PEP Guidelines

Michelle Moorhouse

20 Jun 2015

DISCLAIMERS AND WARNINGS

Disclaimer: different roles
Warnings: GL very dry topic!

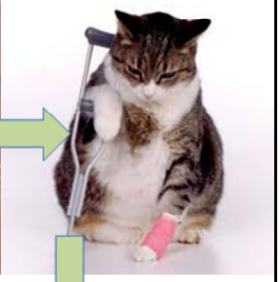
Discussion points

- GL development process
- Background / underlying philosophy
- Recommendations
- Should I give ARVs?
- Which ARVs?
- Risk versus benefit
- Investigations
- Other considerations

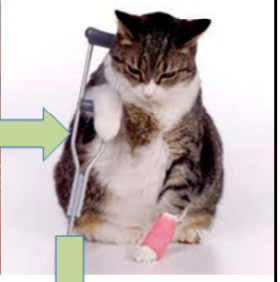
- Topics selected reflect areas of significant change, new sections or areas that may have been clarified
- Where evidence presented, evidence that was available at time guidelines were updated

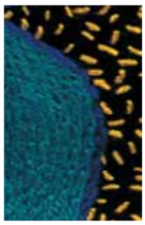
- Question I am often confronted with – are GLs absolute rules or recommendations?
- Answer: depends, several factors which include your qualifications, scope of practice and experience
- Example: experienced NIMART nurse; inexperienced junior doctor

Process for GL development



Process for GL development

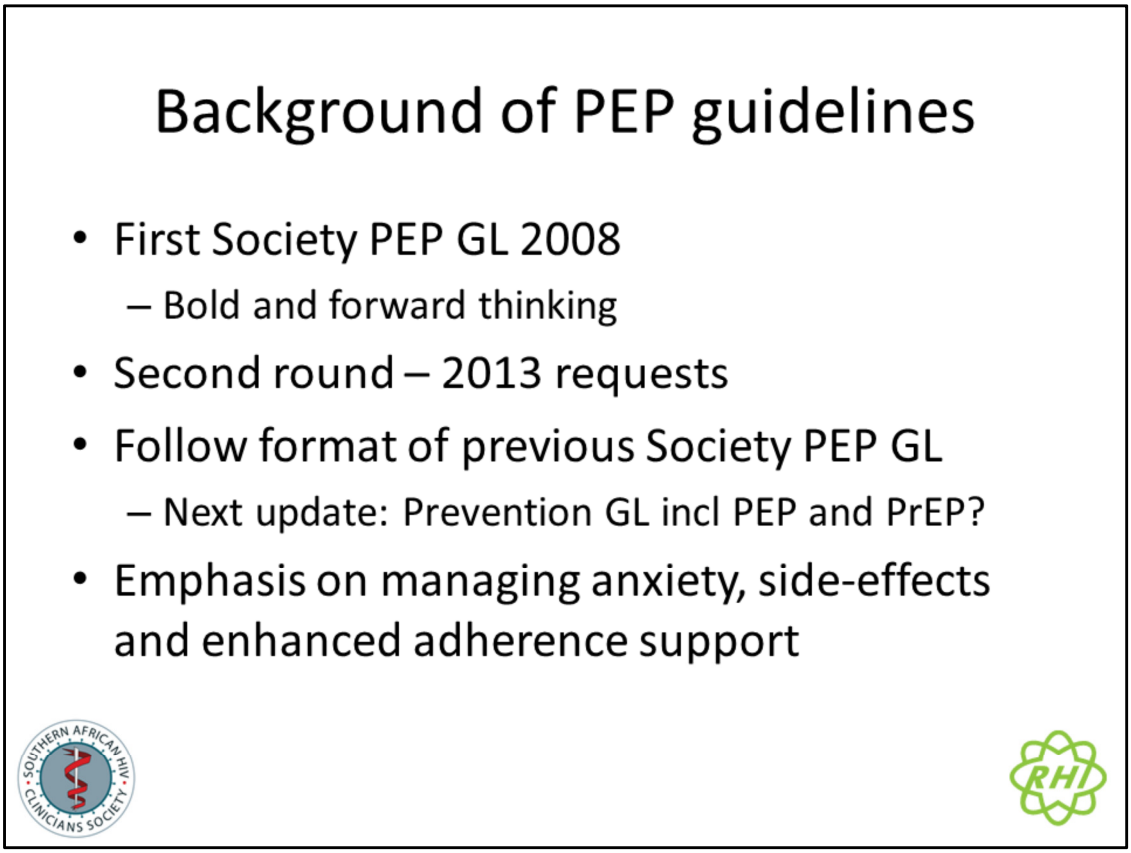




GUIDELINES

POST-EXPOSURE PROPHYLAXIS

WINTER 2008 — THE SOUTHERN AFRICAN JOURNAL OF HIV MEDICINE

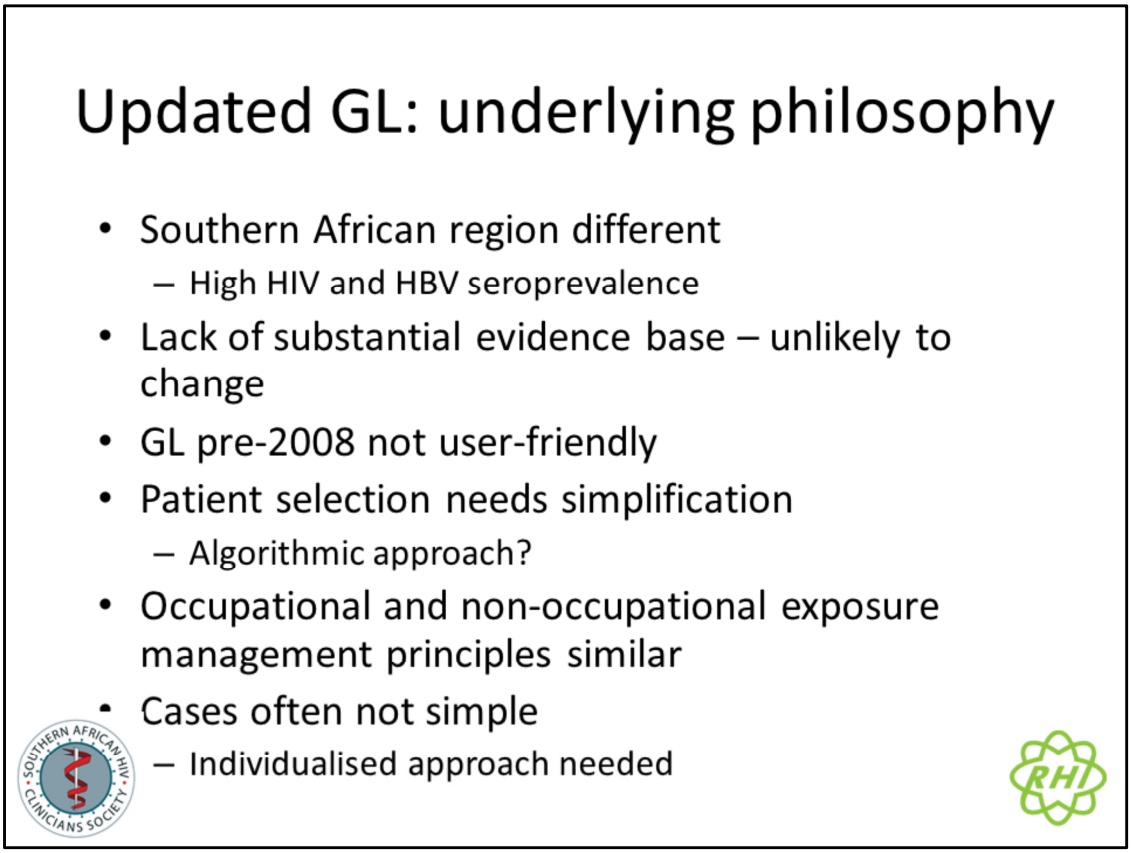


- 2008: first Society PEP GLs by SA/MM
    - No distinction occupational versus non-occupational (SW with burst condom versus medical student?)
    - 3 drugs
    - All exposures treated
- WHO now followed suit WRT occupational versus non-occupational(GL published Dec 14)
- DOH GLs
    - Risk stratification
    - 2 or 3 drugs
    - In EDL; recently updated

