al. have shown in an explanted colonic model that (at least in vitro) cell-associated HIV DNA is an effective means of mucosal HIV infection (Kolodkin-Gal 2013).

Whilst RCT and well-designed prospective studies support the relationship between HIV VL and infectiousness in the setting of sexual risk there is no such data supporting the relationship between VL and infectiousness in occupational exposure to HIV. The US occupational exposure guidelines (CDC 2013) state that an undetectable VL in a source following an occupational exposure does not rule out the possibility of HIV transmission and advocates that PEP still be offered. This is at odds with the British HIV Association guideline which states that PEP is not required following occupational exposure to a source with an undetectable VL (Webster 2015).

On balance, the likelihood of HIV transmission from an occupational exposure from a virally suppressed source is likely to be extremely low even in the setting of a high-risk event. Careful choice of a PEP regimen unlikely to cause harm mitigates risk associated with 28 days of ART, thus the Australian guidelines continue to recommend that PEP be considered and offered to a HCW occupationally exposed to HIV regardless of the source VL.

❖ **Susceptibility to HIV infection**

Change to innate physical or immune defences may alter susceptibility to infection. Disruptions to genital (including anorectal and oral) mucosa by inflammation, infection,

irritation or trauma, for example, can lead to increased susceptibility to HIV transmission (Fleming 1999). Galvin describes decreased expression of HIV receptor sites by a variety of cells due to a genetic mutation conferring decreased susceptibility to HIV infection (Galvin 2004).

❖ STIs, susceptibility and HIV infectiousness

A number of studies describe an association between the presence of an STI and subsequent HIV infection. Although quantification of the association is hampered by study design, diagnostic methodology, sexual behaviour, the STIs investigated, the presence of genital ulcers and other confounding factors, it is generally accepted that STIs, particularly ulcerative STIs (GUD) confer increased susceptibility to HIV infection (Coombs 2003, Fleming 1999, Rottingen 2001). However, in the Australian setting, access to high-quality laboratory and sensitive and specific testing techniques for STIs is quite different from the circumstances in which many of these studies were conducted, and some of the findings may not be generalisable to Australian STI-infected populations at risk of HIV.

The possible reasons for this increased susceptibility are:
a) mucosal disruption (Galvin 2004, Coombs 2003) allowing easier access to mucosal lymphocytes or Langerhans cells. Both ulcerative and non-ulcerative STIs cause cellular infiltration at the site of infection,
b) immune changes causing T-cell activation. Higher levels of CD4 cells have been found in cervical specimens of women with STIs (gonorrhoea, chlamydia and trichomoniasis), as has the expression of CCR5 receptor sites (Galvin 2004),
c) 'recruitment' of and interaction with leucocytes to promote HIV replication by *Chlamydia trachomatis* (Fleming 1999),
d) changes to the genital microbial environment such as those seen in women with bacterial vaginosis (not an STI, but a 'microbial imbalance' in the vagina), vulvovaginal candidiasis and after circumcision in men (Galvin 2004).

A meta-analysis of the risk of HIV infection in individuals who are seropositive for HSV-2 (Wald 2002) described an increased risk of HIV seroconversion of two to four times. The population attributable percentage was 19% when HSV-2 seroprevalence was 22% and rose to 47% when seroprevalence reached 80%. The authors note that the results highlight the potential for HSV infection to confound the effect of sexual behaviour in cross-sectional studies. They also note that estimates of risk from cross-sectional and case-control studies may be misleading if the prevalence of the outcome is high.

From an observational study of four cities in Africa (Buve 2001) HSV infection was an independent risk factor for HIV infection in high- and low-prevalence HIV settings, especially in younger women. An early study by Cameron et al (Cameron 1989) described a risk ratio of HIV seroconversion of 4.7 for men who had acquired a genital ulcer. A Thai nested case-control study of military recruits (Nelson 1997) calculated odds ratios (OR) for men who converted to HIV with serological evidence of GUD (HSV or chancroid) at baseline or evidence of seroconversion during the trial. The adjusted OR for men with prevalent HSV infection who converted to HIV was 3.07. The conclusions to be drawn from a number of studies of HSV and HIV in MSM are not

clear as they suffer from potential classification bias and confounding by sexual behaviour and disease (HSV) activity. Some report significant effects of HSV on the likelihood of HIV seroconversion, others do not (Fleming 1999). Similarly, the results for syphilis infection of heterosexual men and women and MSM are variable, but do provide evidence that syphilis infection increases susceptibility to HIV infection (Fleming 1999).

In a prospective, blinded and controlled study of 890 female sex workers in Nairobi (Kaul 2004), prevalent HSV-2 infection (72.7% at the start of the two-year trial) was independently associated with HIV seroconversion. Subjects were treated with monthly azithromycin or placebo and provided with education and condoms. Although the rates of bacterial STIs declined, this intervention did not decrease the incidence rate of HIV.

> **There is a clear association between ulcerative STIs and increased susceptibility to HIV infection; the association between non-ulcerative STIs or non-STI genital tract infections is less clear, but HIV susceptibility appears to increase with the inflammatory changes associated with these conditions.**

Fleming's group concludes (Fleming 1999) that despite the problems in interpreting the findings from the many observational, case-controlled or prospective studies, 'trial data leave little doubt that other STDs facilitate HIV transmission through direct, biological mechanisms'. They question 'how this component (STD detection and treatment as part of HIV prevention) should be implemented for maximal impact on HIV incidence in specific populations'.

The impact of STI control to prevent HIV at a population level has been variable and generally disappointing. Controlling the rates of STIs early in an HIV epidemic and reducing the prevalence, incidence and shedding of HSV are two areas that may affect HIV incidence (Galvin 2004). Although two RCTs of HSV suppression have failed to show an effect on HIV incidence (Watson-Jones 2008, Celum 2008).

Fleming et al (Fleming 1999) draw several conclusions from the intervention studies in Mwanza (reduced HIV incidence associated with continuous clinical services for symptomatic STIs, early in epidemic) and Rakai (no change to HIV incidence associated with intermittent mass treatment, later in epidemic). Firstly, that continuous STI services are logically more effective at STI control than infrequent, intermittent mass treatment. They consider that symptomatic STIs have a greater role in HIV transmission than asymptomatic infections because of the heightened inflammatory response and disruption of epithelial surfaces. Additionally, the role of STIs earlier in an epidemic is greater than in the later stages. This is because of an assumed independence from STIs of biological and behavioural susceptibility as the epidemic progresses. Finally, they consider that the local incidence, prevalence and spectrum of STIs is critical to the transmission dynamics at this population level and note the effect of different diagnostic techniques for individual conditions on these assessments.

Many studies examining HIV shedding with a co-existent STI have been limited by technological and methodological difficulties (Galvin 2004). HIV shedding is generally increased with ulcerative STIs. This may be directly because of epithelial breaches as well as a systemic immunosuppression, as with HSV infection. The presence of inflammation associated with ulcerative and non-ulcerative STIs is also associated with

increased HIV shedding (Fleming 1999, Rottingen 2001, Cohen 1997). One study described higher levels of HIV RNA in semen, compared with the blood levels of men with asymptomatic urethritis, but the study numbers were very small and the significance of this for men with limited inflammation is unclear (Winter 1999).

Nagot et al. (Nagot 2006) presented data on the effect of active HSV-2 replication on HIV plasma VL. In an RCT of 140 women, 70 subjects treated with valacyclovir experienced significant reductions in HIV VL and HSV-2 shedding, compared with the control group.

Page-Shafer et al. determined that the presence of STIs (gonorrhoea, syphilis, herpes, warts, hepatitis B) was marginally associated with the risk of HIV seroconversion ($p=0.067$), after controlling for RAI and condom use in 105 pairs of MSM (Page-Shafer 1997).

Regarding the impact of male circumcision on the incidence of STIs, and consequent role in HIV transmission, results have been mixed. In an RCT in Rakai, Uganda, Tobain's group (Tobain 2009) found a reduction in the incidence of HSV-2 infection and prevalence of human papilloma virus (HPV) infection in circumcised men. There was no difference in the incidence of syphilis between the control and intervention arms. Analyses of the attributable risk of STIs in HIV transmission in circumcised men (including MSM) demonstrate that these STIs play a modest role in HIV prevention of circumcised men (Gray 2009, Desai 2006, Templeton 2009, Jameson 2010).

> **Ulcerative STIs are associated with increased HIV infectiousness due to increased HIV shedding and greater exposure to infected cells. Non-ulcerative STIs appear to play a lesser role in HIV infectiousness, primarily through increased HIV shedding.**

❖ Male circumcision

Male circumcision is the removal of some or the entire prepuce of the penis. It is usually undertaken as part of religious or cultural rites in neonates or boys. There are medical indications for circumcision, for example phimosis or recurrent infections. For many years it has been observed that there may be a protective effect of circumcision on HIV acquisition by heterosexual men.

A lack of circumcision has been associated with an increase in susceptibility to HIV infection in observational studies (Quinn 2006, Buchbinder 2005, Perisse 2009). This was confirmed in three RCTs in Africa: Orange Farm, South Africa (ANRS 1265 2005); Rakai, Uganda (Gray 2007) and Kisumu, Kenya (Bailey 2007). The results showed that in these high HIV-prevalence, resource-poor environments adult male circumcision reduced the acquisition of HIV by between 38% and 66% over a 24-month period (Siegfried 2009). Each trial finished early because of the strong treatment effect demonstrated. Other authors caution that male circumcision in these settings cannot be regarded as a 'silver bullet', but rather must be combined with other approaches with an awareness of potentially negative aspects of circumcision programs (risk compensation, early resumption of intercourse, complications from surgery etc). (Hallett 2008, Templeton 2010). Findings from an Australian study describe a

decreased transmission rate in MSM who are circumcised insertive partners practising IAI (Templeton 2009).

The biological bases proposed to explain this protective effect against HIV relate to:
- increased surface area of an intact foreskin
- the plentiful supply of Langerhans cells on the underside of the foreskin (for which HIV-1 shows a tropism)
- reduction in inflammation secondary to improved hygiene
- reported associated decrease in the incidence and prevalence of STIs especially GUD.

The evidence of circumcision as a protective measure against female-to-male transmission of HIV is strong. Circumcision also provides a long-term protection for women at a population level by reducing the prevalence of HIV-infected men (Weiss 2009). There is a lack of generalisability of these data to MSM and for assessing the effect of male circumcision on HIV transmission through anal or oral intercourse (Smith 2010).

Templeton reported that although circumcision did not significantly reduce the risk of HIV infection in the cohort, there was a significant reduction in HIV incidence in the subgroup of men who preferred to take the insertive role in anal intercourse; after controlling for age and UAI (hazard ratio 0.11, 95% CI 0.03–0.80, P = 0.041) (Templeton 2009). A study by Grulich et al. demonstrated no association between circumcision and decreased susceptibility for men practising IAI. However, the sample size was small (Grulich 2001). More recent analyses of MSM support this initial finding (Sanchez 2011; Londish 2010; Jameson 2010).

It is also proposed that circumcision reduces the risk of GUD and other STIs and may decrease transmission of chlamydia to female partners (CDC 2016).

