Post exposure prophylaxis (PEP) & non-occupational post exposure prophylaxis (nPEP) after exposure to HIV

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What is an “exposure”? 

Blood or other potentially infectious body fluids/tissue 

- Percutaneous injury 
  - e.g. needle-stick or cut with a sharp instrument
- Contact with mucous membranes 
  - Eye, mouth, genital, anal
- Contact with non-intact skin 
  - Chapped, abraded, dermatitis

→ possibility of HIV transmission : requires consideration of PEP
Potentially infectious body fluids

**“At risk”**
- Blood
- Semen
- Vaginal secretions
- CSF
- Synovial, pleural, peritoneal or pericardial fluid
- Amniotic fluid

**“Not at risk”**
- Tears
- Sweat
- Urine & faeces
- Saliva & sputum
- Nasal secretions
- Vomitus

*unless these secretions contain visible blood*
Case study 1: Brazil 1999

• Source: 31 year old ♂ - HIV status unknown
• Injured: 59 year old widowed mother
• Bit his mother on her hand during a seizure
  – Blood present & mother needed a sutures
• ♂ Dx: Neurotoxoplasmosis & HIV-1 seropositive
• Mother 27 days later: seroconversion
  – Sequencing of tat gene: same HIV-1 quasispecies
• Possibility of transmission by human bite seems to be negligible due to the small number of infecting particles & inhibitors in saliva BUT cases with blood in the biter’s mouth may deserve special attention

Case study 2: West Indies 1999

- Injured: 52 year old policeman
  - HIV ELISA positive & confirmed by WB
  - HBV: immune
  - HCV: antibodies negative

- 3 weeks later
  - HCV seroconversion (EIA, RIBA & HCV RNA)
  - Sexual partner HIV & HCV negative

- 10 weeks earlier: acute mononucleosis-like syndrome

- 3 weeks before onset of illness (13 weeks before positive HIV test)
  - Punched a man in the teeth while making an arrest
  - Noticed 2 wound on his hand, covered with blood, but did not wash it immediately after the incident
  - Few days later: Lymphangitis requiring antibiotic Rx
  - Man known to be infected with HIV-1, HTLV-1, HBV, HCV

- 15 months later: HTLV-1 negative

Case study 3: Italy 2004

• 24 year old ♂ who had receptive anal intercourse 30 hours earlier with an HIV-infected ♂ partner – condom rupture
  – HIV ELISA, WB & DNA PCR negative
  – HCV ELISA & WB negative
• Rx: – AZT + 3TC + indinavir for 4 weeks, refused HBV vaccine
• 3 months later: HIV ELISA negative, but HCV antibodies & RNA positive
• 6 months later: HIV ELISA negative
• 8 months later: HIV ELISA, WB & DNA PCR positive
  – Patient denied any further instances of at risk behaviour
• Suggested that in HIV & HCV co-infection
  – Enhancement of the sexual transmission of HCV
  – Delayed HIV seroconversion
  – PEP failure

Case study 4: South Africa 2000

• At an accident scene near Mooi River toll plaza in 2000
  – A KZN medical attendant treated an HIV positive pedestrian (who later died) when a Gauteng♀’s car was involved in a crash
  – Without taking the necessary precautions, he then treated the Gauteng♀ who had bleeding wounds

• High Court 2009-2010
  – Medical witnesses confirmed that that the Gauteng♀ was probably infected at the time of the accident
  – The judge found that the medical attendant did not take the necessary precautions to prevent infection & held the Health Department liable for any damages

• Universal precautions should **always** be taken when handling any potentially infectious body fluid
Risk of transmission of HIV

- Risk varies widely depending on type of exposure
- For contact with HIV-containing blood, the following infectiousness is assumed
  - Percutaneous: 0.3% (20/6135)
  - Mucosal exposure: 0.1% (1/1143)
  - Intact skin: 0% (0/2712)
  - Non-intact skin: ~0.1% (No confirmed cases, theoretical risk)