Background of PEP guidelines

- DOH
  - Original GL 1993: AZT tds + IDV
  - Later AZT/3TC
  - Now in EDL: TDF/FTC + ATV/r OR LPV/r
- WHO end 2014
  - TDF + 3TC/FTC + LPV/r OR ATV/r (adults)
  - AZT + 3TC + LPV/r (children ≤10 years)
- Alignment with principles of WHO GL
  - Promote simplification
  - Harmonisation across guidelines
  - Specific adherence support

- 2008: first Society PEP GLs by SA/MM
  - No distinction occupational versus non-occupational (SW with burst condom versus medical student?)
  - 3 drugs
  - All exposures treated
- WHO now followed suit WRT occupational versus non-occupational(GL published Dec 14)
- DOH GLs
  - Risk stratification
  - 2 or 3 drugs
  - In EDL; recently updated



- Southern Africa differs from other regions, particularly in terms of very high HIV and HBV seroprevalence.
- PEP guidelines lack a substantive evidence base to guide advice. It is unlikely that this will change considerably, as randomised studies of different drug regimens for PEP are not feasible owing to the complexity of exposure, low event rate, and inability to ethically have a placebo group. Evolving basic science understanding, along with further studies on animals and PMTCT findings, will continue to guide policy makers. In addition, data from PrEP studies will also provide valuable data relevant to PEP interventions.
- PEP guidelines prior to the SAHIVCS 2008 PEP guideline were not user friendly and rarely acknowledged the complex range of situations that occur with HIV.
- Selecting patients for appropriate PEP administration must be simplified. Algorithmic approaches for antiretroviral treatment (ART) regimens have simplified antiretroviral management at the treatment and management levels. The same approach is possible for PEP regimens in this region.
- The approach to occupational, sexual and other forms of HIV exposure (bites, assaults, trauma, injecting drug use, etc.) is similar.
- Cases of exposure are often not simple, do not lend themselves to simple categorisation, and require an individualised approach. However, concepts to guide the attending clinician are relatively simple and allow an effective intervention in most cases.

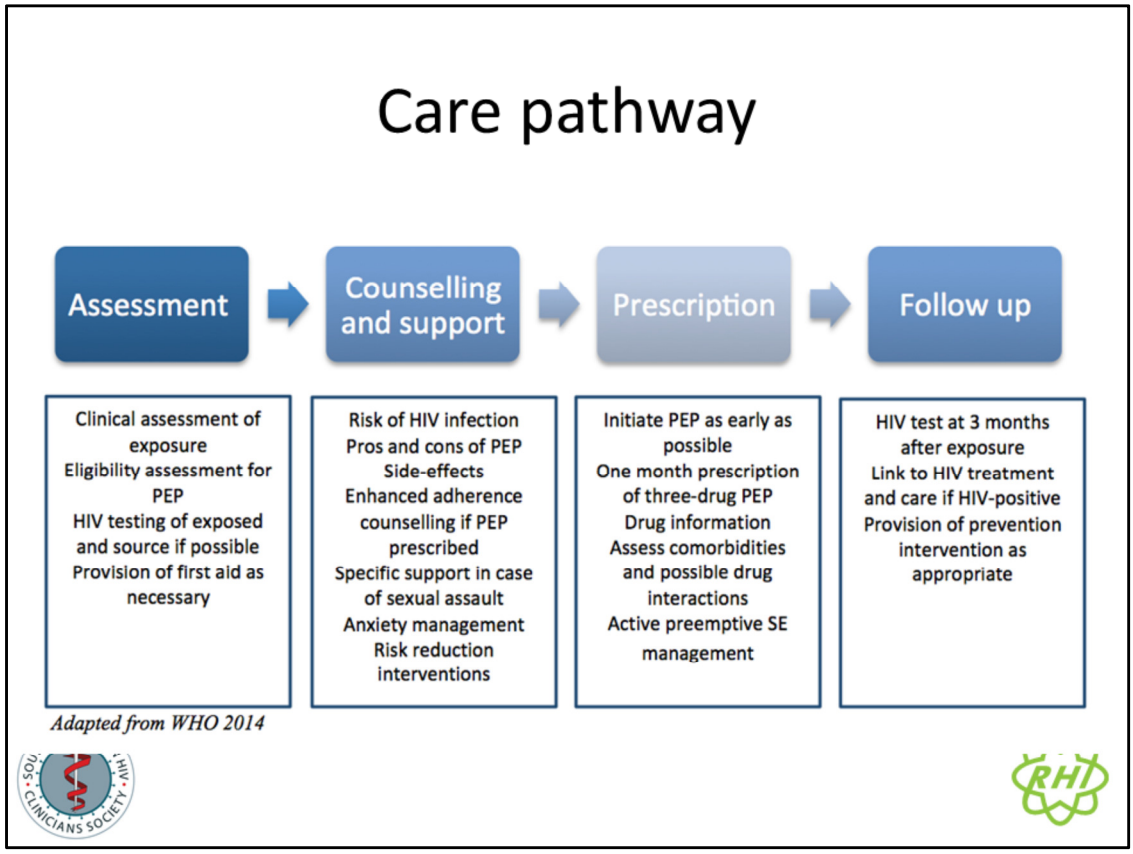
Summary of PEP recommendations

Number of ARVs
Should contain 3 drugs
Preferred regimen for adults and adolescents
TDF + 3TC/FTC (preferably as FDC) is preferred **backbone** RAL is preferred **third drug** (except in pregnancy: ATV/r preferred) **Alternative** third drugs: ATV/r; LPV/r; DRV/r or EFV
Preferred regimen for children ≤35kg or unable to swallow tablets
AZT + 3TC is preferred backbone in children ≤35kg (if AZT poorly tolerated, use d4T) RAL is preferred third drug in children where available (if no RAL, use LPV/r)
Prescribing frequency
Full month at initial assessment. Avoid starter packs
Frequency of follow up
Initial assessment; 2 weeks, 6 weeks and 3 months post exposure
Adherence support
Enhanced adherence counselling

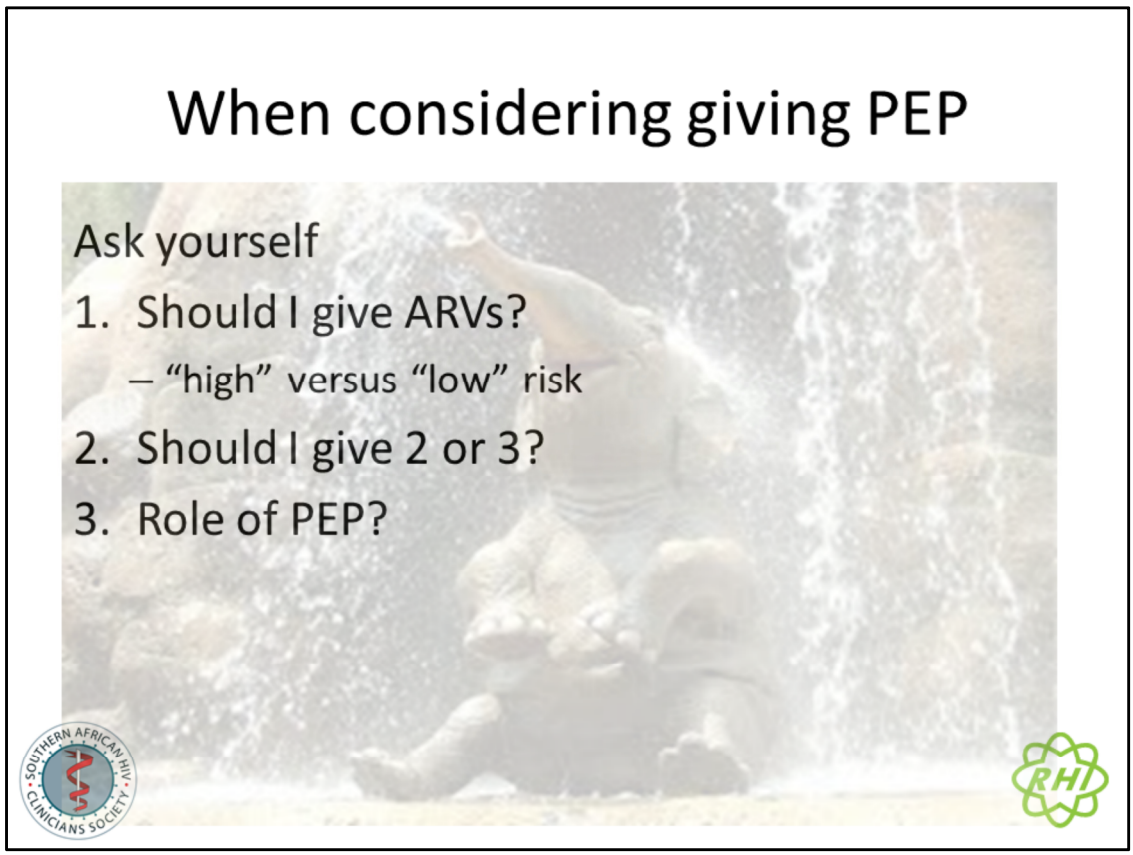
- No evidence that prevention of HIV transmission by AZT in the setting of PEP is due to anything other than inhibition of viral replication.
- Supports the use of TDF, the potency of action of which is equivalent to AZT, yet which is far better tolerated over 28 days
- TDF is usually avoided in patients on ART with renal failure or eGFR <50 mL/min
- Less concern in the setting of PEP due to the short duration of TDF administration.
- **Comparative data from three randomised trials for ART and PrEP and from observational studies with PEP support the use of TDF + XTC as the preferred backbone in PEP.**
- **Indirect comparisons between AZT + 3TC versus TDF + XTC across 15 studies demonstrate less PEP discontinuation due to adverse events in individuals receiving TDF + XTC than AZT + 3TC.**
- Where there are concerns regarding the use of TDF, d4T is very well tolerated when it is used for short periods, and given the poor tolerability of AZT in PEP regimens, would be the recommended NRTI to use in such cases.