> **Susceptibility to HIV infection is associated with disruption to epithelial defences and expression of HIV receptor sites at a cellular level.**
>
> **Circumcision appears to be protective for heterosexual men in resource-poor populations.**
>
> **Circumcision may reduce the risk of HIV infection in MSM exposed to HIV through IAI.**
>
> **There is no clear evidence of decreased per-contact probability of HIV infection for female partners of circumcised HIV-infected men.**

Post-exposure prophylaxis drug regimens

A range of views exists about the number and types of antiretroviral drugs to use following occupational exposure to HIV. Evidence is drawn from animal studies, human case-control studies from occupational settings, small prospective studies in mostly MSM, data on MTCT and PrEP. Guidelines have also been developed using data extrapolated from the treatment of established HIV infection with ART.

Many factors influence decision-making and recommendations for PEP. These 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,
- evidence of the efficacy of specific agents used for prophylaxis, and
- the risk and benefit of PEP to the exposed individual.

There are other issues to consider in the choice of antiretrovirals; these include:
- the potential efficacy of two, three or more antiretroviral drugs,
- the risk of resistance and treatment failure (or treating a seroconverting patient),
- the frequency and severity of side effects and the tolerability of and adherence to the regimen,
- the site of action of drugs, related to the HIV replicative life cycle,
- the pharmacokinetic profile of different drugs or drug classes,
- the potential for drug/drug interactions
- the known efficacy of AZT monotherapy in the occupational setting,
- the inoculum size in non-occupational exposure in contrast to the circulating VL in an infected person, and
- the cost benefit/effectiveness.

All of these points will shape the choice of drugs. Decisions necessarily will be based on data from prospective studies using various antiretroviral drugs and classes in PEP and assumptions rather than Level 1 evidence. An example is the move to exclude protease inhibitors (PI) from PEP regimens. This is because of high rates of toxicity, high potential for drug-drug interactions and their action against HIV replication, which is later in the virus life cycle. Protease inhibitors prevent mature HIV protein formation within cells in which HIV is already integrated into host-cell DNA, that is, a protease inhibitor can only act within an individual in which at least one cell is already HIV-infected (McAllister 2011). An alternate view is that HIV is taken into the host very quickly. In a study of female macaques who were inoculated with SIV, virus was found within the vaginal mucosa within 60 minutes of vaginal exposure (Hu 2000). If this is analogous to the situation in humans then HIV will have integrated into the host cell DNA, in many cases before PEP is commenced. Hence the inclusion of a PI will not be redundant; instead, an important response to prevention.

There is the additional factor of the decision-making process 'at the coal face', with a potentially HIV-exposed patient in front of a clinician, in the absence of strong, evidence-based guidelines and generally without sufficient background information on which to accurately assess transmission risk. Again, the difference between prescribing short-term preventive treatment for a person without disease and prescribing on-going therapy to someone with HIV will lead to different approaches and treatment decisions.

What regimen to use
The ideal drug or drug combination for PEP should have the following characteristics:
- low-impact side-effect profile,
- safe to use,

- mode of action prior to HIV integration into target cell DNA (i.e. not a protease inhibitor),
- rapid absorption,
- low likelihood of drug-drug interactions, and
- favourable resistance profile.

No drug or drug combination for use in PEP fulfil this strict criteria; however, agents and combinations that meet most, if not all, have been evaluated.

Tolerability, adherence and safety

Regimen completion rates in PEP recipients are less than optimum and are almost always driven by toxicity.

In a systematic review and meta-analysis by Ford et al., 2014, the completion rate of a 28-day treatment course was generally poor at 56% (95% CI 50.9-62.2%), highest among the MSM group of the NPEP (67.2%, 95% CI 59.5-74.9%) and lowest among the sexual assault group (40.2%, 95% CI 31.2-49.2%). Toxicity-driven discontinuation was more common with 3-drug regimens than with 2-drug regimens (2% versus 9% respectively) (Ford 2014).

Most studies of PEP have found high rates of side effects. Poynten's group examined a group of 1601 participants prescribed NPEP, using a range of drug combinations, in South Eastern Australia (Poynten 2007). It found an adherence rate of 80%; side effects were reported by 66% of participants.

In seven PEP studies published since 2001 and reviewed by McAllister at al. (McAllister 2013), 51% of the total 1009 participants reported at least one adverse event and around 20% failed to complete the 28-day course (Rabaud 2001; Winston 2005, Rabaud 2005, Burty 2008; Mayer 2008 Tosini 2010; Diaz-Brito 2012).

Higher rates and regimen discontinuation have been associated with prescribing AZT (Rabaud 2004; Winston 2005; Schechter 2004), NVP (Puro 2003; Benn 2001), IDV (Parkin 2000; Wang 2000; Bernasconi 2000), other PIs (Rabaud 2001; 2004; Balano 2004). There are high rates of gastrointestinal side effects and regimen discontinuation associated with lopinavir/ritonavir, atazanavir and efavirenz (Diaz-Brito 2012; Hill 2009; Wiboonchutikul 2016). Rabaud et al. (2005) found that of 98 patients on zidovudine-lamivudine and lopinavir-ritonavir, 58 experienced adverse effects, which led to premature discontinuation of PEP in 20 cases. Higher rates of side effects have also been associated with the increasing (absolute) number of ARVs in the regimen (Wang 2000; Larsen 2003; Balano 2004).

The impact of the milder side effects on adherence is variable. There are reports of side effects being tolerated and adherence being reasonably maintained (Schechter 2004), or PEP regimens being changed by the removal of a suspect drug – with or without substitution of another, because of intolerance, but still the course has been completed (Puro 1999; Puro 2000). Other studies describe 'minor' side effects (as described above) leading to the total discontinuation of treatment (Rabaud 2004).

Generally, side effects have not been severe; they are predominantly gastrointestinal (nausea, vomiting, diarrhoea). Headaches, malaise/fatigue and skin rashes are also frequent (Parkin 2000; Bernasconi 2000; Baskan 2005; Woolley 2003; Puro 1999). Transient rises in liver transaminases have been described (Puro 2003; Allan 2001). Changes in other metabolic markers (triglycerides and cholesterol) have been found in association with the use of regimens containing protease inhibitors (Allan 2001; Italian Registry 2000). Luzzati et al (Luzzati 2002) reported hyperprolactinaemia and galactorrhoea associated with a PI-based occupational PEP regimen. These metabolic side effects are generally minor and quite reversible at the end of the treatment course (Puro 2003; Allan 2001; Luzzati 2002).

In addition to reported side effects and resultant regimen discontinuation, many of these reports contain relatively high proportions of subjects who are lost to follow-up for reasons unknown but possibly attributable to regimen-associated toxicity.

Side-effects reporting and their impact on regimen completion rates has improved with newer drug regimens. Ford et al. (2015) conducted a systematic review of the safety and efficacy of 2- and 3-drug regimens. They found completion rates of 78.4% (95% CI, 66.1%-90.7%) for people receiving a tenofovir-based regimen and 58.8% (95% CI, 47.2%-70.4%) for a zidovudine-based regimen. The rate of PEP discontinuation due to an adverse event was lower among people taking tenofovir-based regimen (0.3%; 95% CI, 0%-1.1%) versus a zidovudine-based regimen (3.2%; 95% CI, 1.5%-4.9%). For the 3-drug comparison, PEP completion rates were highest for the tenofovir-based regimens (tenofovir+emtricitabine with lopinavir/ritonavir, 71.1%; 95% CI, 43.6%-98.6%; tenofovir/emtricitabine with raltegravir, 74.7%; 95% CI, 41.4%-100%; tenofovir/emtricitabine with boosted darunavir, 93.9%; 95% CI, 90.2%-97.7%) and lowest for zidovudine+lamivudine with lopinavir/ritonavir (59.1%; 95% CI, 36.2%-82.0%). Discontinuations due to adverse drug reactions were lowest for tenofovir/emtricitabine with raltegravir (1.9%; 95% CI, 0%-3.8%) and highest for zidovudine/lamivudine with boosted atazanavir (21.2%; 95% CI, 13.5%-30.0%).

Prospective Australian studies in MSM of newer agents (raltegravir, rilpivirine or dolutegravir) used as a third drug in a PEP regimens (McAllister 2013; Foster 2015; McAllister 2016) found that these are well tolerated with high rates of adherence (89%, 92%, 90% respectively) and regimen completion rates (92%, 92%, 90% respectively).

There have been no RCTs examining, much less quantifying, the effect of less than 100% compliance with any PEP regimen on efficacy. In Roland's series (Roland 2005b) 3 of the 7 PEP failures (43%) had their adherence rated as poor or fair.

It is clear that sub-optimal adherence to ART as HIV treatment results in poor outcomes in terms of morbidity and mortality (Bangsberg 2001). Theoretically, a high level of adherence to a 28-day course of PEP is also required to optimise the success of this intervention.

Serious adverse events in participants on PEP have been reported. Patel et al. (2004) found 12 cases of non-HIV-infected individuals developing severe cutaneous toxicity after 7 to 12 days of nevirapine-containing regimens, 30 cases developed

hepatotoxicity after 8 to 35 days of single-agent nevirapine (n = 8) or nevirapine-containing (n = 22) regimens. In one case, when PEP was prescribed for occupational exposure, the patient required a liver transplant after fulminant hepatitis developed (Johnson 2000). Easterbrook et al. (2003) found the initiation of abacavir was significantly associated with the development of hypersensitivity reactions. Indinavir, when used in PEP, has also been described as a cause of nephrolithiasis in a number of reports (van der Ende 2002). Protease inhibitors should also be avoided because of the high rates of potential drug interactions with other commonly used licit and illicit medications (McAllister et al. 2013). The combination of didanosine and stavudine should not be used because of the high risk of lactic acidosis and peripheral neuropathy (Boubaker 2001; Moore 2000). Raltegravir may cause chemical and symptomatic rhabdomyolysis when used in PEP (McAllister 2013).

PEP regimens for pregnant women need to be carefully assessed for teratogenic effects and for evidence of possibly pregnancy-specific adverse effects. Efavirenz (EFV) is contraindicated in pregnancy. There have been a number of case reports of pancreatitis and lactic acidosis (fatal for both the mother and infant in one case) in pregnant women treated with d4T and ddI (used for treatment, not PEP) (Sarner 2002; Mandelbrot 2003).

On this basis, regimens containing AZT and PIs should be avoided, and NVP, abacavir, ddI/ d4T and EFV are contraindicated.

> **On the basis of the effect of ART compliance on treatment outcomes in HIV - infected people, 100% adherence to PEP is strongly recommended.**
>
> **Drugs included in PEP regimens should be selected on the basis of safety and tolerability.**

In cases of renal impairment, where creatinine clearance is less than 60mL/min, tenofovir should not be used. Zidovudine with lamivudine with doses adjusted to the degree of renal function are recommended for the 2-drug regimen/base (CDC 2016).

Mode of action
Protease inhibitors prevent mature HIV protein formation within cells in which HIV is already integrated into host-cell DNA, that is, a PI can only act within an individual in which at least one cell is already HIV-infected (McAllister 2011). An alternate view is that HIV is taken into the host very quickly. In a study of female macaques who were inoculated with SIV, virus was found within the vaginal mucosa within 60 minutes of vaginal exposure (Hu 2000). If this is analogous to the situation in humans then HIV will have integrated into the host cell DNA, in many cases before PEP is commenced. Hence the inclusion of a PI will not be redundant; instead, an important response to prevention.