Henderson DK. Management of needlestick injuries: a house officer who has a needlestick. JAMA 2012;307:75.
Risk of transmission of HIV

- Risk ↑ with exposure to ↑ number of viral particles e.g.
  - Deep injury
  - A device visibly contaminated with the patient's blood
  - Needle placement in a vein or artery
  - Hollow needle
  - High HIV VL e.g. terminal illness in the source patient, acute seroconversion
Risk of transmission of HIV

• Risk of other types of exposure incompletely defined (observational studies) & risk estimates vary enormously
  – Type of sexual act strongly influences level of risk
  – Several co-factors affect risk e.g.
    • Source HIV VL
    • Mucosal integrity e.g. genital ulcerative disease, genital trauma
    • Immune response at site of transmission e.g. other STIs
    • Circumcision (↓ risk for ♂)

Abers JA, Daskalakis D. Nonoccupational exposure to HIV in adults. Up to date 2013
Risk of transmission of HIV

- Estimated per act risk for acquisition of HIV
  - Blood transfusion: 90%
  - Needle-sharing IVDU: 0.67%
  - Receptive anal intercourse: 0.5% (1/200)
  - Receptive penile-vaginal intercourse: 0.1% (1/1000)
  - Insertive anal intercourse: 0.065% (6/10 000)
  - Insertive penile-vaginal intercourse: 0.05% (5/10 000)
  - Receptive oral intercourse: 0.01% (1/10 000)
  - Insertive oral intercourse: 0.005%

Abers JA, Daskalakis D. Nonoccupational exposure to HIV in adults. Up to date 2013
Background to PEP/nPEP decisions - some basic principles
Evidence for PEP & nPEP

• PEP guidelines lack a substantive evidence base to guide advice i.e. efficacy has NOT been demonstrated by a RCT

• This will not change: RCT of different drug regimens for PEP are not feasible due to the
  – complexity of exposures
  – relative inefficiency of HIV transmission → low event rate
  – inability to ethically have a placebo group

SAHIVCS. PEP guidelines. SA J HIV Med 2008
Evidence for PEP & nPEP

• What guides decision making?
  – Evolving basic science understanding & biological plausibility
  – Supported by animal model data
  – Retrospective case-control studies of occupational PEP utilizing several ARV regimens
  – PMTCT findings

Mayer et al. AIDS 2012;59:354–9
Evidence for PEP & nPEP

• Retrospective case-control studies:
  – Prophylaxis with a single substance (AZT) decrease the probability of an infection by ~80%*

• Transmissions despite the use of PEP
  – CDC: Occupational HIV transmission to HCWs in the US
    • Up to December 2001 – 57 documented cases
    • Jan 2002 to Feb 2011 - only one reported case confirmed
    • 143 possible seroconversions (not documented)

Post exposure management
Immediate management of the exposed area

Do

• Wounds: Wash the exposed site thoroughly with running water
• Eye or mouth exposure: Irrigate with water or saline
• Skin: Wash with soap & water, rinse

Don’t

• Panic
• Put the pricked finger in the mouth
• Squeeze the wound to bleed it
• Scrub the wound
• Use bleach, chlorine, alcohol, betadine, iodine or other antiseptics/detergents on the wound
When to initiation PEP?

• Time is the most important factor
• Goal: Initiate PEP as soon as possible, preferably within 1 to 2 hours of exposure
• Best chance to prevent transmission: ≤24 hours
• ≥72 hours: initiating PEP not reasonable

Determining HIV status of the source

- PEP starter pack should be initiated while awaiting test results
- Can do HIV rapid, but confirm with a HIV 4\textsuperscript{th} generation/combo ELISA
- If the HIV ELISA is negative, but the source patient is at high risk for acute seroconversion: Consider PEP
Ability of screening tests to detect early HIV infection has improved substantially over the past decade.