There may be a risk of hepatic flares in individuals infected with HBV who discontinue PEP containing TDF, 3TC or FTC, as has been seen in some patients on ART who switch away from these drugs. These individuals should be monitored for hepatic flare if these drugs are not continued for HBV treatment. Where HBV

testing is available, those with unknown HBV status should be tested for active HBV infection, to assess the need for ongoing HBV therapy.



- Gloves should be worn, and where appropriate, protective eyewear.
- Clean water or saline should be available to immediately irrigate any mucosal exposure or percutaneous injury. Use non-caustic soap. Only use water or saline if the exposure involves the eye.
- Needles should NOT be re-sheathed, and manipulation of the needle following withdrawal from the patient must be kept to the absolute minimum.
- Wherever possible, safety equipment for blood taking should be available, particularly in the hospital and clinic setting where the risk of exposure to HIV-infected blood is highest. It is imperative that the cost of cheaper equipment and disposal must be weighed against the potential increased risk of exposure that using such equipment entails.
- Needles and tools for any surgical practice, including traditional circumcision, should never be re-used without rigorous chemical disinfection/sterilisation according to national or local guidelines.
- All needles and sharp objects should be disposed of into a dedicated biohazard sharps bin. Syringes and other blunt instruments should NOT be disposed of in these bins, but rather in regulation biohazard bins for disposal of blunt biohazard objects.
- Aappropriate management of sharps bins



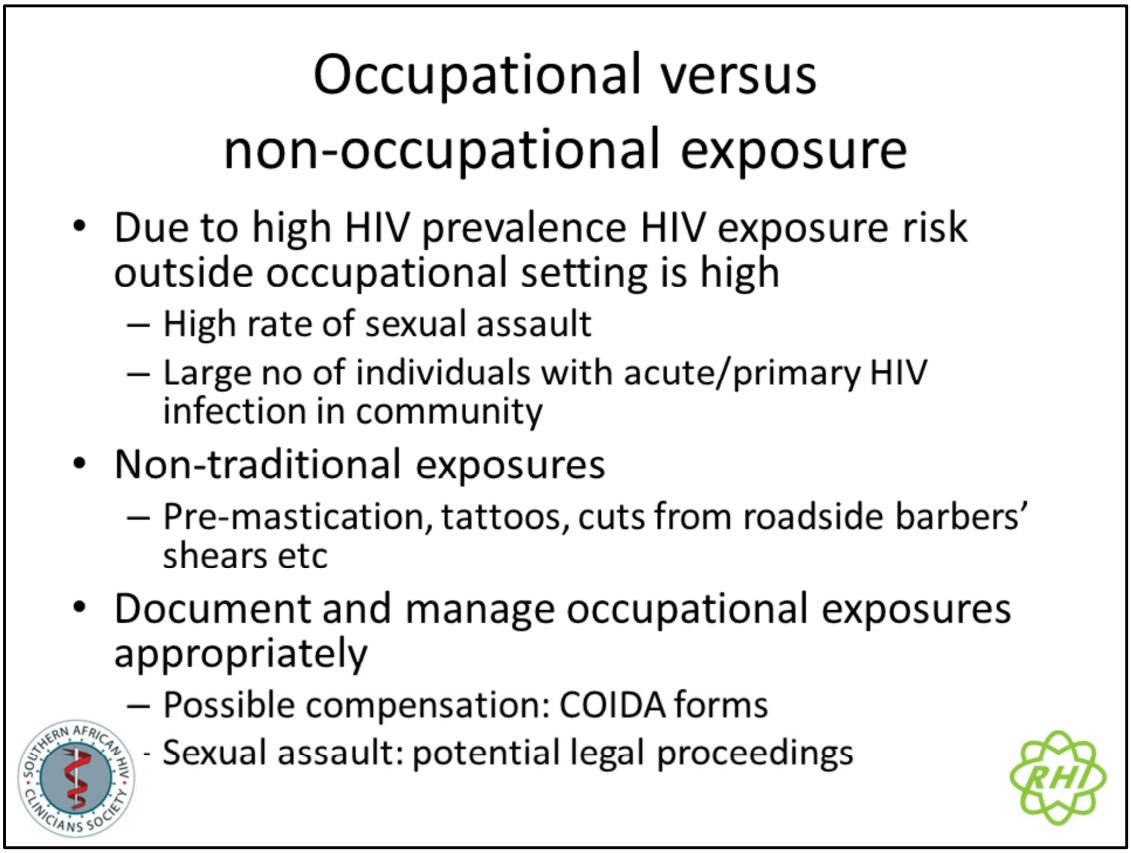
Who should get PEP? Let's start with who doesn't NEED PEP

Which exposures do NOT require PEP?

1. Exposed is HIV-positive
2. Source confirmed HIV-negative (window period excluded)
3. Exposure to bodily fluids which do not pose risk
   - Tears, non-bloodstained saliva, sweat and urine

Standard precautions should be used in every setting where blood or infectious body fluid contact is possible

1. Exposed individual is already HIV-positive
2. Source is confirmed HIV-negative by laboratory ELISA test and the window period has been excluded
3. Exposure is to bodily fluids which do not pose significant risk of HIV transmission: tears; non-bloodstained saliva, sweat and urine



- While the actual management of exposure is the same whether the exposure was occupational or non-occupational, it is essential **to document and manage** occupational exposures appropriately, for possible subsequent **compensation** (including completion of the appropriate Compensation for Occupational Injuries and Diseases Act (COIDA) forms).
- This is also important for cases of **sexual assault** where legal and criminal proceedings may ensue.
- Occupational exposure **prevention** requires strong management oversight in all settings.
- **Non-occupational** exposure requires an understanding of core **transmission** principles, combined with clinical common sense.
- In the southern African setting, all **unknown source exposures** should be assumed to be HIV-positive.
- **Evidence** regarding occupational and non-occupational risks of transmission for Southern Africa is limited, and may underestimate transmission risk in our setting.