Absorption and time to Tmax
There is no evidence to support the choice of drugs for PEP based on drug pharmacokinetics. In the occupational setting access to PEP is generally rapid; however, there can be a significant gap between the risk event and assessment for

PEP following non-occupational exposures. In a prospective study of 100 Australian MSM accessing PEP (Foster 2015) the mean time between exposure and presentation for care was 30 hours (range 2-72, SD 21).

Given that time to first dose of PEP may impact on efficacy (Shih 1991; Tsai 1998; Roland 2005b) PEP agents that are rapidly absorbed are desirable. TDF and FTC are rapidly absorbed and Tmax is 1 and 1-2 hours respectively. Tmax for rilpivirine, raltegravir and dolutegravir are 4 to 5 hours, 3 hours and 2 to-3 hours respectively and roughly comparable to that of PIs.

Drug interactions

NRTIs (in particular TDF and FTC) have few or no drug/drug interactions with prescribed, proscribed and over-the-counter medications. Generally speaking, integrase inhibitors have less significant or potentially serious drug/drug interactions than PIs. In a prospective Australian study of 125 MSM receiving NPEP (McAllister 2013), almost half of the study participants were taking at least one other prescribed medication regularly. These medicines included antipsychotics, antidepressants, hypnotics, benzodiazepines, opiates, corticosteroids, anticonvulsants, proton pump inhibitors, antihistamines, beta-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors and phosphodiesterase type 5 (PDE5) inhibitors. Eight potential drug interactions in eight study participants were identified where, had a PI been the third component of the regimen, concomitant PI use would have been an absolute contraindication in two cases (simvastatin and St John's Wort) or a relative contraindication in six [phenytoin, sildenafil (two participants), vardenafil, carbamazepine and budesonide]. In addition, of the 121 participants who provided a substance use history, 89 (74%) indicated regular drug use. Other than alcohol 37 (42%) used at least one illicit, 'recreational drug'. Of these, 18 (49%), nine (24%) and seven (19%) were using methamphetamine (ice), gamma-hydroxybutyrate (GHB) and 3,4-methylenedioxy-N-methylamphetamine (ecstasy), respectively.

There is virtually no research in this area, although there have been case reports of death and near-fatal reactions between ecstasy and/or GHB and the PIs ritonavir and saquinavir (Gruber 2010, Henry 1998, Harrington 1999). These high rates of 'recreational drug' use in young MSM (mean age 34 years) was not unexpected but the high rate of prescribed co-medication was unexpected.

Resistance

HIV resistance to ART is relevant to prescribing PEP for two reasons. The first is that transmission of drug-resistant virus is known to occur and potentially have an impact on PEP efficacy. The second is that theoretically resistant HIV can be selected after an unsuccessful course of PEP, resulting in longer-term therapeutic challenges for the HIV-positive patient.

In 2004, Australian researchers reported the first two cases of transmitted triple-class, drug-resistant HIV-1 in Australia. Baseline testing of a newly diagnosed man showed four reverse transcriptase resistance mutations (affecting two drug classes) and six protease resistance mutations. A source patient was identified, and a likely second

case newly infected one year later, suggesting sequential transmission.

Knox et al. (Knox 2016) reported the case of a man on daily PrEP with Truvada who became infected with a multi-drug-resistant strain (including resistance to tenofovir and emtricitabine) of HIV despite apparently very consistent adherence to PrEP.

Jochimsen (Jochimsen 1997) looked at failures of ZDV PEP. In two-thirds of the cases of PEP failure the source case was receiving ZDV, therefore the transmission of resistance may have contributed to the failure.

In 2014, data from the reference laboratories in Victoria and NSW showed the prevalence of drug resistance in newly acquired HIV infections to be 4.1% for NRTIs, 3.1% for NNRTIs and 1% for PIs. Currently integrase resistance testing is not routinely performed (The Kirby Institute 2014).

A strong paper by Bassett et al. (Bassett 2004) examined the efficacy, toxicity and resistance of 2- or 3-drug regimens for occupational post-exposure prophylaxis. It presents an argument for reconsidering the benefit of three-drug therapy for prophylaxis. It provides a sensitivity analysis, weighing up two drugs against three, considering variables such as antiretroviral resistance rate, drug toxicity, discontinuation rate, overall efficacy and efficacy with resistant virus. Estimates of the efficacy values (two-drug PEP is equal to AZT monotherapy 79%), and efficacy with resistance were made. Once the prevalence of drug resistance reaches 15%, the three-drug regimen is preferred. The importance of a complete 28-day course was also emphasised as an important factor.

Knowledge concerning background antiretroviral resistance prevalence patterns in local HIV populations may be useful to consider when selecting a PEP regimen. Theoretically, PEP may apply selection pressure for the development of resistant virus in a seroconverting patient. It is unlikely that this would occur within the period between treatment initiation and review of baseline HIV results.

> **In Australia NRTI-resistant strains of virus are low and that of integrase inhibitors is unknown but likely to be very low. Within individuals, transmission of resistant virus has been cited as a cause of PEP failure.**

Number and choice of antiretrovirals

In the treatment of HIV, triple therapy usually provides superior viral suppression to dual therapy and has been the basis for the recommendation of three drugs for higher-risk exposures. However, there is no evidence to support the greater efficacy of three drugs over two in the setting of post-exposure prophylaxis. Postpartum PEP data supports the use of two or three drugs, Nielsen-Saines et al. (2012) found that within 1684 infants enrolled in the Americas and South Africa (566 in the zidovudine-alone group, 562 in the two-drug group, and 556 in the three-drug group), the overall rate of in utero transmission was 5.7% (93 infants), with no significant differences among the groups.

There is no consensus about whether two or three antiretroviral drugs should be used for PEP. The World Health Organization has conditionally recommended the use of three antiretroviral drugs in all cases of PEP (Ford 2015). They also suggested the use of FTC-based backbone (either with 3TC or FTC) and a third drug LPV/r or ATV/r or where available RAL, DRV/r, or EFV.

Arguments against the universal use of three-drug PEP include:
- the viral inoculum is infinitesimally small following non-occupational exposure, compared with the amount of virus requiring potent ART for full suppression in an HIV-infected individual;
- single-agent PEP (AZT monotherapy) resulted in an 81% reduction in the risk of HIV infection in a study of occupational exposures;
- increased side effects and/or more difficult dosing schedules may result in decreased adherence which may lead to decreased efficacy;
- resistance levels in Australia are lower than those reported overseas and there is a cost differential when a third drug is added.

Data from a systematic review of drugs used in PEP which demonstrated superiority of TDF, emtricitabine and lamivudine in terms of tolerability and regimen completion rates (Ford 2015) forms the basis of the recommendation that these (in combination as tenofovir-emtricitabine as Truvada) or as tenofovir with lamivudine be the preferred two-drug Australian PEP regimen.

The choice of a third drug for use in Australian PEP in adults is based on prospective studies of raltegravir, rilpivirine and dolutegravir in Australian MSM (McAllister 2013; Foster 2015; McAllister 2016). While these studies are small and provide no information on the use of a third drug in non-MSM populations, they are the highest level of evidence available concerning which agents to use in PEP.

The National PEP Guidelines Expert Reference Group determined that: for transmission risks equal to or greater than 1/1000, two or three drugs should be recommended; for risks less than 1/1000 and equal to or greater than 1/10,000, two drugs are considered. PEP is not recommended for lower-risk exposures. These arbitrary levels of risk assessment were set to assist easier implementation of PEP regimens (in the absence of evidence for or against).

Cost benefit of PEP
There have been a number of published reports modelling the cost-effectiveness or cost benefit of OPEP and NPEP. These studies make assumptions about a number of variables including transmission rates, PEP efficacy and adherence to the prescribed course. There is no data to guide preference for a one-, two- or three-drug regimen on the basis of cost-effectiveness. No studies were found that included indirect costs in the analysis. Indirect benefits (such as opportunity for preventive education) were referred to in some papers, but not assessed.

A retrospective cost analysis of NPEP in Australia concluded that 'Despite the lack of certainty about key factors such as PEP effectiveness and risk of HIV transmission

after single exposure… it may not be cost-effective to provide NPEP after all types of risk exposures'. It was only cost-effective, using a threshold of $50,000, when the exposure was RAI with an HIV-infected source (Guinot 2009). Estimates were highly sensitive to the per-act transmission risk. Lower-risk exposures incurred considerably greater costs than higher-risk exposures such as unprotected RAI with a known HIV-positive source. In this study, only the direct costs of health care provision were considered.

Most studies conclude that there is a cost benefit in providing NPEP when the source individual is known to be HIV-positive or if the exposure is RAI between MSM whether the source status is known to be HIV-positive or not (Pinkerton 2004; Pinkerton 2004a; Pinkerton 1998; Pinkerton 1998a; Pinkerton 1997; Hamers 2001). Herida et al. (Herida 2005) describe prescription of PEP as cost-saving for men and women having RAI with HIV-positive partners and as cost-effective for men having RAI with partners of unknown HIV status, for IDU sharing with HIV-positive users, and health care workers with deep needle-stick injuries from HIV-positive sources. Receptive vaginal intercourse with HIV-positive men and sharing needles with PWID of unknown HIV status were possibly cost-effective. If the source's HIV status was unknown, NPEP was not cost-effective unless RAI between men was the exposure. NPEP has not been a cost-effective intervention for other exposures such as IVI or IAI, and universal provision is not economically efficient (Pinkerton 1998). Although PEP is an expensive intervention, the lifetime costs of HIV treatment alone (without considering indirect costs) are much higher.

Separate debates have developed about the affordability of NPEP programs and the proportion of health budgets required to support them. Different perceptions of the assumptions made in analyses have been a major factor in the variety of conclusions drawn (Pinkerton 2000; Low-Beer 2000; Merchant 2000; Braitstein 2001).

Programs which support targeted prescription of PEP to individuals exposed to known HIV-positive sources in the occupational and non-occupational setting have been found to confer cost savings and the additional benefits of decreased psychological stress and physical and emotional side effects of antiretrovirals (Greub 2001; Braitstein 2001; Greub 2002; Postma 2002).

Behavioural interventions have been determined to be more cost-effective than NPEP, especially if NPEP use is not confined to high-risk exposures (Pinkerton 1997). This emphasises the importance of incorporating preventive and self-efficacy education into the NPEP consultation and follow-up.

> **(N)PEP may be cost-effective for high-risk exposures with a known HIV-positive source. If indirect benefits are considered, this may increase. Preventive behavioural strategies may be more cost-effective than (N)PEP.**

Behavioural risk-reduction strategies and NPEP
There is inconsistent evidence that the availability and provision of NPEP has led; or will lead, to an increase in unprotected exposures or 'at risk/higher risk' behaviour.

Studies from the US (Martin 2001; Waldo 2000) and Brazil (Schechter 2001; 2004) suggest that knowledge of NPEP, its availability and use by MSM was associated with unchanged or decreased risk behaviour.

In contrast, Poynten shows that risk behaviour continues after NPEP therefore those who receive NPEP continue to be at a higher risk of HIV (Poynten 2009). These results are in keeping with the study by Heuker et al. 2012 where it was shown that MSM who recently had PEP prescribed had a higher incidence of HIV when compared with controls.

MSM who also use crystal methamphetamine are another group with a uniquely increased risk of seroconversion following NPEP (Oldenburg et al. 2015). These participants were significantly more likely to seroconvert over the follow-up period (aHR 3.61, 95% CI 1.51 to 8.60) when compared to MSM who did not use crystal methamphetamine. Also, they were found to have returned more frequently for repeat PEP (aOR 5.13, 95% CI 2.82 to 9.34) and more likely to have unprotected anal intercourse despite the knowledge of their partner's HIV positivity.

