

A Prospective Study of Post-exposure Prophylaxis Following Sexual Assault in South Africa

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Background

- Recent CDC Guidelines recommending the use of post-exposure prophylaxis (PEP) following non-occupational HIV exposures distinguish between exposure sources of known and unknown HIV status, a distinction that makes less sense in the context of high HIV prevalence in sub-Saharan Africa.
- It has been government policy to offer PEP following sexual assault in South Africa since April, 2002.
- Little is known however, about:
 - What proportion of survivors are eligible for PEP based on exposure type and time of presentation for medical care
 - How many of those who are offered PEP will accept it
 - Adherence to and side effects with PEP in the complex emotional setting of sexual assault
 - Ongoing HIV risk behavior and seroconversion in the context of high HIV prevalence
 - The human and financial resources required to facilitate effective, comprehensive care for sexual assault survivors
- This on-going pilot study was designed to explore adherence and side effect rates in preparation for subsequent studies aimed at evaluating adherence to a shorter, simpler PEP regimen—in combination with mental health interventions and HIV prevention counseling strategies—for use in the context of sexual assault in high HIV prevalence areas.

Methods

Study design

- Observational cohort of subjects enrolled within 2 weeks of a sexual assault involving potential HIV transmission and followed for 6 months.

Study setting and subjects

- Thutuzela, the Rape Center at Jooste Hospital in Mannenberg, a township outside of Cape Town, South Africa.
- Subjects presenting **within 72 hours** who test HIV negative, or refuse HIV testing but are not known to be HIV-infected, are offered PEP and study enrollment. Subjects presenting **after 72 hours** are not offered PEP but are offered enrollment.
- Patients are recruited from the Rape Center by a study nurse after they have completed the standard of care interventions, including history, physical and forensics examination, emergency contraception, sexually transmitted infection prophylaxis and PEP.

Interventions

- Medications:
 - All subjects seen within 72 hours of the assault are offered PEP as standard of care prior to study enrollment, but are not required to take it in order to participate.
- Medication adherence counseling:
 - Subjects seen initially during study hours received adherence counseling in conjunction with the initial PEP prescription.
 - Subjects seen after study hours and enrolled within 5 days are provided with adherence counseling at the first study visit.
 - Additional counseling is provided at the week 1 visit.
- Case management, referrals and follow-up:
 - Follow-up study visits are offered at the Rape Center, the study office, or the subject's home.
 - Three nurses are employed to assist in the baseline pre-study medical and forensic care. They are responsible for study enrollment and for completing all study documentation. They provided intensive case management including tracking and referrals for clinical, mental health, social work, family planning and other care needs.
 - A study psychologist, gynecologist, and HIV specialist are available for consultation.
- Forensic examination and court testimony:
 - The study nurses are trained in the forensics examination and supervised by an experienced study physician. The clinician performing the forensic examination must also be available to testify in court.

Measurements

- Subject demographics and characteristics of the assault are obtained by structured interview and abstraction from standard medico-legal documents completed for all sexual assault survivors.
- Adherence is assessed at 1 and 4 weeks after study enrollment by self-report of missed doses in the prior 4 days. Reasons for missing doses or early medication discontinuation are assessed by structured interview.
- Symptoms are assessed at baseline, 1, 4, 12 and 26 weeks through structured interview. For subjects seen initially after study hours and enrolled within the next 5 days, symptom assessment occurs after PEP initiation and week 4 assessments occur after PEP is discontinued.
- Subjects are followed for 6 months for potential interim HIV exposure, obtained by structured interview, and for HIV seroconversion.

Results

Enrollment

- 135 eligible subjects were enrolled between March 2004 to September 2004.
- Of these, 131 (97%) received PEP. 4 of these were prescribed PEP > 72 hours following the assault.

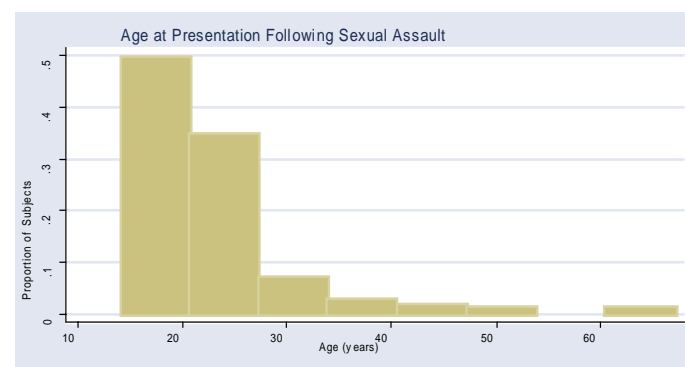
Baseline Subject Characteristics

- 133 (99%) subjects were female.
- The median age was 21 years (range, 14 to 67).
- 103 (76%) were African and the remainder were “Coloured”
- Most subjects were single (85%), unemployed (79%), had not graduated from high school (84%), and reported low total household incomes (80% had total annual household incomes of <= \$5,000)