Selecting patients for PEP interventions

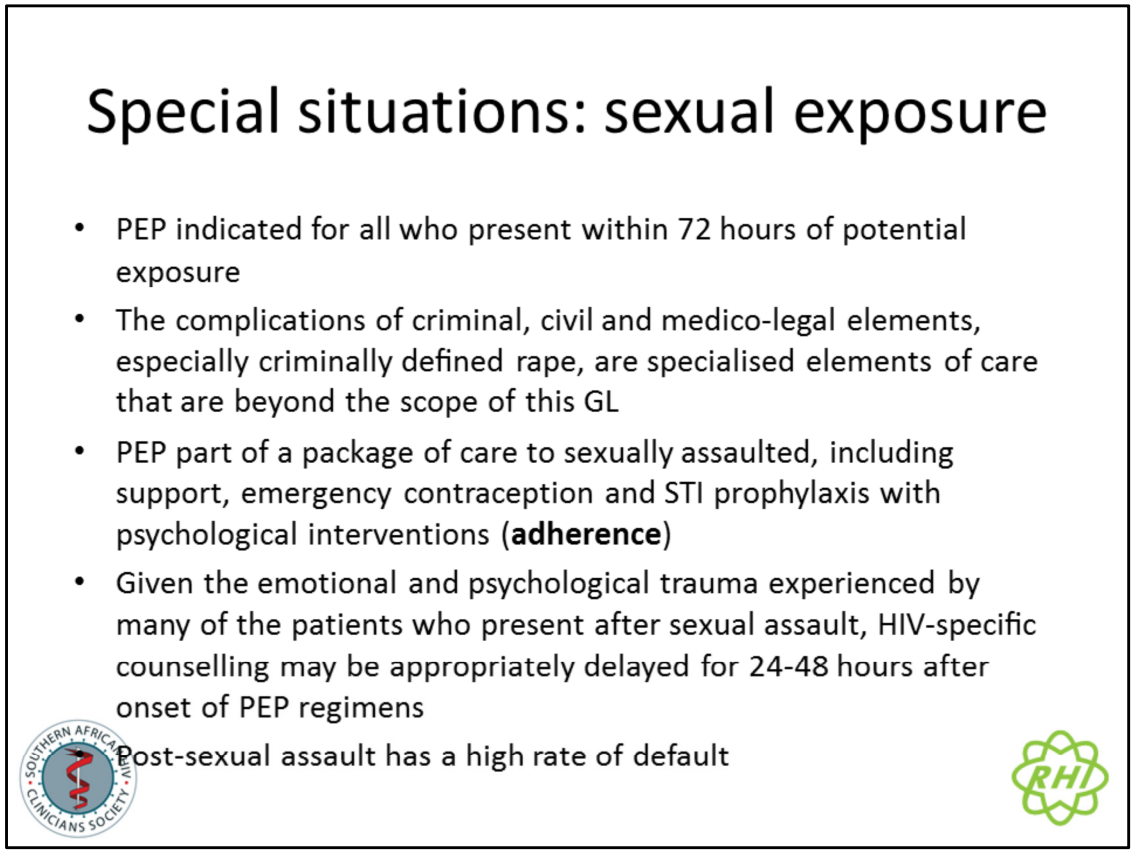
	Status of the source		
	HIV-positive	Unknown	HIV-negative
Percutaneous exposure to blood or potentially infectious fluids	**Triple prophylaxis**	**Triple prophylaxis**	**No PEP**
Mucous membrane exposure, including sexual exposure, mucocutaneous splash or open wound contact, with blood or potentially infectious fluids	**Triple prophylaxis**	**Triple prophylaxis**	**No PEP**
Mucous membrane exposure, including sexual exposure, mucocutaneous splash or open wound contact, with **non-infectious** fluids	**No PEP**	**No PEP**	**No PEP**

Same as previous guideline

Special situations: healthcare

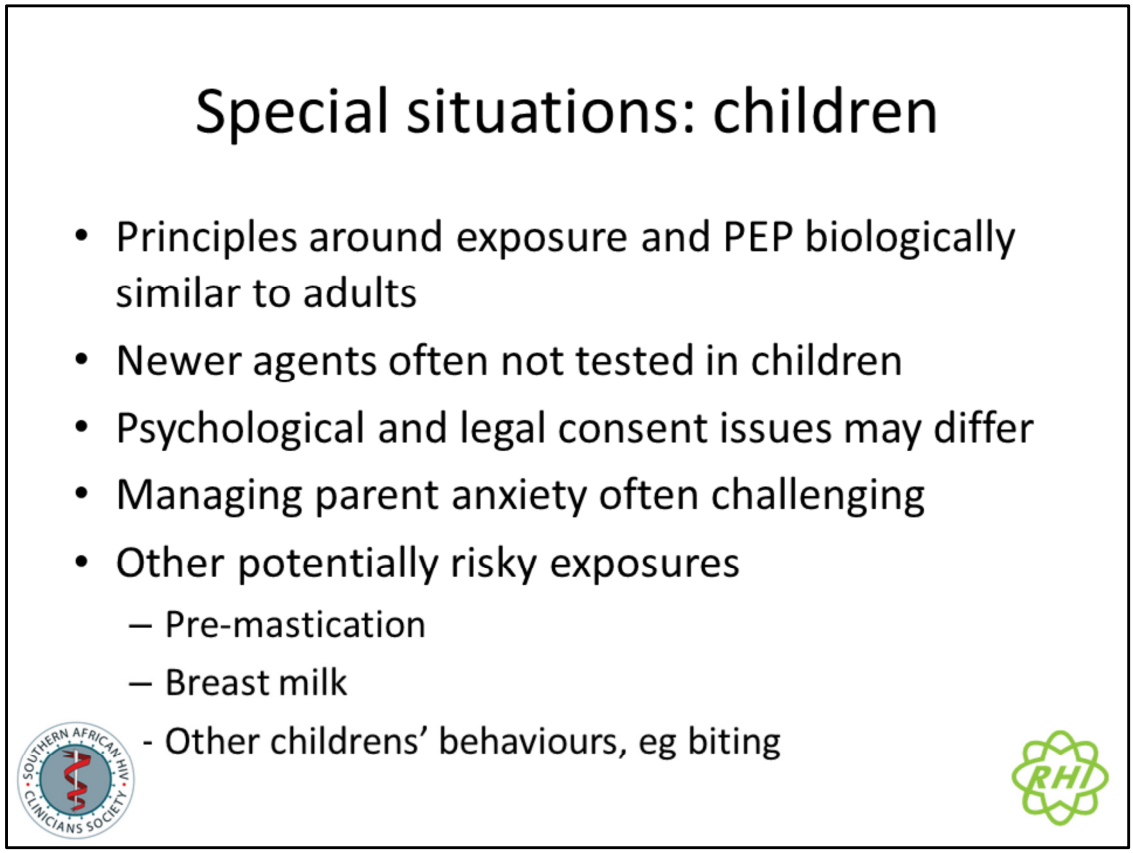
- Potentially hazardous exposure to blood-borne viruses in the workplace
- All occupational exposure should be regarded as preventable and deserving of investigation until proven otherwise
- Standard precautions
- Best practice should be enforced with the aid of unions to ensure that employers and employees are creating a safe working environment

- Within the hospital or clinic environment, it is the ultimate responsibility of that institution's infection control team to monitor and ensure that sharps bins are being sealed when three-quarters full and disposed of correctly. However, on a day-to-day basis this responsibility falls to the nursing sister in charge of the ward or clinic.
- Outside of the healthcare setting, employers must take responsibility for such monitoring and enforce standard practice as laid out above.
- Best practice should be enforced with the aid of unions within the framework of occupational law to ensure that employers and employees are creating a safe working environment with respect to prevention of blood-borne disease acquisition.



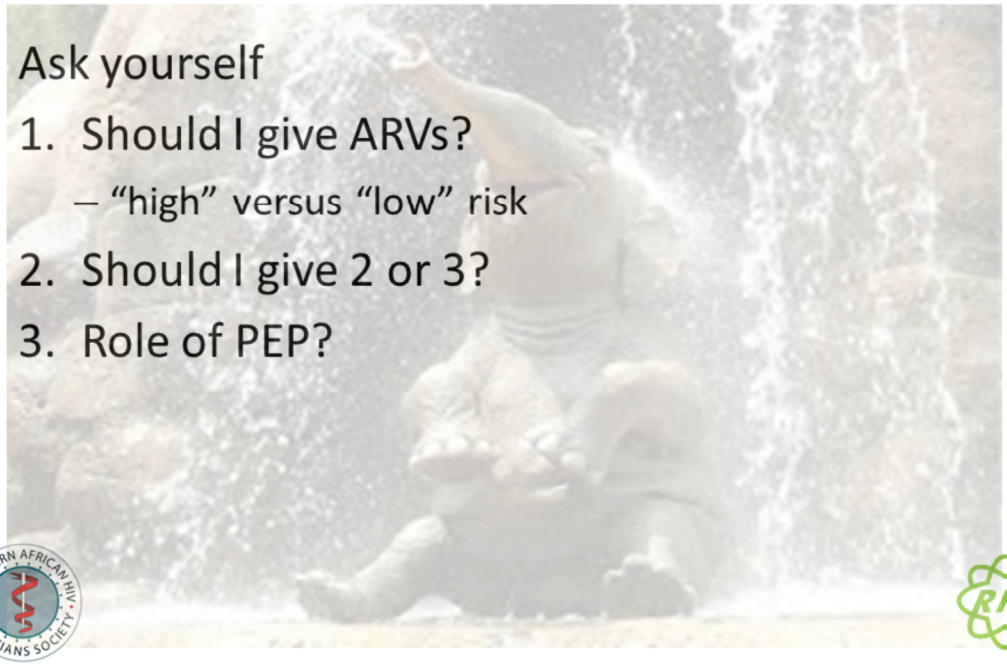
- PEP is indicated for those who present within 72 hours of unprotected risky sexual activity, including but not limited to, penetrative intercourse, and including but not limited to, survivors of sexual assault.
- As a public health intervention, equal access to treatment of all sexual exposures, including rape, is essential to equality of prophylaxis and minimisation of HIV transmission.
- The complications of criminal, civil and medico-legal elements, particularly in the case of criminally defined rape, are specialised elements of care that are beyond the scope of this guideline. Applicable local guidelines should be consulted in such cases.
- PEP should be given as part of a package of care to women who are subjected to sexual assault, including support, emergency contraception and prophylaxis for additional STIs in combination with psychological interventions (the details of this package of care are beyond the scope of this guideline – please consult applicable local guidelines).
- Other people who have been sexually assaulted need to have psychosocial issues addressed in combination with PEP as part of a package of care. This would include men, children and adolescents who have been sexually assaulted.
- Given the emotional and psychological trauma experienced by many of the patients who present after sexual assault, HIV-specific counselling may be appropriately delayed for 24-48 hours after onset of PEP regimens.