These studies demonstrating continuing sexual risk behaviour and discrete high-risk populations within populations at risk of HIV acquisition strongly suggest a need for other adjunctive preventive strategies.

Conclusion

Data from animal studies, work on MTCT, non-occupational and occupational exposure and PrEP suggest that PEP may prevent the transmission of HIV. It is recommended that PEP is commenced within 72 hours of exposure and continued for 28 days. Data from systematic reviews and small prospective studies provide guidance about which agents to use as PEP.

References

Abdala N, Reyes R, Carney JM, et al. Survival of HIV-1 in syringes: effects of temperature during storage. Subst Use Misuse 2000;35:1369–83.

Acheampong EA, Parveen Z, Muthoga LW et al. Molecular interactions of human immunodeficiency virus type 1 with primary human oral keratinocytes. J Virol 2005;79(13):8440–53.

AIDSinfo Drug Database. US Department of Health and Human Services http://aidsinfo.nih.gov/DrugsNew/Default.aspx

Al-Hajjar SH, Frayha HH, Al-Hazmi M, Batawi R, McIntosh K, Sax P E, . . . Henrich T J. Prevention of HIV-1 Transmission with Post-Exposure Prophylaxis after Inadvertent Infected Blood Transfusion. AIDS 2014; 28(10):1539-541. doi:10.1097/QAD.0000000000000268

Allan D, Behrman A. Lipid abnormalities in a healthcare worker receiving HIV prophylaxis. Int J STD AIDS 2001;12(8):532–4.

Anderson RM, May RM. Epidemiological parameters of HIV transmission. Nature 1988 (June 9);333:514–19.

Anonymous. Transmission of HIV by a human bite. Lancet 1987;2:522.

ANRS 1265. Auvert B, Taljaard D, Lagarde E et al. Randomised, controlled intervention trial of male circumcision for reduction of HIV infection risk: the ANRS 1265 Trial. PLoS Med 2005;2(11):e298.

Armishaw J, Hoy JF, Watson KM et al. Non-Occupational Post Exposure Prophylaxis (NPEP) in Victoria - responding to high rates of re-presentation and low rates of follow-up. Int J STD AIDS 2011 (in press).

Australia and New Zealand Paediatric Infectious Diseases Group (ANZPID). ANZPID guidelines for post-exposure prophylaxis (PEP) after non-occupational exposure to blood borne viruses in children. ANZPID, Australia, 2016.

Attia S, Egger M, Muller M et al. Sexual transmission of HIV according to viral load and antiretroviral therapy: systematic review and meta-analysis. AIDS.2009;23(11):1397–404.

Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM). Literature Review for the National guidelines for Post-exposure Prophylaxis after Non-occupational Exposure to HIV. HIV Journal Club, ASHM. Sydney, NSW, 2006.

Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM). Draft National HIV Testing Policy. 2014. Available at: http://testingportal.ashm.org.au/resources/2014_National_HIV_Testing_Policy_v1.pdf

Australian Antiretroviral Guidelines Panel. DHHS Guidelines for the use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents, with Australian Commentary. 2016. Available at http://arv.ashm.org.au/

Australian National Council on AIDS, Hepatitis and Related Disease (ANCAHRD). Guidelines for the management and post exposure prophylaxis of individuals who sustain nonoccupational exposure to HIV. ANCAHRD Bulletin 2001 No 28.

Baggaley RF, Boily M-C, White RG et al. Risk of HIV-1 transmission for parenteral exposure and blood transfusion: a systematic review and meta-analysis AIDS 2006, 20:805–12.

Baggaley RF, White RG, Boily M-C. Systematic review of oro-genital HIV-1 transmission probabilities. Int J Epidemiol. 2008:37;1255–65.

Baggaley RF, White RG, Boily M-C. HIV transmission risk through anal intercourse: systematic review, meta-analysis and implications for HIV prevention. Int J Epidemiol. 2010;39:1048–63.

Bailey RC, Moses S, Parker CB et al. Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomised, controlled trial. Lancet 2007;369(9562):643–56.

Bangsberg DR, Perry S, Charlebois ED et al. Non-adherence to highly active antiretroviral therapy predicts

progression to AIDS. AIDS 2001;15:1181–83.

Baskan EB, Akalin H, Tunali S et al. Sequential cutaneous eruptions to antiretroviral drugs in occupational post- exposure prophylaxis for HIV infection. Eur Acad Dermatol Ven 2005;19(5):I–412.

Bassett IV, Freedberg KA, Walensky RP. Two drugs or three? Balancing efficacy, toxicity, and resistance in postexposure prophylaxis for occupational exposure to HIV. Clin Infect Dis 2004 (August 1);39:395–401.

Bell DM. Occupational risk of human immunodeficiency virus infection in healthcare workers: an overview. Am J Med 1997;102(suppl 5B):9–15.

Benn PD, Mercey DE, Brink N et al. Prophylaxis with a nevirapine containing triple regimen after exposure to HIV-1. Lancet (Mar 3) 2001;357:687–8.

Bernasconi E, Ruef C, Jost J, Francioli P, Sudre P. National registry for non-occupational post HIV exposure prophylaxis in Switzerland: ten-year results [Abstract]. Presented at the XIII International AIDS Conference, 2000; Durban, South Africa.

Bloch M, Carr A, Vasak E et al. The use of human immunodeficiency postexposure prophylaxis after successful artificial insemination. Am J Obstet Gynecol 1999;181(3):760–1.

Boily MC, Baggaley RF, Wang L et al. Heterosexual risk of HIV-1 infection per sexual act: systematic review and meta-analysis of observational studies. Lancet Infect Dis. 2009;9(2):118–29.

Boubaker K, Flepp M, Sudre P et al. Hyperlactatemia and antiretroviral therapy: the Swiss HIV Cohort Study. Clin Infect Dis. 2001;33:1931–7.

Bourry O, Mannioui A, Sellier P, et al. Effect of short-term HAART on SIV load in macaque tissues is dependent on time of initiation and antiviral diffusion. Retrovirology 2010;7:78–89.

Braitstein P, Chan K, Beardsell A et al. Another reality check: the direct costs of providing post-exposure prophylaxis in a population-based programme. AIDS 2001;15(17):2345–7.

Braitstein P, Chan K, Beardsell A et al. Safety and tolerability of combination antiretroviral post-exposure prophylaxis in a population-based setting [letter]. JAIDS 2002;29(5):547–8.

British Association for Sexual Health and HIV (BASHH) (Guidelines working group). UK Guidelines for the use of HIV Post-Exposure Prophylaxis Following Sexual Exposure (PEPSE) 2015.

Brocklehurst P, Volmink J. Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection. The Cochrane Database of Systematic Reviews 2002, Issue 2. Art. No.: CD003510. DOI: 10.1002/14651858.CD003510.

Buchbinder S, Vitinghoff, E, Heagarty P et al. Sexual risk, nitrite inhalant use, and lack of circumcision associated with HIV seroconversion in men who have sex with men in the United States. J Acquir Immun Def Synd 2005;39(1):82–9.

Burty C, Pavel S, Ghomari K et al. Tolerability of fosamprenavir/ritonavir associated with zidovudinelamivudine used as postexposure prophylaxis for HIV infection. J Acquir Immun Def Synd 2008; 49: 334–6.

Buve A, Carael M, Hayes RJ et al. The multicentre study on factors determining the differential spread of HIV in four African cities: summary and conclusions. AIDS 2001; 15(S4):5–14.

Cameron DW, Simonsen JN, D'Costa LJ et al. Female to male transmission of human immunodeficiency virus type 1: risk factors for seroconversion in men. Lancet 1989;2(8660);403–7.

Cardo DM, Culver DH, Ciesielski CA et al. A case-control study of HIV seroconversion in health care workers after percutaneous exposure. N Engl J Med 1997;337:1485–90.

Celum C, Wald A, Hughes J et al. Effect of aciclovir on HIV-1 acquisition in herpes simplex virus 2 seropositive women and men who have sex with men: a randomised, double-blind, placebo-controlled trial. Lancet 2008; 371(9630):2109–19.

Centers for Disease Control and Prevention (CDC). Serious adverse events attributed to nevirapine regimens for postexposure prophylaxis after HIV exposures--worldwide, 1997--2000. MMWR 2001;49:1153-6.

Centers for Disease Control and Prevention (CDC). Updated U.S. Public Health Service guidelines for the management of occupational exposures to HIV and recommendations for postexposure prophylaxis. 2013. https://stacks.cdc.gov/view/cdc/20711

Centers for Disease Control and Prevention (CDC). CDC HIV/AIDS Science Facts: Male Circumcision and Risk for HIV Transmission and Other Health Conditions: Implications for the United States. 2008. www.cdc.gov/hiv/resources/factsheets/PDF/circumcision.pdf

Centers for Disease Control and Prevention (CDC). Results of FEM-PrEP Clinical Trial Examining Pre-Exposure Prophylaxis (PrEP) for HIV Prevention Among Heterosexual Women. 2011 http://www.cdc.gov/hiv/prep/femprep.htm

Centers for Disease Control and Prevention (CDC). Updated Guidelines for Antiretroviral Postexposure Prophylaxis After Sexual, Injection Drug Use, or Other Non-occupational Exposure to HIV – United States. 2016. Available from: https://stacks.cdc.gov/view/cdc/38856

Choopanya K, Martin M, Suntharasamai P et al. Antiretroviral prophylaxis for HIV infection in injecting drug users in Bangkok, Thailand (the Bangkok Tenofovir Study): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2013;331:2083–90.

Ciesielski C, Metler P. Duration of time between exposure and seroconversion of healthcare workers with occupationally acquired infection with human immunodeficiency virus. Am J Medicine. 1997;102(5B):115–6.

Cohen MS, Hoffman IF, Royce RA et al. Reduction of concentration of HIV-1 in semen after treatment of urethritis: implications for the prevention of sexual transmission of HIV-1. Lancet 1997;349:1868–73.

Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, et al. Prevention of HIV-1 Infection with Early Antiretroviral Therapy. N Engl J Med 2011;365:493–505

Connor EM, Sperling RS, Gelber R et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. N Engl J Med 1994;331:1173–80.

Coombs RW, Reichelderfer PS, Landay AL. Recent observations on HIV type 1 infection in the genital tract of men and women. AIDS 2003;17(4):455–80.

Cordes C, Moll A, Kuecherer C et al. HIV transmission despite HIV post-exposure prophylaxis after non-occupational exposure. (correspondence) AIDS 2004;18(3): 582–4.

Cu-Uvin S, Delong AK, Venkatesh KK et al. Genital tract HIV-1 RNA shedding among women with below detectable plasma viral load. AIDS 2010:24:2489–97.

de Gruttola V, Fineberg HV. Estimating prevalence of HIV infection: considerations in the design and analysis of a national seroprevalence survey. JAIDS 1989;2(5):472–80.

del Romero J, Marincovich B, Castilla J et al. Evaluating the risk of HIV transmission through unprotected orogenital sex. AIDS 2002;16(9):1296–7.