4th generation Ag/Ab combination assays = detect both IgG & IgM antibodies

Testing & follow up of the injured

• HIV serologic testing
  – @ baseline, 6 weeks, 3 months & 6 months
  – The majority of individuals who seroconvert will do so within the first 3 months

• Testing @ 12 months controversial
  – One case report of delayed seroconversion who acquired both HIV & HCV

• NB: Seek medical advise immediately if any symptoms consistent with acute HIV seroconversion syndrome develops
Risk reduction counselling

• Should the injured acquire HIV infection, HIV can be transmitted to other parties: the greatest risk is the first 6 to 12 weeks
• Until the 6 month HIV ELISA is negative
  – Avoid blood or tissue donation
  – Avoid breast feeding or pregnancy
  – Avoid unprotected sex i.e. abstinence or condom use advised
• Discontinuation of breast feeding advised
Duration of PEP

- Current recommended: 28 days
  - Primate studies with AZT
- The optimal duration of PEP is unknown
2 vs 3 drug regimens

2 Drugs
Less side effects

3 Drugs
More effective
Side effect management

• Incidence of adverse events related to PEP
  – 3 drug regimens: >60%
  – 2 drug regimens containing AZT: >30%
• Adverse effects are generally not severe
• Experience suggests that a substantial proportion of individuals for whom PEP is recommended fail to complete their prescribed regimen
• But: Significantly less side effects with newer ARVs

Mayer et al. AIDS 2012;59:354–9
Side effect management

• A simple, well-tolerated & effective 3-drug PEP regimen could obviate the need to make difficult (and potentially arbitrary) decisions between using 2 drugs or 3 drugs for PEP

Mayer et al. AIDS 2012;59:354–9
Preferred ARV regimens for PEP

Entry inhibitors

NRTIs ← Backbone

NNRTIs

Integrase inhibitors

Integrase

Protease inhibitors

Life cycle of HIV
HIV - PEP

Preferred
Once a day
• Tenofovir (TDF) + emtricitabine (FTC) (Truvada®)

Alternatives
Twice a day
• Stavudine 30mg (d4T) + lamivudine (3TC)
• AZT + 3TC (Combivir®)

Preferred
Twice a day
• Raltegravir 400mg (Insentress®)

Alternatives
Once a day
• Atazanavir (Reyataz®)/ritonavir
• Darunavir (Prezista®)/ritonavir
• Efavirenz 600mg (part of FDC)
• Rilpivirine (part of Complera®)

Twice a day
• Lopinavir/ritonavir (400/100) (Aluvia® 2 tabs)
Current 1st line “recommendation”

- **Truvada®**: 1 tablet once a day
  - Fixed-dose combination of 300mg tenofovir DF (TDF) & 200mg emtricitabine (FTC)

- **Raltegravir**: 1 tablet (400mg) twice a day
Truvada
(Tenofovir + Emtricitabine)

When NOT to take:

• Absolute contra-indications
  – Previous hypersensitivity to the drug(s)

• Relative contra-indications
  – Kidney disease
    • used cautiously with any drugs that can cause renal toxicity (cause kidney problems)
Truvada (Tenofovir + Emtricitabine)

• Side effects
  – Diarrhoea
  – Nausea & vomiting
  – Flatulence
  – Dizziness
  – Fatigue
  – Headache
  – Rash of change in skin colour
  – Insomnia

Emtricitabine
Raltegravir

Advantages

• Site of action
• Safe
• Efficacious
• Excellent tolerability
• Not affected by food
• Rare drug interactions
• For nPEP: ↑ concentrations in the female genital tract than PIs & NNRTIs
• Not current 1st line ART

Disadvantages

• Twice a day dosing
• Side effects
  – Rare cases of a severe systemic-cutaneous reaction resembling Stevens-Johnson syndrome
• Cost
Raltegravir, Tenofovir DF, and Emtricitabine for Postexposure Prophylaxis to Prevent the Sexual Transmission of HIV: Safety, Tolerability, and Adherence

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Acquir Immune Defic Syndr 2012;59:354-9