- It is recognised that the post-sexual assault situation has a high rate of therapy default, complicating all aspects of management.



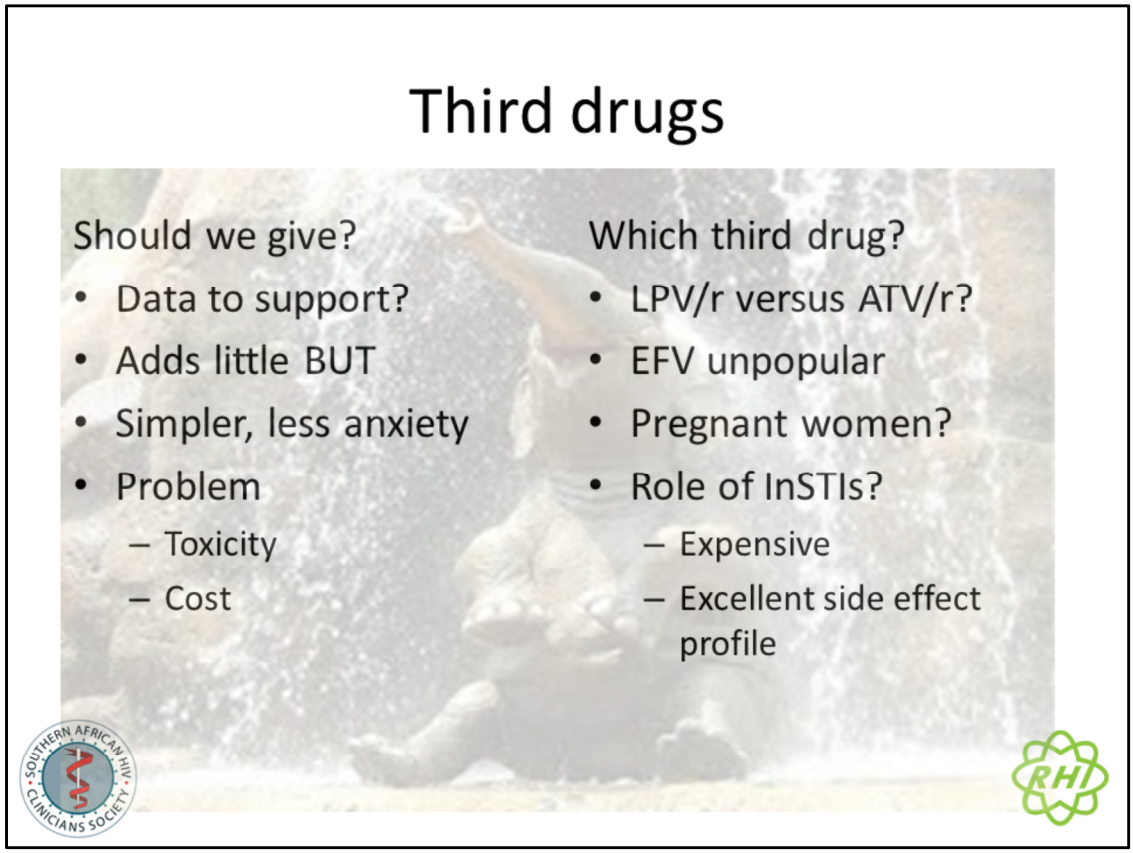
- Principles around exposure for children are biologically similar to those for adults. As in pregnancy, newer agents have often not been tested in children and dosages may not have been determined. Therefore, recommended medications and dosages may differ and it is important to check doses carefully.
- Psychological and legal consent issues may differ from adults, and clinicians should be guided by local legislation. Children often do not give accurate histories, and anxious parents, especially in the context of possible sexual assault, may require significant counselling and careful referral.
- Pre-mastication of food is commonly practised in both developed and developing countries, and several cases of transmission from caregiver to children have been described in the USA. This practice should be actively discouraged.
- Another source of potential infection, through breast milk, is using wet nurses, as well as milk kitchens (the practice of pooling breast milk, and then transferring to bottles in healthcare facilities).
- Children are exposed to other children's behaviours, which may have transmission risks, such as biting. Most cases of biting do not pose a risk of HIV transmission in children, but if there is blood in the mouth of the biting individual (eg bleeding gums due to gingivitis), or if the skin of the bitten child is breeched, then there is a theoretical risk of transmission.
- Managing parent anxiety is often a huge challenge.

When considering giving PEP



Ask yourself

1. Should I give ARVs?
   - "high" versus "low" risk
2. Should I give 2 or 3?
3. Role of PEP?



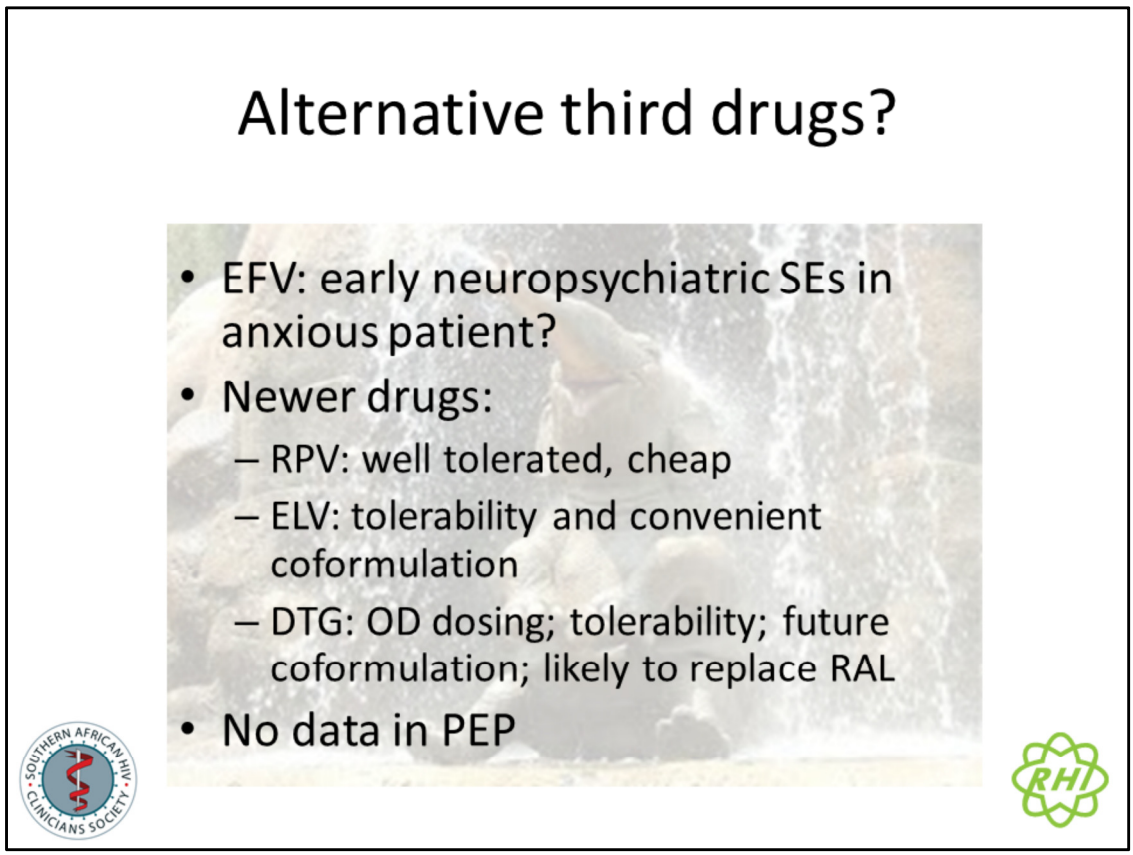
Data: evolving basic science understanding; animal studies; PMTCT and PrEP studies. RCT not feasible (exposure complexity; unethical placebo; low event rate)