Department of Health (National HIV Testing Policy Expert Reference Committee – a joint working party of the Blood Borne Virus and STI Subcommittee (BBVSS) and the Ministerial Advisory Committee on Blood Borne Viruses and Sexually Transmissible Infections (MACBBVS). 2011 National HIV Testing Policy. Commonwealth of Australia, Department of Health. Canberra 2013. Accessed at: http://www.testingportal.ashm.org.au/resources/2011_National_HIV_Testing_Policy_v1.3.pdf

Department of Health. Seventh National HIV Strategy 2014 - 2017. Commonwealth of Australia, Department of Health. Canberra 2014. Accessed at: http://www.health.gov.au/internet/main/publishing.nsf/Content/8E87E65EEF535B02CA257BF0001 A4EB6/$File/HIV-Strategy2014-v3.pdf

Desai K, Boily M-C, Garnett GP et al. The role of sexually transmitted infections in male circumcision effectiveness against HIV - insights for clinical trial simulation. Emerg Themes Epidemiol. 2006;3(19).

de Vincenzi I. A longitudinal study of human immunodeficiency virus transmission by heterosexual partners. European Study Group on Heterosexual Transmission of HIV. N Engl J Med

1994;331:341–6.

Diaz-Brito V, León A, Knobel H, et al; DATEMPEP study group. Post-exposure prophylaxis for HIV infection: a clinical trial comparing lopinavir/ritonavir versus atazanavir each with zidovudine/lamivudine. Antivir Ther. 2012;17:337–46.

Do A, Ciesielski C, Metler R et al. Occupationally acquired human immunodeficiency infection (HIV) infection: National case Surveillance Data during 20 years of the HIV epidemic in the United States. Inf Control Hosp Epi 2003;24(2):86–96.

Doyle T, Geretti AM. Low level viraemia on HAART: significance and management. Current Opinion in Infectious Diseases 2012;25:17–25.

Easterbrook PJ, Waters A, Murad S, et al. Epidemiological risk factors for hypersensitivity reactions to abacavir. HIV Med. 2003;4:321–4.

European Study Group on Heterosexual Transmission of HIV. Comparison of female to male and male to female transmission of HIV in 563 stable couples. BMJ 1992(Mar28);304:809–13.

Fideli US, Allen SA, Musconda R et al. Virologic and immunologic determinants of heterosexual transmission of human immunodeficiency virus type 1 in Africa. AIDS Res Hum Retro 2001;17(10):901–10.

Fiore JR, Zhang YJ, Bjorndal A et al. Biological correlates of HIV-1 heterosexual transmission. AIDS 1997;11:1089–94.

Fleming D, Wasserheit J. From epidemiological synergy to public health policy and practice: the contribution of other sexually transmitted diseases to sexual transmission of HIV. Sex Trans Inf 1999;75(1):3–17.

Ford N, Shubber Z, Calmy A et al. Choice of antiretroviral drugs for postexposure prophylaxis for adults and adolescents: a systematic review. CID 2015; 60(S3): S170-6.

Ford N, Venter F, Irvine C et al. (b) Starter Packs versus full prescription of antiretroviral drugs for postexposure prophylaxis: a systematic review. Clin Infect Dis 2015;60:S182-6.

Foster R, McAllister J, Read TR et al. Single-tablet emtricitabine-rilpivirine-tenofovir as HIV post-exposure prophylaxis in men who have sex with men. Clin Infect Dis 2015; 61: 1336–41.

Fournier S, Maillard A, Molina J-M. Failure of postexposure prophylaxis after sexual exposure to HIV. (correspondence) AIDS 2001;15(3):430.

Galvin SR, Cohen MS. The role of sexually transmitted diseases in HIV transmission. Nature Reviews Microbiology 2004;2:33–42.

Garcia-Lerma JG, Cong ME, Mitchell J et al. Intermittent prophylaxis with oral truvada protects macaques from rectal SHIV infection. Science Translational Medicine 2010;14:14ra4.

Garcia-Lerma J, Otten R, Qari S et al. Prevention of rectal SIV transmission in macaques by tenofovir/emtricitabine combination [Abstract]. Presented at the 13th Conference on Retroviruses and Opportunistic Infections,2006; Denver, USA, #32LB.

Ghys PD, Fransen K, Diallo MO et al. The associations between cervicovaginal HIV shedding, sexually transmitted diseases and immunosuppression in female sex workers in Abidjan, Côte d'Ivoire. AIDS 1997;11:F85-F93.

Grant RM, Lama JR, Anderson PL et al. Preexposure Chemoprophylaxis for HIV Prevention in Men Who Have Sex with Men. N Engl J Med 2010;363:2587–99.

Gray RH, Wawer MJ, Brookmeyer R et al. Probability of HIV-1 transmission per coital act in monogamous, heterosexual, HIV-1 discordant couple in Rakai, Uganda. Lancet 2001(April14);357:1149–53.

Gray R, Wawer M, Thoma M et al. Male circumcision and risks of female HIV and sexually transmitted infections acquisition in Rakai, Uganda. [Abstract]. Presented at the 13th Conference on Retroviruses and Opportunistic Infections 2006; Denver USA. #128.

Gray RH, Kigozi G, Serwadda D et al. Male circumcision for HIV prevention in men in Rakai, Uganda: a

randomised trial. Lancet 2007:369(9562):657–66.

Gray RH, Serwadda D, Tobian AAR et al. Effects of genital ulcer disease and herpes simplex virus type 2 on the efficacy of male circumcision for HIV prevention: analyses from the Rakai trials. PLoS Med 2009;6(11):e1999187.

Greub G, Maziero A, Burgisser P et al. Spare post-exposure prophylaxis with round-the-clock HIV testing of the source patient. [Letter] AIDS 2001;15(18):2451–2.

Greub G, Gallanta S, Zumb P et al. Spare non-occupational post exposure prophylaxis by active contacting and testing of the source person. AIDS 2002; 16:1171–6.

Gruber VA, McCance-Katz EF. Methadone, Buprenorphine, and street drugs interactions with antiretroviral medication. Curr HIV/AIDS Rep 2010; 7: 152–160.

Grulich A, Hendry O, Clark E et al. Circumcision and male-to-male transmission of HIV. AIDS 2001;15(9):118–9.

Grulich AE. Epidemiologically targeted post-exposure prophylaxis against HIV: an under-utilized prevention technology. [Editorial] HIV Medicine 2003;4(3):193–4.

Grulich AE, Bavinton BR, Jin F, et al. HIV Transmission in male serodiscordant couples in Australia, Thailand and Brazil. 2015 Conference on Retroviruses and Opportunistic Infections. Seattle, 23–24 February 2015. Abstract 1019LB.

Grulich AE et al. HIV transmission in male serodiscordant couples in Australia, Thailand and Brazil. 2015 Conference on Retroviruses and Opportunistic Infections (CROI 2015), 23-26 February 2015, Seattle. Late breaker poster 1019 LB. http://www.croiconference.org/sessions/hiv-transmission-male-serodiscordant-couples-australia-thailand-and-brazil

Grulich AE, Zablotska I. Commentary: Probability of HIV transmission through anal intercourse. Int J Epidemiol 2010;39:1064–5.

Guay LA, Musoke P, Fleming T et al. Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: HIVNET 012 randomised trial. Lancet 1999;354:795–802.

Guinot D, Ho MT, Poynten IM et al. Cost-effectiveness of HIV nonoccupational post exposure prophylaxis in Australia. HIV Medicine 2009;10(4):199–208.

Gulholm T, Jamani S, Poynten IM & Templeton DJ Non-occupational HIV post-exposure prophylaxis at a Sydney metropolitan sexual health clinic. Sexual Health 2013;10(5):438–41. doi:http://dx.doi.org/10.1071/SH13018

Haidari G, Fidler S,Fox J et al. Acute HIV infection after initiation of post-exposure prophylaxis following sexual exposure: Reasons, challenges and suggested management. HIV Medicine 2015; (Supple 2):23.

Hallett TB, Singh K, Smith JA et al. Understanding the impact of male circumcision interventions on the spread of HIV in Southern Africa. PLoS ONE 2008;3(5):e2212.

Hamers FF, Lot F, Larsen C et al. Cost-effectiveness of prophylaxis following non-occupational exposure to HIV infection in France [Abstract]. Presented at the 8th Conference on Retroviruses and Opportunistic Infections.2001; Chicago USA#230.

Harrington RD, Woodward JA, Hooton TM, Horn JL. Life-threatening interactions between HIV-1 protease inhibitors and the illicit drugs MDMA and gammahydroxybutyrate. Arch Intern Med 1999; 159: 2221–4.

Hawkins D, Asboe D, Barlow K et al. Seroconversion to HIV-1 following a needlestick injury despite combination post-exposure prophylaxis. JID 2001;43:12–18.

Henderson DK. HIV in the healthcare setting. In: Mandell GL, Bennett JE, Dolin R, eds. Principles and Practice of Infectious Diseases. 7th ed. New York, NY: Elsevier Churchill Livingstone; 2009:3753-770.

Henderson DK, Fahey BJ, Willy M et al. Risk for occupational transmission of human immunodeficiency

virus type-1 associated with clinical exposures. Ann Intern Med 1990;113(10):740–6.

Henry JA, Hill IR. Fatal reaction between ritonavir and MDMA. Lancet 1998;28:1751–2.

Herida M, Larsen C, Lot F et al. Cost effectiveness of the post-exposure prophylaxis for HIV infection in France: 1999 to 2003 [Abstract]. Presented at the 12th Conference on Retroviruses and Opportunistic Infections.2005; Boston USA.

Heuker J, Sonder GJ, Stolte I, Geskus R, & van den Hoek A. (2012). High HIV incidence among MSM prescribed postexposure prophylaxis, 2000-2009: indications for ongoing sexual risk behaviour.AIDS 2012 26(4):505–12. doi:10.1097/QAD.0b013e32834f32d8

Hill A, Balkin A. Risk factors for gastrointestinal adverse events in HIV treated and untreated patients. AIDS Rev. 2009 Jan-Mar;11(1):30–8.

Hu DJ, Dondero TJ, Rayfield MA et al. The Emerging Genetic Diversity of HIV: The Importance of Global Surveillance for Diagnostics, Research, and Prevention. JAMA 1996;275 (3):210–6.

Hu J, Gardner MB, Miller CJ. Simian immunodeficiency virus rapidly penetrates the cervicovaginal mucosa after intravaginal inoculation and infects intraepithelial dendritic cells. J Virol 2000;74(13):6087–95.

Hull P, Mao L, Rossteuscher K, Marion-Landais S, Prestage G, Zablotska I, de Wit J, Holt M. Gay community periodic survey Canberra 2013 [monograph on the internet] Centre for Social Research in Health: UNSW Australia, 2014. [Accessed DEC2015] Available from https://csrh.arts.unsw.edu.au/media/CSRHFile/GCPS_Canberra_2013_report.pdf

Hull P, Mao L, Kolstee J, Duck T, Prestage G, Zablotska I, de Wit J, Holt M. Gay community periodic survey Sydney 2015. [monograph on the internet] Centre for Social Research in Health: UNSW Australia, 2015 [Accessed DEC2015] Available from https://csrh.arts.unsw.edu.au/media/CSRHFile/CSRH_Report__GCPS_Sydney_2015.pdf

Ippolito G, Puro V, Heptonstall J, et al. Occupational human immunodeficiency virus infection in health care workers: worldwide cases through September 1997. Clin Infect Dis. 1999;28:365–83.