Presented at International AIDS Society meeting, 2009, Cape Town, South Africa
TDF + FTC + Raltegravir: Most commonly reported symptoms

• Reported mild adverse events which tended to be self-limited, not resulting in drug discontinuation
  – Reported mild adverse events
    • 71.4% of diarrhoea episodes
    • 93.8% of abdominal discomfort
    • 78.6% of fatigue
    • 88.9% of nausea &/or vomiting
    • 86.7% of headaches

Mayer KH, et al. Raltegravir, tenofovir DF, and emtricitabine for PEP to prevent the sexual transmission of HIV: safety, tolerability, and adherence. JAIDS 2012;59:354-9
TDF + FTC + Raltegravir: Regimen completion rates of nPEP users

- Completion rates of TDF-FTC-Raltegravir
  - Comparable to that of historical controls who took TDF & FTC alone
  - Superior to the completion rates of those who used AZT & 3TC plus a PI

- For the participants for whom there was a follow-up visit at 4 weeks
  - 67% reported 100% adherence
  - 7% greater than 95% adherence

Mayer KH, et al. Raltegravir, tenofovir DF, and emtricitabine for PEP to prevent the sexual transmission of HIV: safety, tolerability, and adherence. JAIDS 2012;59:354-9
Efavirenz?

For

• Potent & durable
• Convenient dosing
  – Once a day
  – Fixed drug combination (FDC) tablet – single pill once a day
• Site of action before viral integration

Against

• Pregnancy category D
• Side effects common during 1st moth of administration
  – CNS toxicity
  – Rash
  – Headache
  – Dizziness
• Low resistance barrier
  – Current 1st line for ART - transmitted resistance
Drugs NOT to use

• Abacavir
  – Risk of severe hypersensitivity reactions (5-8%)

• Nevirapine
  – Risk of liver toxicity & Stevens-Johnson syndrome

• Indinavir
  – Require significant water intake and is associated with risk of kidney stones
“Every time I cover HIV prevention in a lecture, it’s always kind of embarrassing to cite the “official” PEP guidelines (non-occupational) and (occupational).”

Paul E Sax • March 1st, 2012

Updated U.S. Public Health Service Guidelines for the Management of Occupational Exposures to HIV and Recommendations for Postexposure Prophylaxis
Antiretroviral Postexposure Prophylaxis After Sexual, Injection-Drug Use, or Other Nonocccupational Exposure to HIV in the United States

Recommendations from the U.S. Department of Health and Human Services
“The alternative choices seem particularly curious (read: don’t do it) today — indinavir/ritonavir or efavirenz for PEP? You’ve got to be kidding me.”

Paul E Sax • March 1\textsuperscript{st}, 2012

So what’s an ID/HIV specialist to do?

• The next round of CDC PEP guidelines is in development

• In the mean time?

Paul E Sax • March 1st, 2012

Southern Africa differs from other regions, particularly in terms of very high HIV & hepatitis B seroprevalence.
PEP program, Harvard

- 1st line empiric therapy, not pregnant, no renal problems
  - Tenofovir/emtricitabine + raltegravir
- 1st line therapy, pregnant (or breast feeding, continues to breast feed though not recommended)
  - Zidovudine/lamuvidine + lopinavir/r
- 1st line therapy, abnormal renal function
  - Zidovudine/lamuvidine + raltegravir
- For any exposure to known infected person
  - ART to be selected by HIV expert

Sigal Yawetz, Assistant Professor, Harvard Medical School, Brigham & Women's Hospital, Division of Infectious Disease
From Up to date team of specialists

• 1\textsuperscript{st} empiric therapy, not pregnant, no renal problems
  – Tenofovir/emtricitabine + raltegravir
  – Tenofovir/emtricitabine + ritonavir boosted atazanavir
  – Tenofovir/emtricitabine + ritonavir boosted darunavir

• 1\textsuperscript{st} line therapy, pregnant (or breast feeding)
  – Tenofovir/emtricitabine + raltegravir
  – Zidovudine/lamuvidine + lopinavir/r