Third drug:

- No data if adds additional protection
- Adds little to current prevention
- Pros: simpler, less anxiety
- Cons: toxicity and cost

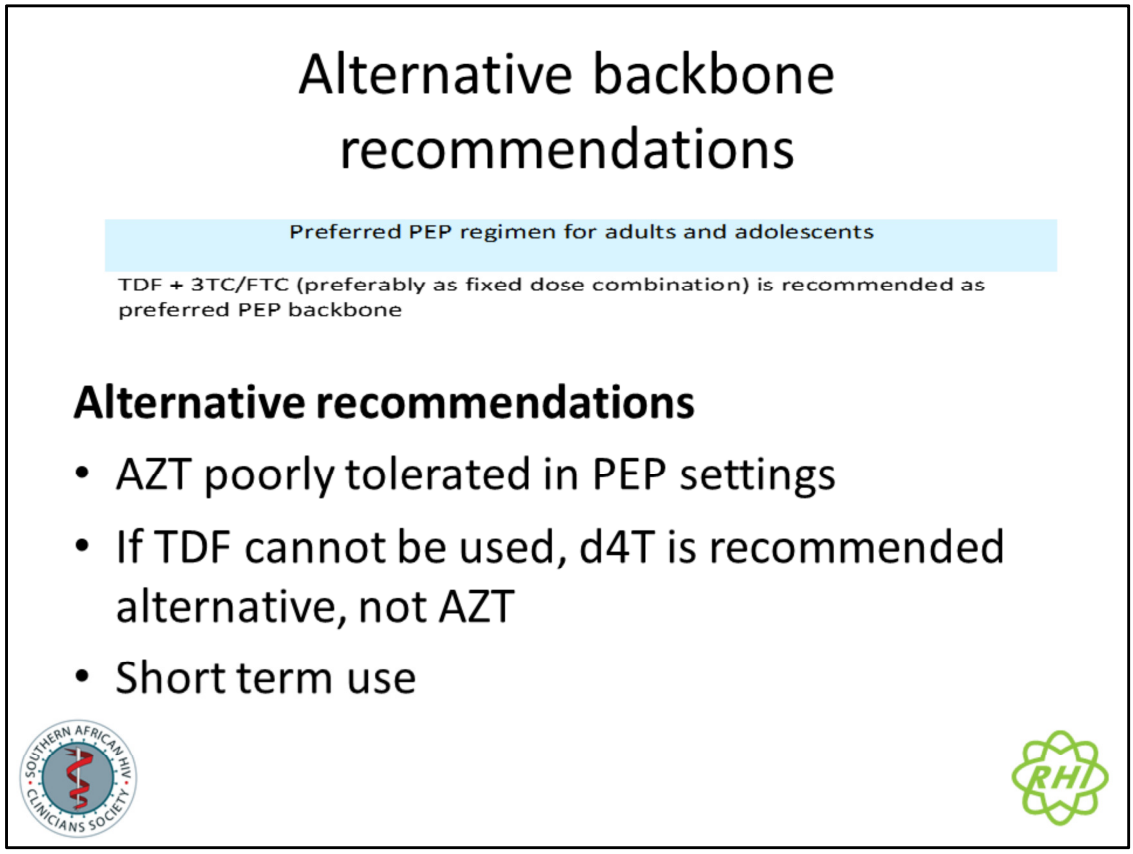
Which third drug?

- LPV/r safer than ATV/r; DRV/r (?)
- EFV unpopular
- InSTIs: excellent side effect profile but costly
- RPV? Higher viral loads in source patient?



Which third drug?

- LPV/r safer than ATV/r; DRV/r (?)
- EFV unpopular
- InSTIs: excellent side effect profile but costly
- RPV? Higher viral loads in source patient?



- No evidence that prevention of HIV transmission by AZT in the setting of PEP is due to anything other than inhibition of viral replication.
- Supports the use of TDF, the potency of action of which is equivalent to AZT, yet which is far better tolerated over 28 days
- TDF is usually avoided in patients on ART with renal failure or eGFR <50 mL/min
- Less concern in the setting of PEP due to the short duration of TDF administration.
- Comparative data from three randomised trials for ART and PrEP and from observational studies with PEP support the use of TDF + XTC as the preferred backbone in PEP.
- Indirect comparisons between AZT + 3TC versus TDF + XTC across 15 studies demonstrate less PEP discontinuation due to adverse events in individuals receiving TDF + XTC than AZT + 3TC.
- Where there are concerns regarding the use of TDF, d4T is very well tolerated when it is used for short periods, and given the poor tolerability of AZT in PEP regimens, would be the recommended NRTI to use in such cases.

There may be a risk of hepatic flares in individuals infected with HBV who discontinue PEP containing TDF, 3TC or FTC, as has been seen in some patients on ART who switch away from these drugs. These individuals should be monitored for hepatic flare if these drugs are not continued for HBV treatment. Where HBV

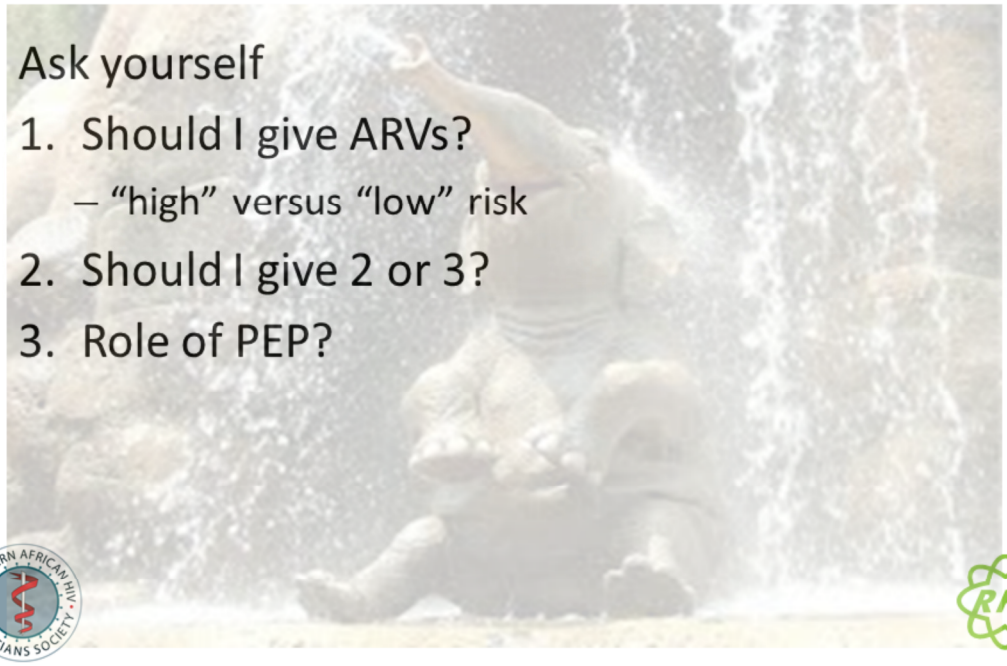
testing is available, those with unknown HBV status should be tested for active HBV infection, to assess the need for ongoing HBV therapy.