Ippolito G, Puro V, Petrosillo N et al. Simultaneous infection with HIV and hepatitis C virus following occupational conjunctival blood exposure [letter]. JAMA 1998;280(1):28.

Irvine C, Egan KJ, Shubber Z, Van Rompay KKA, Beanland RL, & Ford N Efficacy of HIV Postexposure Prophylaxis: Systematic Review and Meta-analysis of Nonhuman Primate Studies. Clin Infect Dis 2015;60(suppl 3):S165-S169. doi:10.1093/cid/civ069

Italian Multicenter Study. The risk of occupational human immunodeficiency virus infection in health care workers. Arch Intern Med 1993(Jun 28);153:1451–58.

Italian Registry of Antiretroviral Postexposure Prophylaxis. Effect of short-course of antiretroviral agents on serum triglycerides of healthy individuals. AIDS 2000;14(15):2407–08.

Jameson DR, Celum CL, Manhart L et al. The association between lack of circumcision and HIV, HSV-2, and other sexually transmitted infections among men who have sex with men. Sex Trans Dis 2010;37(3):147–52.

Jin F, Jansson J, Law M et al. Per-contact probability of HIV transmission in homosexual men in Sydney in the era of HAART. AIDS 2010;24(6):907–13.

Jochimsen EM. Failures of zidovudine postexposure prophylaxis. Am J Med 1997;102:52–5.

Johnson S, Baraboutis JG, Sha BE et al. Adverse effects associated with use of nevirapine in HIV postexposure for 2 health care workers [Letters]. JAMA 2000;284:2722–3.

Joyce MP, Kuhar D, Brooks JT. Occupationally acquired HIV infection by healthcare personnel - United States, 1985–2013. CROI 2015. Seattle, Washington. Poster number 1027.

Kahn JO, Martin JN, Roland ME et al. Feasibility of postexposure prophylaxis (PEP) against human immunodeficiency virus infection after sexual or injection drug use exposure: the San Francisco PEP Study. JID 2001;183(5):707–14.

Kaplan EH. Modeling HIV infectivity: must sex acts be counted? JAIDS 1990;3:55–61.

Kaplan EH, Heimer R. A model-based estimate of HIV infectivity via needle sharing. J Acquir Immun Def Synd 1992;5:1116–18.

Kaplan EH, Heimer R. HIV incidence among New Haven needle exchange participants: updated estimates from syringe tracking and testing data. J Acquir Immun Def Synd 1995;10:175–6.

Katzenstein T, Dickmeiss E, Aladdin H et al. Failure to develop HIV infection after receipt of HIV-contaminated blood and postexposure prophylaxis. Ann Intern Med 2000;133(1):31–4.

Kaul R, Kimani J, Nagelkerke NJ et al. Monthly antibiotic chemoprophylaxis and incidence of sexually transmitted infections and HIV-1 infection in Kenyan sex workers. JAMA 2004;291(21):2555–62.

Kaup FJ, Boga JA, Bruno SF et al. Immunohistochemical detection of simian immunodeficiency virus (SIV) in rectal mucosa of experimentally infected rhesus macaques (Macaca mulatta). Acta Histochemica 2001;103(1):79–88.

Keele BF, Giorig EE, Salazar-Gonzalez JF et al. Identification and characterisation of transmitted and early founder virus envelopes in primary HIV-1 infection. Proceedings of the National Academy of Science USA 2008;105:7552-57.

Knox DC, Darrell TH, Harrigan RP et al. HIV-1 Infection with Multiclass Resistance despite Pre-exposure Prophylaxis (PrEP). Conference on Retroviruses and Opportunistic Infections, Boston, abstract 169aLB, 2016.

Kolodkin-Gal D, Hulot SL, Korioth-Schmitz B et al. Efficiency of cell-free and cell-associated virus in mucosal transmission of human immunodeficiency virus type 1 and simian immunodeficiency virus. Journal of Virology 2013;87:13589–97.

Kuhar D, Henderson D, Struble K, Heneine W, Thomas V, Cheever L, Gomaa A, Panlilio A, and US Public Health Service Working Group. (2013). Updated US Public Health Service Guidelines for the Management of Occupational Exposures to Human Immunodeficiency Virus and Recommendations for Postexposure Prophylaxis. Infection Control and Hospital Epidemiology, 34(9), 875-892. doi: 10.1086/672271

Lacombe K, Daguenel-Nguyen A, Lebeau V et al. Determinants of adherence to non-occupational post HIV exposure prophylaxis.[Letter] AIDS 2006;20(2):291–4.

Larsen C, Lot F, Basselier B et al. Prescription and toxicity of postexposure prophylaxis for occupational and non-occupational exposure to HIV in France [Abstract]. Presented at the 2nd IAS Conference on Pathogenesis and Treatment, Paris, France 2003.

Lee E, Lea T, Mao L, Hanan L, O'Brien R, Narciso L, Prestage G, Zablotska I, de Wit J, Holt M. Gay community periodic survey Adelaide 2014 [monograph on the internet] Centre for Social Research in Health: UNSW Australia, 2015. [Accessed DEC2015] Available from https://csrh.arts.unsw.edu.au/media/CSRHFile/GCPS_2014_Adelaide_combined_new_1.pdf

Lee E, Mao L, Atkinson C, Brown S, Warner M, Heywood J, Prestage G, Zablotska I, de Wit J, Holt M,. Gay community periodic survey Queensland 2014. [monograph on the internet] Centre for Social Research in Health: UNSW Australia, 2015a. [Accessed DEC2015] Available from https://csrh.arts.unsw.edu.au/media/CSRHFile/GCPS_Queensland_2014_web_FINAL.pdf

Lee E, Mao L, von Doussa H, Batrouney C, West M, Prestage G, Zablotska I, de Wit J, Holt M. Gay community periodic survey Melbourne 2015. [monograph on the internet] Centre for Social Research in Health: UNSW Australia, 2015b. [Accessed DEC2015] Available from https://csrh.arts.unsw.edu.au/media/CSRHFile/1_GCPS_2015_Melbourne_FINAL.pdf

Lee E, Hull P, Mao L, Comfort J, Chanmugam M, Laing S, Fragomeni S, Prestage G, Zablotska I, de Wit J, Holt M, Gay community periodic survey Perth 2014. [monograph on the internet] Centre for Social Research in Health UNSW Australia, 2015c. [Accessed DEC2015] Available from https://csrh.arts.unsw.edu.au/media/CSRHFile/GCPS_2014_Perth_report.pdf

Le Grand R, Vaslin B, Larghero J et al. Post-exposure prophylaxis with highly active antiretroviral therapy could not protect macaques from infection with SIV/HIV chimera. AIDS 2000;14(12):1864–66.

Leynaert B, Downs A, de Vincenzi I. Heterosexual transmission of HIV. Am J Epid 1998;148(1):88–96.

Londish GJ, Templeton DJ, Regan DR et al. Minimal impact of circumcision on HIV acquisition in men who have sex with men. Sex Health 2010;7:464–70.

Lorello G, la Port C, Pilon R et al. Discordance in HIV viral loads and antiretroviral drug concentrations comparing semen and blood plasma. HIV Medicine 2009;10:548-54.

Low-Beer S, Weber AE, Bartholomew K et al. A reality check: the cost of making post-exposure prophylaxis available to gay and bisexual men at high sexual risk. [Letter] AIDS 2000 Feb 18;14(3):325–6.

Luzzati R, Crosato IM, Mascioli M et al. Galactorrhoea and hyperprolactinaemia associated with HIV postexposure chemoprophylaxis [correspondence]. AIDS 2002;16(9):1306–7.

Maldarelli F, Palmer S, King MS et al. ART suppresses plasma HIV-1 RNA to a stable set point predicted by pretherapy viraemia. PLoS Pathogens 2007;3:e46

Mandelbrot L, Kermarrec N, Marcollet A et al. Case report: nucleoside-induced lactic acidosis in the third trimester of pregnancy [correspondence]. AIDS 2003;17(2):272–3.

Martin JN, Roland ME, Bamberger JD et al. Post-exposure prophylaxis (PEP) for sexual exposure to HIV does not lead to increases in high risk behaviour: the San Francisco PEP Project [Abstract]. Presented at the 8th Conference on Retroviruses and Opportunistic Infections, 2001; Chicago, USA. #224.

Mastro T, de Vincenzi I. Probabilities of sexual HIV-1 transmission. AIDS 1996;10(SA):S75-S82.

Mayer KH, Goldhammer H, Cohen D et al. Enhanced tolerability and adherence using Tenofovir/3TC for non-occupational post-exposure prophylaxis (NPEP). Presented at XV International AIDS Conference 2004. Bangkok, Thailand.

Mayer K, Mimiaga MJ, Cohen D et al. Tenofovir DF plus lamivudine or emtricitabine for nonoccupational postexposure prophylaxis (NPEP) in a Boston community health centre. J Acquir Immune Defic Syndr 2008; 47: 494–9.

Mayer KH, Mimiaga MJ, Gelman M, Grasso C. Raltegravir, Tenofovir DF and Emtricitabine for postexposure prophylaxis to prevent the sexual transmission of HIV: safety, tolerability and adherence. J Acquir Immune Defic Syndr 2012; 59:354–359.

McAllister J and Carr A. Should a protease inhibitor be standard of care for HIV postexposure prophylaxis? (correspondence). AIDS 2011;25:721.

McAllister J, Read P, McNulty A, Tong WWY, Ingersoll A, Carr A. Raltegravir-emtricitabine-tenofovir as HIV nonoccupational post-exposure prophylaxis in men who have sex with men: safety, tolerability and adherence. HIV Med, 2013;15:13-22.

McAllister J, Towns J, McNulty A et al. Dolutegravir with tenofovir disoproxil fumarate-emtricitabine as HIV post-exposure prophylaxis in gay and bisexual men. 21st International AIDS Conference, Durban July 18-22b 2016. WEPEC231

Merchant RC. Nonoccupational HIV postexposure prophylaxis: a new role for the emergency department. Ann Emerg Med 2000;36(4):366–75.

Miller RJ, Cairns JS, Bridges S et al. Human immunodeficiency virus and AIDS: insights from animal lentiviruses. J Virol 2000;74:7187–95.

Moodley D, Moodley J, Coovadia H et al. A multicenter randomized controlled trial of nevirapine versus a combination of zidovudine and lamivudine to reduce intrapartum and early postpartum mother-to-child transmission of human immunodeficiency virus type 1. JID 2003;187:725–35.

Moore RD, Wong WM, Keruly JC, et al. Incidence of neuropathy in HIV-infected patients on monotherapy versus those on combination therapy with didanosine, stavudine and hydroxyurea. AIDS. 2000;14:273-\–8.

Musicco M, Lazzarin A, Nicolosi A et al. Antiretroviral treatment of men infected with human immunodeficiency virus type 1 reduces the incidence of heterosexual transmission. Arch Intern Med 1994(Sep12);154:1971–6.

Nagot N, Ouedraogo A, Mayaud P et al. Effect of HSV-2 suppressive therapy on HIV-1 genital shedding and plasma viral load: at proof of concept randomized double-blind placebo controlled trial (ANRS 1285 trial) [Abstract]. Presented at the 13th Conference on Retroviruses and Opportunistic Infections 2006; Denver USA, #787.