• 1\textsuperscript{st} line therapy, abnormal renal function
  – Zidovudine/lamuvidine + raltegravir
  – Stavudine/lamuvidine + raltegravir

John G Bartlett, Professor of Medicine, Johns Hopkins University
David J Weber, Professor of Medicine, University of North Carolina
PEP for drug resistant virus

• If no resistance testing is available, an HIV specialist can often predict which mutations may be present if the source patient has virologic failure on the current regimen

• This is particularly helpful since results from resistance testing performed after exposure will not be available soon enough to affect the choice of PEP
PEP for drug resistant virus

• General principles
  – History of drug resistance, but viral suppression on current ART
    • PEP regimen using the same medications or medications with similar patterns of susceptibility
  – On ART with detectable VL
    • Choose other medications that are unlikely to show cross-resistance
  – Resistant strains that were documented in the past on a prior regimen are less relevant for drug selection for PEP since these probably make up only the minority species in the source patient
PEP for children?

• Not many guidelines available
• Most recent:

Guideline Summary NGC-8028
Guideline Title
HIV post-exposure prophylaxis for children beyond the perinatal period.

Bibliographic Source(s)
### Table: Recommended Regimens For Pediatric Post-Exposure Prophylaxis

| Children >6 months-13 years of age and >10 kg<sup>b</sup> | Zidovudine 10 mg/mL syrup
| | 9 mg/kg q12h, up to 300 mg PO twice daily  
| **Plus** | Lamivudine 10 mg/mL syrup
| | 4 mg/kg q12h, up to 150 mg PO twice daily  
| **Plus** | Lopinavir/ritonavir<sup>c</sup> 80/20 mg per mL elixir
| | Lopinavir 10 mg per kg/RTV 2.5 mg per kg twice daily,  
| | Up to 400/100 mg (5 mL) PO twice daily  
| For those who cannot swallow pills |  

| Adolescents ≥13 years of age | Zidovudine 300 mg PO twice daily + Lamivudine 150 mg PO twice daily  
| | [may administer as Combivir 1 tablet PO twice daily]  
| **Plus** | Tenofovir<sup>d</sup> 300 mg PO once daily  
| **OR<sup>e</sup>** | Zidovudine 300 mg PO twice daily  
| **Plus** | Emtricitabine 200 mg PO once daily + Tenofovir<sup>d</sup> 300 mg PO once daily  
| | [may administer as Truvada<sup>d</sup> 1 tablet PO once daily]  

<sup>a</sup> For specific on-label dosing, please consult the product literature.  
<sup>b</sup> Administer within 72 hours of last possible exposure  
<sup>c</sup> Lopinavir/ritonavir 80/20 mg per mL elixir  
<sup>d</sup> Tenofovir disoproxil fumarate 300 mg per tablet  
<sup>e</sup> Patients may need to be monitored closely for signs of renal dysfunction and other adverse effects  

**PEP for children?**
“Principles around exposure for children are biologically similar to those for adults”
Red Cross Children’s Hospital, Cape Town

• After sexual assault in children:
  – Twice a day regimen
    • Zidovudine 180 mg/m² body surface area (BSA) plus
    • Lamivudine 4 mg/kg plus
    • Lopinavir/ritonavir 230 mg/m² BSA
  – All patients are given enough medication for 28 days at discharge
    • 22.6% of patients return for all their follow up visits
    • 39.6% did not return for any scheduled follow up visits

PEP for children?

- PEP options may also include tenofovir & raltegravir in future
  - Paediatric formulations (syrup, granules or chewable tablets) are FDA approved in the US, but not yet MCC approved in South Africa
    - Tenofovir FDA approved from age 2 years / >10 kg
    - Raltegravir FDA approved from age 2 years/ >10 kg
  - But: More safety data in children probably needed before generally used for first line PEP

- In the mean time some experts use abacavir (ABC) as an alternative in children if AZT cannot be used
Until we have new guidelines.....

PEP