Selecting ARV regimens for PEP

In adults and adolescents ≥35 kg
Preferred **backbone**: TDF + FTC/3TC *
Preferred **third drug**: RAL (except pregnant women: ATV/r)
Alternative third drugs: ATV/r; LPV/r; DRV/r or EFV
Administer **first dose** of PEP ASAP (any suitable 3 ARVs)
All PEP regimens must be administered for **one month**
* AZT poorly tolerated as PEP; TDF + 3TC/FTC better tolerability and similar cost to AZT + 3TC. Where TDF contra-indicated, use d4T (better tolerated than AZT in PEP)

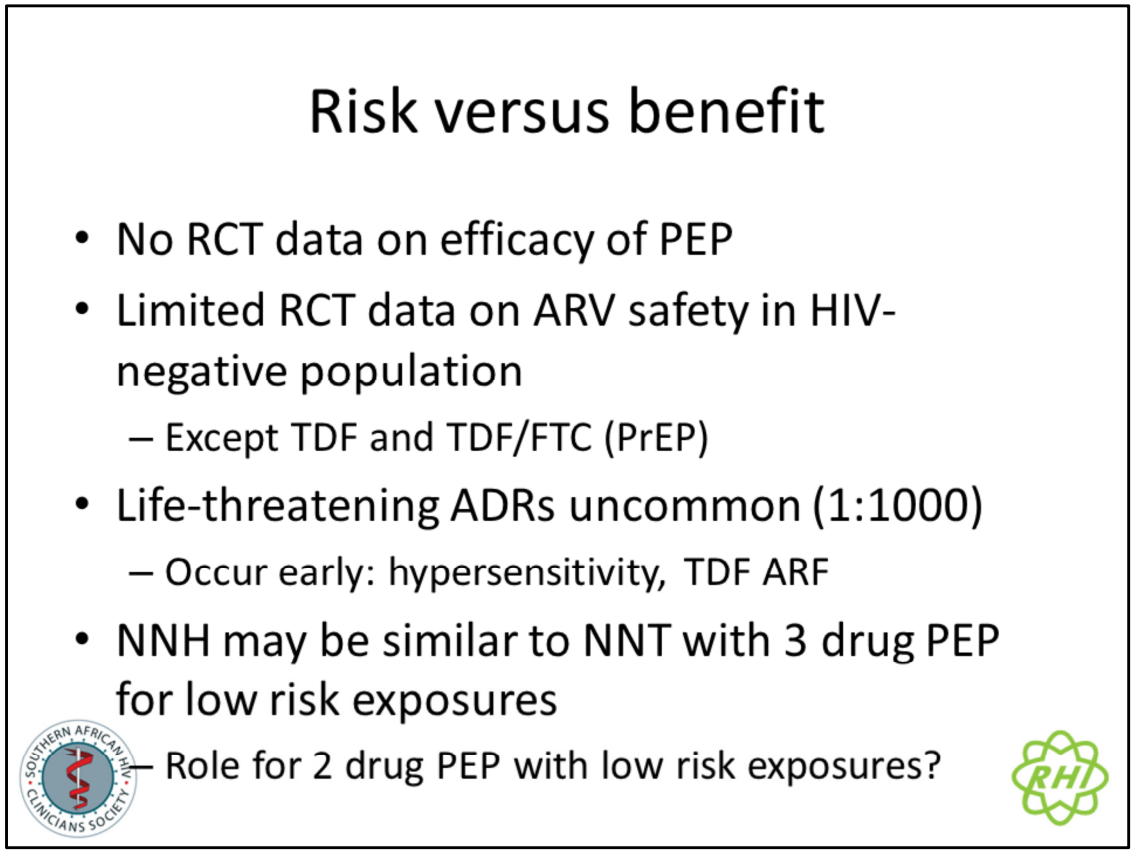
The choice of PEP combinations is based on available evidence in both prevention (including PrEP and PMTCT) and treatment settings; side-effect profiles; ease of use; local guidelines; and availability. In addition, these PEP guidelines are aligned with the latest WHO PEP guidelines, released in Dec 2014, which now recommend three drugs as the preferred option for PEP, and no differentiation in regimen according to the type of exposure, namely occupational versus non-occupational. This is part of a move towards simplification of prescribing to improve availability of PEP and to reduce time to PEP initiation. With the availability of less toxic and better tolerated drugs, providing a three-drug regimen supports simplified prescribing by removing the need to evaluate the risk of resistance, which was the basis upon which the decision to initiate two- versus three-drug PEP was previously made. While PEP completion rates are generally less than optimal, there is evidence that completion rates are similar when comparing two-drug to three-drug PEP.

When considering giving PEP



Ask yourself

1. Should I give ARVs?
   - "high" versus "low" risk
2. Should I give 2 or 3?
3. Role of PEP?



- PLWH have a near-normal lifespan provided that ART is not started too late, so the risks of PEP need to be more carefully considered than in the past.
- Newer ARVs considerably safer than most of the older agents.
- Most international guidelines on PEP, including those of the SAHIVCS, recommend 3 ARVs for both low- and high-risk exposures.
- No controlled data on the efficacy of any PEP regimen.
- Limited controlled data on the safety of ARVs in HIV-uninfected people, except for TDF plus FTC from PrEP trials.
- Cannot be assumed that ARV safety will be similar in HIV-infected and HIV-uninfected people, as illustrated by the severe toxicity of NVP when used in PEP.
- Not possible to accurately determine risk to benefit ratios for PEP.
- Life-threatening adverse drug reactions from currently recommended antiretroviral drugs are uncommon, likely occurring in about 1 in 1 000 people, except for FTC and 3TC, which are considerably safer.
- People on PEP are at risk of life-threatening reactions, as many of them occur early (e.g. acute renal failure from TDF, severe hypersensitivity reactions).
- NNH (with life-threatening adverse drug reactions) may be similar to or lower than the NNT to prevent one HIV infection when three-drug PEP is used following low-risk exposures.
- In the absence of definitive data, clinical judgement needs to be used when balancing risks and benefits for PEP.

- Reasonable to start three-drug PEP following an HIV exposure event.
- Low threshold to switch or stop offending ARVs, should potentially severe adverse drug reactions occur.
- May still be a place for two drug PEP for very low-risk exposures.

Investigations simplified

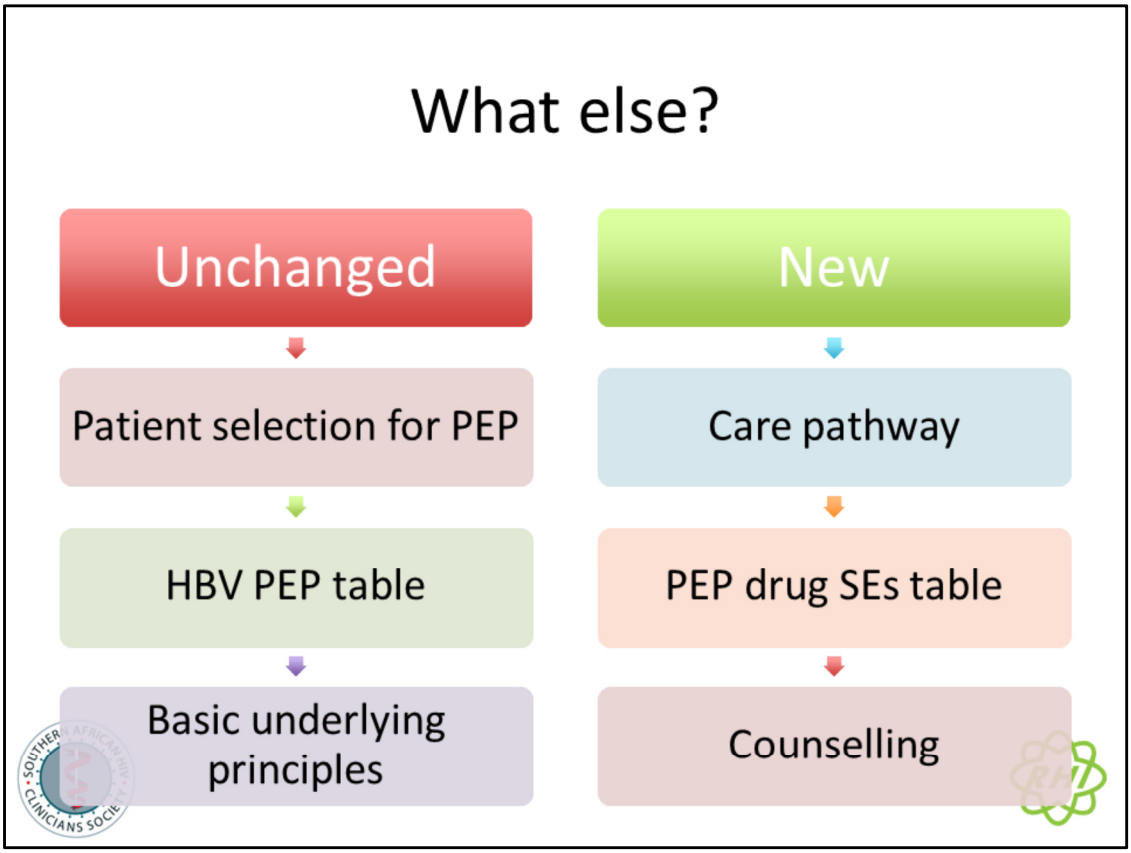
Timing of bloods pre- and post PEP					
	Source	Exposed individual			
	Baseline	Baseline	2 weeks	6 weeks	3 months
HIV	X*	X*		X**	X**
HBV (HBsAg)	X***	X***			X***
HCV	HCV Ab	HCV Ab§		HCV PCR§	
Syphilis	RPR/TP Ab	RPR/TP Ab§			
Creatinine		If TDF used	If TDF used		
FBC		If AZT used	If AZT used		