National Centre in HIV Epidemiology and Clinical Research. (2010) HIV, viral hepatitis and sexually transmissible infections in Australia Annual Surveillance Report 2010. National Centre in HIV Epidemiology and Clinical Research, The University of New South Wales, Sydney, NSW. http://www.nchecr.unsw.edu.au

National Centre in HIV Social Research. University of NSW. 2006. http://nchsr.arts.unsw.edu.au/publications/

National Health and Medical Research Council. How to review the evidence: systematic identification and review of the scientific literature. Commonwealth of Australia. 2000.

Nelson KE, Eiumtrakel S, Celentano D et al. The association of herpes simplex virus type 2 (HSV-2), Haemophilus ducreyi and syphilis with HIV infection in young men in northern Thailand. JAIDS 1997;16:293–300.

New York State Department of Health AIDS Institute. HIV post-exposure prophylaxis for children beyond the Perinatal period, New York State Department of Health AIDS Institute, NY, 2010. Available at: http://www.hivguidelines.org/clinical-guidelines/post-exposure-prophylaxis/hiv-post-exposure-prophylaxis-for-children-beyond-the-perinatal-period/

Nielsen-Saines K, Watts HD, Veloso VG et al. Three postpartum antiretroviral regimens to prevent intrapartum HIV infection. N Engl J Med 2012; 366:2368–79.

Oldenburg CE, Jain S, Mayer KH, & Mimiaga MJ. . Post-exposure prophylaxis use and recurrent exposure to HIV among men who have sex with men who use crystal methamphetamine. Drug and Alcohol Dependence 2015;146:75-80. doi:http://dx.doi.org/10.1016/j.drugalcdep.2014.11.010

Otten RA, Smith DK, Adams DR et al. Efficacy of postexposure prophylaxis after intravaginal exposure of pig-tailed macaques to a human-derived retrovirus (human immunodeficiency virus type 2). J Virol 2000;74:9771–5.

Page-Shafer K, Veugelers PJ, Moss AR et al. Sexual risk behavior and risk factors for HIV-1 seroconversion in homosexual men participating in the Tricontinental Seroconverter Study, 1982-1994. Am J Epidemiol 1997;146(7):531–42.

Parkin JM, Murphy M, Anderson J et al. Tolerability and side-effects of post-exposure prophylaxis for HIV infection.Lancet 2000;355:722–34.

Patel SM, Johnson S, Belknap SM et al. Serious adverse cutaneous and hepatic toxicities associated with nevirapine use by non-HIV-infected individuals JAIDS 2004;35:120–125.

Pedrana A, Hellard M, Guy R, Wilson K and Stoove M. The difference in self-reported and biological measured HIV prevalence: Implications for HIV prevention. AIDS Behav. 2012 Jan; 16(6):1454-1463.

Penazzato, M., Dominguez, K., Cotton, M., Barlow-Mosha, L., & Ford, N. (2015). Choice of Antiretroviral Drugs for Postexposure Prophylaxis for Children: A Systematic Review. Clinical Infectious Diseases, 60(suppl 3), S177-S181. doi:10.1093/cid/civ110

Peng B, Tully PJ. Sharps injury and body fluid exposure among health care workers in an Australian tertiary hospital. Asia-Pacific Journal of Public Health. 2008;20:139-47.

Perisse ARS, Shechter M, Blattner W. Association between male circumcision and prevalent HIV infections in Rio de Janeiro, Brazil. J Acquir Immun Def Synd 2009;50(4):435–7.

PETRA Study Team. Efficacy of three short-course regimens of zidovudine and lamivudine in preventing early and late transmission of HIV-1 from mother-to-child in Tanzania, South Africa and Uganda (PETRA study): a randomised, double-blind placebo-controlled trial. Lancet 2002;359(9313):1178–86.

Pinkerton SD, Holtgrave DR, Bloom FR. Postexposure treatment of HIV [Letter]. N Engl J Med 1997;337:500–1.

Pinkerton SD, Holtgrave DR. Prophylaxis after sexual exposure to HIV [Letter]. Ann Intern Med 1998;129:671.

Pinkerton SD, Holtgrave DR, Bloom FR. Cost effectiveness of postexposure prophylaxis following sexual exposure to HIV. AIDS 1998a;12(9):1067–78.

Pinkerton SD, Holtgrave DR, Kahn JG. Is post-exposure prophylaxis affordable? [Letter] AIDS 2000;14:325.

Pinkerton SD, Martin JN, Roland ME et al. Cost effectiveness of postexposure prophylaxis after sexual or injection drug exposure to human immunodeficiency virus. Arch Intern Med 2004;164:46–54.

Pinkerton SD, Martin JN, Roland ME et al. Cost-effectiveness of HIV postexposure prophylaxis following sexual or injection drug exposure in 96 metropolitan areas in the United States. AIDS 2004a;18:2065–73.

Postma MJ, Bos JM, de Jong-van den Berg LTW et al. HIV post-exposure prophylaxis: enhancing its pharmaco-economic profile by discriminate prescribing. AIDS 2002;16(8):1177–79.

Powers KA, Poole C. Pettifor AE et al. Rethinking the Heterosexual Infectivity of HIV-1: A Systemic Review and Meta-analysis. Lancet Infect Dis 2008;8(9):553–63.

Poynten IM, Smith DE, Cooper DA et al. The public health impact of widespread availability of non-occupational post-exposure prophylaxis against HIV. HIV Medicine. 2007:8:374–81.

Puro V, Ippolito G. Antiretroviral prophylaxis [Abstract]. Presented at the 6th Conference on Retroviruses and Opportunistic Infections 1999; Chicago, USA,:#212.

Puro V. Post-exposure prophylaxis for HIV infection. Italian Registry of Post-Exposure Prophylaxis. Lancet 2000;355(9214):1556–7.

Puro V, Soldani F, De Carli G et al. Drug-induced aminotransferase alterations during antiretroviral HIV post-exposure prophylaxis. AIDS 2003;17(13):1988–90.

Quinn TC, Wawer MJ, Sewankambo N et al. Viral load and heterosexual transmission of human immunodeficiency virus type 1. N Engl J Med 2000;342(13):921–9.

Quinn T. Circumcision and HIV transmission: the cutting edge. [Abstract]. Presented at the 13th Conference on Retroviruses and Opportunistic Infections 2006; Denver USA #120.

Rabaud C, Bevilacqua S, Beguinot I et al. Tolerability of postexposure prophylaxis with zidovudine, lamivudine and nelfinavir for human immunodeficiency virus. Clin Infect Dis 15 May 2001;32:1494–5.

Rabaud C, Burty C, Valle C et al. Post-exposure prophylaxis of HIV infection: Comparison of the tolerability of 3 PEP regimens [Abstract]. Presented at the XV International AIDS Conference, Bangkok, Thailand, 2004:TuPeB4651.

Rabaud C, Burty C, Grandidier M et al. Tolerability of postexposure prophylaxis with the combination of zidovudine-lamivudine and lopinavir-ritonavir for HIV infection. Clin Infect Dis 2005;40:303–305.

Rich JD, Dickinson BP, Carney JM et al. Detection of HIV-1 nucleic acid and HIV-1 antibodies in needles and syringes used for non-intravenous injection. AIDS 1998;12:2345–50.

Richman KM, Rickman LS. The potential for transmission of human immunodeficiency virus through human bites. JAIDS 1993;6:402–6.

Ridzon R, Gallagher K, Ciesielski C et al. Brief report: Simultaneous transmission of human immunodeficiency virus and hepatitis C virus from a needlestick injury. N Engl J Med 1997; 336(13):919–22.

Rodger A, Bruun T, Weait M, et al. Partners of people on ART - a New Evaluation of the Risks (The PARTNER study): design and methods. BMC Public Health. 2012, 12:296.

Rodger AJ, Cambiano V, Bruum T et al. Sexual activity without condoms and risk of HIV transmission in serodifferent couples when the HIV-positive partner is using suppressive antiretroviral therapy. JAMA. 2016;316:171-81.

Roland M. (2005a) Post exposure prophylaxis following non-occupational exposures. Background paper
for the WHO. 3–5 Sep 2005 http://hivinsite.ucsf.edu/pdf/p01-kb-new/kbr-07-02-07-roland.pdf

Roland ME, Neilands TB, Krone M et al. (2005b) Seroconversion following nonoccupational postexposure
prophylaxis against HIV. Clin Infect Dis 2005;41(Nov 15):1507–13.

Rothenburg R, Scarlett M, del Rio C et al. Oral transmission of HIV. AIDS 1998;12(16):2095–105.

Rottingen JA, Cameron DW, Garnett GP. A systematic review of the epidemiologic interactions between
classic sexually transmitted diseases and HIV. Sex Trans Dis 2001;28(10):579–97.

Royce RA, Sena A, Cates W et al. Current concepts: sexual transmission of HIV. N Engl J Med 1997;
336(15):1072–78.

Safran SA, Mayer KH, Ou SS et al. Adherence to Early Antiretroviral Therapy: Results From HPTN 052, a
Phase III, Multinational Randomized Trial of ART to Prevent HIV-1 Sexual Transmission in
Serodiscordant Couples. J Acquir Immun Def Synd. 2015 Jun 1;69(2):234–40.

Sanchez J, saly Rosas VG, Hughes JP et al. Male circumcision and risk of HIV acquisition among men
who have sex with men. AIDS 2011;25:519–23.

Sarner L, Fakoya A. Acute onset lactic acidosis and pancreatitis in HIV-1 pregnant women taking antiviral
medication. Sex Transm Inf Feb 2002;78:58–9.

Savage J and the National PEP Guidelines Reference Group. Literature review for the National Guidelines
for post-exposure prophylaxis after non-occupational and occupational exposure to HIV (Revised).
Australasian Society for HIV Medicine. Sydney, NSW, 2011 Available at www.ashm.org.au/pep-
guidelines.

Schechter M, Lago M, Moriera R et al. Behavioral impact of the availability of post-sexual-exposure
chemoprophylaxis (PEP) for HIV: a prospective cohort study [Abstract]. Presented at the 1st IAS
Conference of Pathogenesis and Treatment, Buenos Aires, Argentina, 2001. #154.

Schechter M, do Lago R, Mendelsohn AB et al. Behavioral impact, acceptability, and HIV incidence among
homosexual men with access to postexposure chemoprophylaxis for HIV. JAIDS 2004;35(5):519–
25.

Sellier P, Mannioui A, Bourry O, Dereuddre-Bosquet N, Delache B et al. (2010) Antiretroviral Treatment
Start-Time during Primary SIVmac Infection in Macaques Exerts a Different Impact on Early Viral
Replication and Dissemination. Public Library of Science ONE 5(5): e10570.
doi:10.1371/journal.pone.001057

Shaffer N, Chuachoowong R, Mock PA et al. Short-course zidovudine for perinatal HIV-1 transmission in
Bangkok, Thailand: a randomised controlled trial. Lancet 1999(March 6);353:773–80.

Shih C-C, Kaneshima H, Rabin L et al. Postexposure prophylaxis with zidovudine suppresses human
immunodeficiency virus type 1 infection in SCID-hu mice in a time dependent manner. J Infect Dis
1991;163(March):625–6.

Siegfried N, Muller M, Deeks JJ, Volmink J. Male circumcision for prevention of heterosexual acquisition of
HIV in men. Cochrane Database of Systematic Reviews 2009, Issue 2

Smith DK, Herbst JH, Zhang X et al. Condom effectiveness for HIV prevention by consistency of use
among men who have sex with men in the United States. J Acquir Immun Def Synd 2015;68:337–
44.