Table 1. Baseline Demographics

Characteristic	Subjects	Characteristic	Subjects
Age – yr (median; IQR)	21 (17-24)	Others living in home – (median; IQR)	4 (3, 6)
Female sex – no. (%)	133 (99)	Pregnant at enrollment – no. (%)	5 (4)
Race/Ethnicity - no. (%)		Education – no. (%)	
African	103 (76)	None through grade 6	11 (8)
“Coloured”	32 (24)	Grade 7 – 11	103 (76)
Primary Language – no. (%)		High School Graduate	11 (8)
Xhosa	100 (74)	College, University, Graduate School	10 (9)
Afrikaans	26 (19)	Employed – no (%)	29 (21)
English	7 (5)	Household Income (Rand) – no (%) (R1=US\$6)	
Zulu	2 (1)	<= R5,000	19 (14)
Marital Status – no. (%)		R5,001-10,000	32 (24)
Single/never married	115 (85)	R10,001-20,000	36 (27)
Married	6 (4)	R10,001-30,000	20 (15)
Separated	6 (4)	R30,001-40,000	14 (10)
Divorced	6 (4)	>R40,000	14 (10)
Live-in partner	2 (1)		
Children – no. (%)			
None	85 (63)		
1-2	43 (32)		
>=3	7 (5)		

Figure 2. Age of Sexual Assault Survivors



Characteristics of the Potential HIV Exposure

- Vaginal penetration was reported by 129 (96%), while anal and oral penetration were reported infrequently, in 18 (13%) and 3 (2%) respectively. HIV status was usually unknown (97%).
- Twenty-eight (21%) subjects were assaulted by more than 1 perpetrator
- 17 (9%) subjects reported previous sex with the perpetrator
- Almost half of subjects (48%) reported a previous negative HIV test.

Characteristic	No. (%)
Potential HIV Exposure Route	
Vaginal receptive intercourse	129 (96)
Anal receptive intercourse	18 (13)
Oral receptive intercourse with ejaculation	5 (4)
Total perpetrators	192
Number of Perpetrators	
1	106 (79)
2	16 (12)
more than 2	12 (9)
HIV Status of perpetrator unknown	187 (97)
Prior intercourse with any perpetrator	17 (9)
Subject tested for HIV in past	65 (48)

Table 2. Characteristics of the Potential HIV Exposure

Characteristics of the Assault

- Almost half (48%) of perpetrators were known to the subject, commonly being neighbors, friends or ex-boyfriends
- Assaults often involved abduction to the perpetrator's home (39%) or an open space (36%)
- A weapon was used in over half (54%) of assaults

Characteristic	No. (%)
Any perpetrator known to subject	92 (48)
Neighbor	22 (12)
Friend	20 (10)
Ex-boyfriend	10 (5)
Lives with perpetrator	6 (4)
Abducted	77 (57)
Location of assault	
Perpetrator's home	52 (39)
Open space	48 (36)
Subject's home	17 (13)
Other	18 (13)
Any weapon used	73 (54)
Gun	32 (24)
Knife	31 (23)
Bottle, screwdriver, other	15 (11)

Table 3. Characteristics of the Assault

PEP Timing

- Mean time from the assault to PEP initiation was 19 +/- 14 hours¹.

Characteristic	No. (%)
Days to examination following assault	
Same day	43 (32)
Within 1 day	74 (55)
Within 2 days	9 (7)
Within 3 days	1 (1)
>3 - 14 days	7 (5)
Time to PEP ²	
< 24 hours	96 (77)
24 - 48 hours	20 (16)
48 - 72 hours	9 (7)

Table 4. Timing of Examination and Post-Exposure Prophylaxis

¹ Some missing data in process of being reconciled, thus these numbers should be considered approximate. This analysis includes 125 subjects.

PEP Adherence

- Study follow-up rates at weeks 1 and 4 were 96% and 89% respectively.
- 17 (13%) of 131 subjects discontinued PEP prior to 28 days; 7 of these were within the first week.
- 30 (25%) of 119 subjects taking PEP at week 1 reported missing any doses in the prior 4 days.
 - Reasons included: forgetting (61%), being away from home (45%), concern about people noticing (16%), change in routine (10%).
- Side effects, pill burden or feeling overwhelmed were reported less frequently.
- Subjects reported good understanding of dosing instructions.
- Median days of PEP medication completed was 27 (IQR 27, 28). However, 35 (27%) either discontinued PEP or missed at least one dose in the prior 4 days at the week 1 visit

Table 5. Adherence to Post-Exposure Prophylaxis

Characteristic	No. (%)
Discontinued PEP prior to 28 days	17 (13)
Side effects	5
Missed > 3 days of meds	10
Believe took enough	1
Other patient choice	1
Discontinued within first week	2 (2)
Missed doses in subjects still taking PEP and seen in follow-up at week 1 (n=119)	
1 day ago	10 (8)
2 days ago	9 (8)
3 days ago	16 (13)
4 days ago	15 (13)
Any missed doses in prior 4 days	30 (25)
Total discontinued or missed any dose in prior 4 days	35 (27)
Did not understand dosing instructions at week 1 and week 4	2 (2%) and 0

Symptoms

- 71 (49%) of subjects reported one or more >= grade 2 symptoms at their initial visit. The majority of subjects (89%) initiated PEP prior to the initial visit, thus this does not represent symptoms present prior to PEP
- At week 1, when most subjects were taking PEP, 76 (61%) subjects reported one or more >= grade 2 symptoms.
- At week 4, when most subjects had completed PEP, 35 (29%) reported a ± grade 2 symptom. Likewise, at week 12, 22 (22%) of subjects reported one or more >= grade 2 symptoms.

Unprotected Sexual Intercourse following PEP

- At the week 1 visit, subjects were asked about other unprotected intercourse in the preceding 6 months.
 - 74 (57%) reported any unprotected intercourse, most (93%) with a single partner, and most vaginal.
 - In most cases, the partner was believed to be HIV negative or was of unknown HIV status. There were no reports of unprotected sex with a partner who was known to be HIV-infected.
- At weeks 4, 12, and 26: 44 (37%), 49 (49%) and 30 (63%), respectively, reported any unprotected intercourse, most with a single partner, and most vaginal. The partner was believed to be either HIV negative or was of unknown HIV status.

HIV Seroconversions

- There have been 4 seroconversions to date, with 99 and 48 subjects completing the week 12 and 26 visits, respectively (follow-up continues). All were HIV antibody negative at baseline.
- Subject #10066 HIV+ at week 12. Exposure: receptive vaginal intercourse; 1 perpetrator. PEP initiation: 7 hours. Adherence: excellent. Subject reported only protected intercourse at week 4 visit with regular sexual partner/HIV status unknown.

HIV Seroconversions (cont'd)

- This case represents probable failure of PEP to prevent infection despite early initiation and excellent adherence*
- Subject #10027 HIV+ at week 12. Exposure: receptive vaginal intercourse and oral intercourse with ejaculation; 1 perpetrator. PEP initiation: 6 hours. Adherence: excellent. Subject reported unprotected intercourse at baseline and week 4 visit with regular sexual partner/HIV status unknown.
 - This case represents either infection from regular partner or failure of PEP to prevent infection despite early initiation and excellent adherence.*
- Subject #10114 HIV+ at week 12. Exposure: receptive vaginal intercourse; 1 perpetrator. PEP initiation: 17 hours. Adherence: no missed doses at week 1, but completed PEP 5 days after scheduled completion date. Subject reported no sexual activity at baseline, weeks 1 and 12.
 - This case represents probable failure of PEP to prevent infection in the context of incomplete adherence*
- Subject #10079 HIV+ at week 26. Exposure: receptive vaginal intercourse; 1 perpetrator. PEP initiation: 4 hours. PEP medication discontinued at 2 days due to drug rash. Consultant recommended to continue PEP, but subject could not be contacted. Subject reported unprotected intercourse at baseline, missed week 4 and week 12 visits, and at week 26 reported unprotected intercourse 2 months after assault with 2 partners.
 - The source of this new infection is unknown and may have been the sexual assault perpetrator or one of the consensual sex partners. PEP was not provided beyond 2 days.*

- In summary, there has been 1 probable PEP failure in the context of excellent adherence and 1 in the context of poor adherence; 1 new infection whose source is unclear; and 1 new infection in a subject who received only 2 days of PEP medication.

Discussion

- Sexual assault in this setting involves high-risk exposures in terms of potential HIV transmission and, frequently, multiple perpetrators.
- PEP is often available within 48 hours in this community and is well-accepted.
- Symptoms are common, and appear to decrease after the PEP period is over, although without a placebo control it is unclear how much symptoms are associated with PEP versus trauma-associated distress.
- With intensive case management, the availability of home visits (used in 20% of follow-up visits), adherence counseling, and aggressive tracking, relatively few discontinued PEP (13%), but a quarter report missed doses in the first week.
 - These relatively good adherence rates cannot be generalized to settings that lack the human resources required to provide such intensive follow-up.
 - More intensive adherence counseling and/or a shorter course regimen with few side effects may improve adherence. Side effects were a common cause of medication discontinuation, although subjects did not report pill burden or side effects as reasons for missed doses.
 - Home visits might be even more desirable in less densely populated rural areas, where long distance travel is required for follow-up and privacy issues resulting from urban township crowding may be less of a concern.
 - Training of forensic nurses to provide comprehensive care and follow-up of sexual assault survivors should be a priority.
- Unprotected sexual intercourse with partners of unknown HIV status is common preceding and following the sexual assault, despite HIV testing and counseling, and some HIV seroconversions may have resulted from ongoing exposures.
 - Counseling and support to minimize subsequent HIV exposure in this high-HIV prevalence context is critical. Integrating such counseling into post-trauma care is, however, challenging. It is encouraging that many survivors had tested for HIV previously, although discouraging that many did not know the HIV status of their sexual partners.
 - A qualitative sub-study addressing mental health issues and feelings about HIV infection, HIV testing, and PEP following sexual assault will provide formative data critical in developing effective comprehensive counseling strategies.
- Similar pilot studies in other urban, suburban and rural settings in areas of high HIV prevalence can provide data to assist in developing specific programs for use in different communities.

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