* Rapid PLUS 4th generation ELISA
** 4th generation ELISA
*** Can be omitted if exposed individual known to be protected (natural immunity or vaccinated)
§ only if source positive

- HCV testing only if source is PWID, haemophiliac or from high HCV prevalence area
- If HCV-positive, test exposed at BL (HCV Ab) and 6 weeks (HCV PCR)

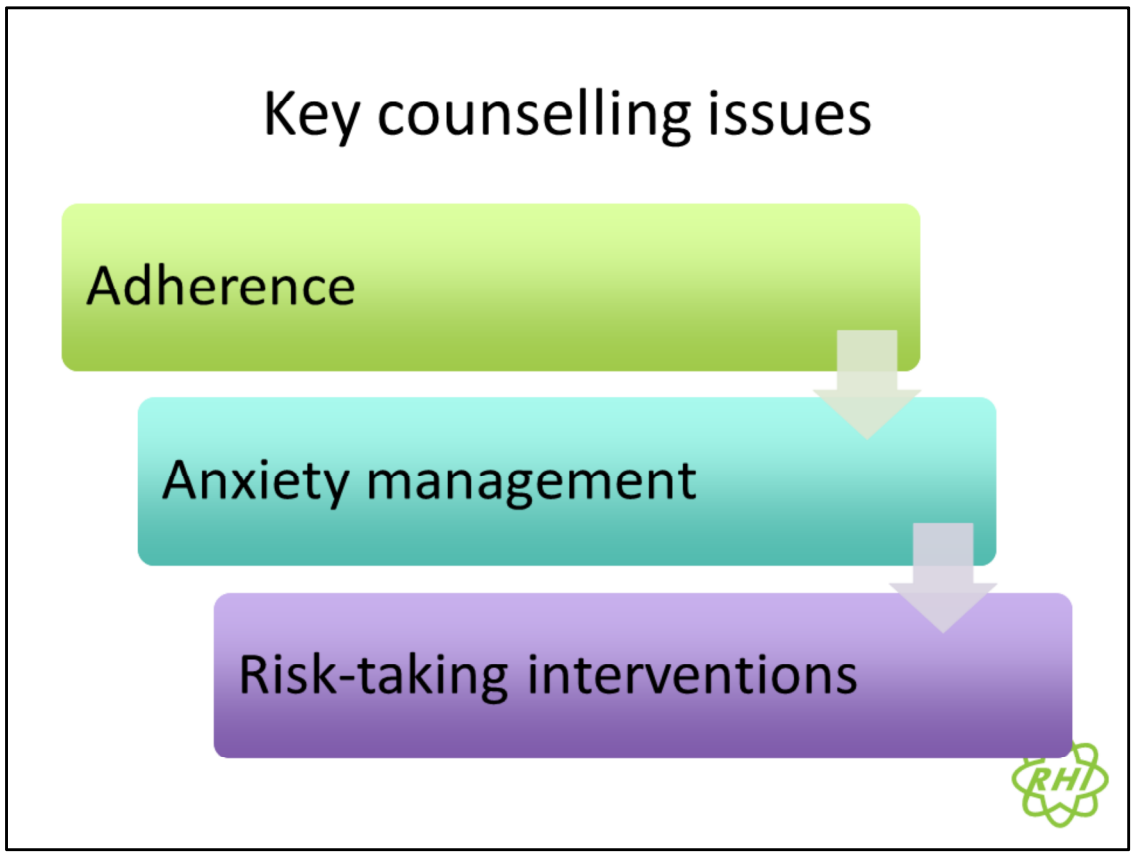
Other considerations

- Potential HIV exposure situations
- Who is at risk?
- Dosage table
- Management of HBV exposure: table
- Side effects of ARVs used as PEP
- Comorbidities affecting choice of PEP ARVs
- Drug safety in pregnancy



Patient selection for PEP table: changed mucocutaneous to mucous membrane

PEP studies report low completion rates, often less than 60% for all populations, but especially adolescents, and PEP following sexual assault. Adherence counselling has been proven to improve adherence in HIV-positive individuals starting ART. Three RCTs comparing standard care counselling to enhanced adherence packages in improving adherence to PEP were identified and reviewed. The enhanced package included individual baseline needs assessments, adherence counselling, and education sessions and telephone calls. The combined effect of the enhanced intervention improved adherence and completion rates compared to standard of care counselling. Based on this, it is likely that some of the methods used to improve ART adherence may well be effective in PEP, such as peer support, alarms, text messages and phone calls.



Anxiety

- Anxiety should not simply be dismissed as baseless with simple reassurance. HIV remains a 'dread disease', despite the success of ART, because it is sexually transmitted, still accounts for significant mortality and morbidity, and has extensive stigma associated with it.
- Anxiety management must be part of the adherence or follow-up support, and may need several interventions.
- Simple telephonic contact and reassurance is almost always adequate.
- The intervention must be individualised, but the following approaches should be integrated:
    - Contextualise the risk: emphasise that acquisition of HIV is unusual through a single exposure, unless the injury is severe (sexual assault, blood transfusion of an infected unit, severe penetrating injury with infected tissue)
    - Even in the case of severe exposure or injury, where PEP is used timeously and the course completed, the risk of transmission is extremely low

Risk-taking interventions

- Counselling should be non-judgemental, practical and solution-focussed. PEP is an ideal time to deal with risk-taking environments, whether unsafe sex (e.g. a one-night stand with unprotected sex), poor occupational health (e.g.

overfull sharps bins) or other (e.g. injecting drug use). Addressing occupational risk must be practical (e.g. report over-full bins to infection control, do not tell an exhausted nurse to 'be more careful').

- Secondary prevention to prevent harm to others (e.g. risk to a spouse after sex with a third party) must be addressed. Exposed individuals should be counselled how to prevent transmission to others, until they undergo the three month post exposure test following PEP:
    - Use of condoms to protect sexual partners
    - To prevent MTCT, avoid pregnancy (provide emergency contraception if necessary) and avoid breastfeeding if possible (high risk of transmission via breast milk during the three months following seroconversion demonstrated in a study from Zimbabwe)
    - Safe injecting practices
    - Avoid blood and tissue donation

Consider offering PrEP to exposed individuals where chronic exposure to HIV is unavoidable or likely to continue (e.g. sex workers). Current evidence indicates that PrEP is effective as part of combination prevention approaches, provided it is used correctly For more information, consult the Southern African HIV Clinicians Society guidelines on the safe use of PrEP in MSM and the US Department of Health and Human Service DHHS clinical practice guideline

Summary of PEP recommendations

Number of ARVs
Should contain 3 drugs
Preferred regimen for adults and adolescents
TDF + 3TC/FTC (preferably as FDC) is preferred backbone RAL is preferred third drug (except in pregnancy: ATV/r preferred) Alternative third drugs: ATV/r; LPV/r; DRV/r or EFV
Preferred regimen for children ≤35kg or unable to swallow tablets
AZT + 3TC is preferred backbone in children ≤35kg (if AZT poorly tolerated, use d4T) RAL is preferred third drug in children where available (if no RAL, use LPV/r)
Prescribing frequency
Full month at initial assessment. Avoid starter packs
Frequency of follow up
Initial assessment; 2 weeks, 6 weeks and 3 months post exposure
Adherence support
Enhanced adherence counselling

Emphasis on anxiety management
Risk taking interventions – role of PrEP?


Sometimes the questions are complicated and the answers are simple.
Michelle Moorhouse
mmoorhouse@wrhi.ac.za
Cell: 076 071 9041
don't cry because it's over. Smile because it happened.

PEP Guidelines

Michelle Moorhouse

20 Jun 2015