Smith DK, Taylor A, Kilmarx PH et al. Male circumcision in the United States for the prevention of HIV
infection and other adverse health outcomes: report from a CDC consultation. Public Health Rep.
2010 Jan-Feb;125 Suppl 1:72–82.

Sperling RS, Shapiro DE, Coombs RW et al. Maternal viral load, zidovudine treatment, and the risk of
transmission of human immunodeficiency virus type 1 from mother to infant. N Engl J Med
1996;335:1621–9.

Spira AI, Marx PA, Patterson BK et al. Cellular targets of infection and route of viral dissemination after an
intravaginal inoculation of simian immunodeficiency virus into rhesus macaques. J Exp Med
1996;183(1):215–25.

LITERATURE REVIEW for the National Guidelines for Post-Exposure Prophylaxis after Non-Occupational and Occupational Exposure to HIV (Revised)

Stahl-Hennig C, Steinman RM, Tenner-Racz K et al. Rapid infection of oral mucosal-associated lymphoid tissue with simian immunodeficiency virus. Science 1999; 285(5431):1261–65.

Strathdee A, & Stickman JK. Epidemiology of HIV among injecting and non-injecting drug users: current trends and implications for interventions. Curr HIV/AIDS Rep. 2010;7 99–106.

Sturmer M, Doerr HW, Berger A et al. Is transmission of HIV-1 in non-viraemic serodiscordant couples possible? Antiviral Therapy 2008;13:729-32.

Taylor D, Durigon M, Davis H et al. Probability of a false-negative HIV antibody test result during the window period: a tool for pre- and post-test counselling. Int J STD AIDS 2015;26(4):215-24.

Templeton DJ, Jin F, Prestage GP et al. Circumcision and risk of sexually transmissible infections in a community based cohort of HIV-negative homosexual men in Sydney, Australia. J Infect Dis. 2009;200(12):1813–19.

Templeton DJ. Male circumcision to reduce sexual transmission of HIV. Curr Opin HIV AIDS. 2010 Jul;5(4):344–9.

The Kirby Institute. HIV, viral hepatitis and sexually transmissible infections in Australia Annual Surveillance Report 2014. The Kirby Institute, UNSW, Sydney NSW 2052. Available at: http://www.kirby.unsw.edu.au

The World Health Organization. Guidelines on post-exposure prophylaxis for HIV and the use of co-trimoxazole prophylaxis for HIV-related infections among adults, adolescents and children: Recommendations for a public health approach: December 2014 supplement to the 2013 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. World Health Organization 2014. Available at: http://apps.who.int/iris/bitstream/10665/145719/1/9789241508193_eng.pdf

Thigpen MC, Poloko M, Kebaabetswe PM, Paxton LA et al. Antiretroviral Preexposure Prophylaxis for Heterosexual HIV Transmission in Botswana. N Engl J Med 2012;367:423–34.

Thomas R, Galanakis C, Vezina S et al. Adherence to post-exposure prophylaxis (PEP) and incidence of HIV seroconversion in a major North American cohort. Ref PLOS ONE | DOI:10.1371/journal.pone.0142534 November 11, 2015

Tobain AAR, Serwedda D, Quinn TC et al. Male circumcision for the prevention of HSV-2 and HPV infections and syphilis. N Eng J Med 2009;360:1298–309

Tong WW, McAllister J White PA et al. Transmission of triple-class, drug-resistant HIV-1 in Australia. Intern Med J 2010;40:657-61

Tosini W, Muller P, Prazuck T et al. Tolerability of HIV postexposure prophylaxis with tenofovir/emtricitabine and lopinavir/ritonavir tablet formulation. AIDS 2010; 24 (15):2375–80.

Tsai CC, Follis K, Sabo A et al. Prevention of SIV Infection in Macaques by (R)-9-(2-Phosphonylmethoxypropyl) adenine. Science 1995;270(5239):1197–9.

Tsai CC, Emau P, Follis K et al. Effectiveness of post inoculation PMPA Treatment For Prevention of Persistent SIV Infection Depends Critically on Timing of Initiation and Duration of Treatment. J Virol 1998;72:4265–73.

UNAIDS. (2010) Report on the global AIDS epidemic. http://www.unaids.org/globalreport/Global_report.htm

UNAIDS (2011) AIDSinfo country fact sheets. Retrieved from http://www.unaids.org/en/dataanalysis/tools/aidsinfo/ countryfactsheets/ prior to 25Sep2011

Van der Ende ME, Regez RM, Schreiji et al. Post-exposure prophylaxis. International Journal of STD AIDS 2002;13 Suppl 2:30-34.

van Rompay KK, Marthas ML, Lifson JD et al. Administration of 9-[2-(phosphonomethoxy)propyl] adenine (PMPA) for prevention of perinatal simian immunodeficiency virus infection in rhesus macaques. AIDS Res Hum Retroviruses 1998;14:761–73.

Varghese B, Maher J, Peterman T et al. Reducing the risk of sexual HIV transmission. Sex Trans Dis

2002;29(1):38–43.

Vernazza L, Troiani L, Flapp MJ et al. Potent antiretroviral treatment of HIV infection results in suppression of seminal shedding of HIV. AIDS 2000;14:117–21.

Vidmar L, Poljak M, Tomazic J et al. Transmission of HIV-1 by a human bite. Lancet 1996; 347:1762.

Vitinghoff E, Douglas J, Judson F et al. Per-contact risk of human immunodeficiency virus transmission between male sexual partners. Am J Epid 1999;150(3):306–11.

Wade NA, Birkhead GC, Warren BL et al. Abbreviated regimens of zidovudine prophylaxis and perinatal transmission of the human immunodeficiency virus. NEJM 1998;339:1409–14.

Wahn V, Kramer HH, Voit T et al. A horizontal transmission of HIV infection between two siblings. Lancet 1986;2:694.

Wald A, Link K. Risk of human immunodeficiency virus infection in herpes simplex virus type 2–infected persons: a meta-analysis. JID 2002;185:445–52.

Waldo CR, Stall RD, Coates TJ. Is offering post-exposure prevention for sexual exposures to HIV related to sexual risk behavior in gay men? AIDS 2000;14:1035–9.

Wang SA, Panlilio AL, Doi PA, White AD, Stek M Jr, Saah A. HIV PEP Registry Group. Experience of healthcare workers taking postexposure prophylaxis after occupational HIV exposures: findings of the HIV Postexposure Prophylaxis Registry. Infect Control Hosp Epidemiol 2000;21:780–5.

Watson-Jones D, Weiss HA, Rusizoka M et al. Effect of herpes simplex suppression on incidence of HIV among women in Tanzania. N Engl J Med. 2008;358(15):1560-71. Epub 2008 Mar 12.

Wawer MJ, Gray RH, Sewankambo NK et al. Rates of HIV-1 transmission per coital act, by stage of HIV-1 infection, in Rakai, Uganda. JID 2005(May 1);191:1403–9.

Webster DP. Is HIV post-exposure prophylaxis required following occupational exposure to a source patient who is virologically suppressed on antiviral therapy. HIV Medicine 2015; 16:73-5.

Weiss HA, Hankins CA, Dickson K. Male circumcision and risk of HIV infection in women: a systematic review and meta-analysis. Lancet Inf Dis 2009;9(11):669–77.

Wiboonchutikul, S., Thientong, V., Suttha, P., Kowadisaiburana, B., & Manosuthi, W. (2016). Significant intolerability of efavirenz in HIV occupational postexposure prophylaxis. J Hosp Infect, 92(4), 372-377. doi:10.1016/j.jhin.2015.12.015

Wiktor SZ, Ekpini E, Karon JM et al. Short-course oral zidovudine for prevention of mother-child transmission of HIV-1 in Abidjan, Côte d'Ivoire: a randomized trial. Lancet 1999; 353:781–5.

Wilson DP, Law MG, Grulich AE et al. Relation between HIV viral load and infectiousness: a model-based analysis. Lancet 2008;372(9635):314–20.

Wilson DP. Data are lacking for quantifying HIV transmission risk in the presence of effective antiretroviral therapy. AIDS 2009;23(11):1431–3.

Winston A, McAllister J, Amin J et al. The use of a triple nucleoside-nucleotide regimen for nonoccupational HIV post-exposure prophylaxis. HIV Medicine 2005;6:191–197.

Winter NJ, Taylor S, Workman J et al. Asymptomatic urethritis and detection of HIV-1 RNA in seminal plasma. Sex Trans Dis 1999;75(4):261–3.

Woolley I, Tapley N, Korman TM. Sequential cutaneous drug reactions to protease inhibitors in the context of occupational post-exposure prophylaxis. AIDS 2003;17:1709.

Working Group of the UK Chief Medical Officer's Expert Advisory Group on AIDS. Review of the evidence on risk of HIV transmission associated with oral sex. Department of Health 2000.

Wulfsohn A, Ventner WDF, Schultze D et al. Post-exposure prophylaxis after sexual assault in South Africa [Abstract]. Presented at the 10th Conference on Retroviruses and Opportunistic Infections 2003; Boston USA.

Yerly S, Kaiser L, Race E et al. Transmission of antiretroviral-drug-resistant HIV–1 variants. Lancet Aug 28 1999;354:729–33.

Zheng W, Smith D, Kippax S, Grulich A. Epidemiologically targeted non-occupational post-exposure prophylaxis (NPEP) in Australia, 1998–2002 [Abstract]. Presented at the 14th ASHM Conference, 2002. Retrieved from www. ashm.org. au/uploads/148c.ppt, June 2008

Zhu T, Wang N, Carr A et al. Genetic characterization of human immunodeficiency virus type 1 in blood and genital secretions: evidence for viral compartmentalization and selection during sexual transmission. J Virol 1996;70:3068–107.

Appendix

Membership of the National PEP Guidelines Expert Reference Group

Name	Representation
Jude Armishaw	CNC, Victorian NPEP Service, VIC
David Baker	GP s100 Prescriber, East Sydney Doctors, NSW
Katherine Brown	Sexual Health Physician, Port Kembla Hospital, NSW
John Dyer	Infectious Diseases Physician, Fiona Stanley Hospital, WA
Paul Gaudry	Fellow of the Australasian College of Emergency Medicine
Dean Gloede	Communicable Disease Control Branch (CDCB), SA Department for Health and Ageing, SA
Andrew Grulich (until June 2016)	HIV Epidemiology and Prevention Program, The Kirby Institute, NSW
Manoji Gunathilake	Sexual Health Physician, Department of Health and Families, NT
Mihaela Ivan	Sexual Health and Viral Hepatitis Team, Department of Health, VIC
Sue Laing	Sexual Health & Blood-borne Virus Program, Department of Health, WA
Russell Levy	Director of Pharmacy, Royal Prince Alfred Hospital, NSW
John McAllister	CNC, NPEP Service, St Vincent's Hospital, NSW
Lea Narciso	CDCB, SA Department for Health and Ageing, SA
Louise Owen	Director, Statewide Sexual Health Service, TAS
Cheryn Palmer	Sexual Health Physician, Princess Alexandra Hospital, QLD
Anna Pierce	Infectious Diseases Physician, Victorian NPEP Service, VIC
Mike Seah	GP s100 Prescriber, ACT
Ben Wilcock	Australian Federation of AIDS Organisations (AFAO)
Elisabeth Wilkinson	National Policy and Education Division, Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM)