

# A Reanalysis of the PEP II Study

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## PEP II Study

- 457 subjects at risk for HIV infection
- Inclusion: post-exposure HIV prophylaxis after a high risk encounter
- Randomly assigned
- Intervention: intensive v. standard counseling
- Outcomes: number of self-reported high risk acts at 6 and 12 months

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## Available Data

	Enhanced	Standard
n	229	228
Baseline	217 (95%)	224 (98%)
6 months	176 (77%)	168 (74%)
12 months	159 (69%)	156 (68%)

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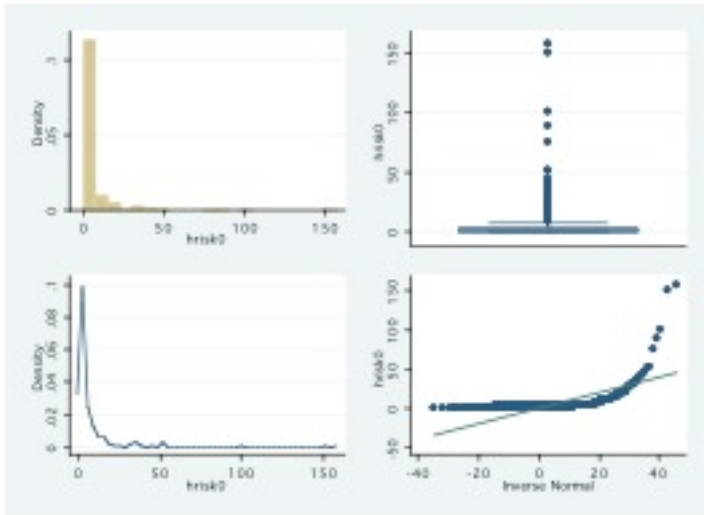
## Baseline Sexual Activity

*Number of High-Risk Acts in 6 mo prior to study*

	Enhanced n=224	Standard n=217
mean	5.4	5.5
median	1	1
range	0-150	0-157

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# Baseline



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# Rank Correlation

Enhanced  
n=143

	hrisk0	hrisk26	hrisk52
hrisk0	1.0000		
hrisk26	0.4066	1.0000	
hrisk52	0.3179	0.4855	1.0000

Standard  
n=140

	hrisk0	hrisk26	hrisk52
hrisk0	1.0000		
hrisk26	0.4230	1.0000	
hrisk52	0.3611	0.4216	1.0000

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## Issues in the Analysis

- Appropriate summary: mean or median
- Dichotomization
- Distribution of the outcome
- Incorporation of baseline values
  - reduce residual variation
  - possible interaction with sexual activity

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## Features of the Data

- Longitudinal: multiple records per subject
- Highly designed: measured at exact times
- Relatively few measured values
- Focused question: does treatment work?

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## Mean is sensible summary

- HIV infection risk:  $\approx 1\%$  per high-risk act
- mean number infections in group  
 $\approx N E(Y) p$
- $N$ : number of subjects
- $p$ : per contact risk
- $E(Y)$ : mean number of contacts
- Infections proportional to  $E(Y)$

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## Distribution

Variable	Obs	Mean	Std. Dev.	Min	Max
hriak0	441	5.444444	14.23607	0	157
hriak26	344	2.694767	9.735114	0	113
hriak52	315	3.212698	11.74365	0	120

Note that variance is much greater than mean  
-- suggests that Poisson is unlikely to fit

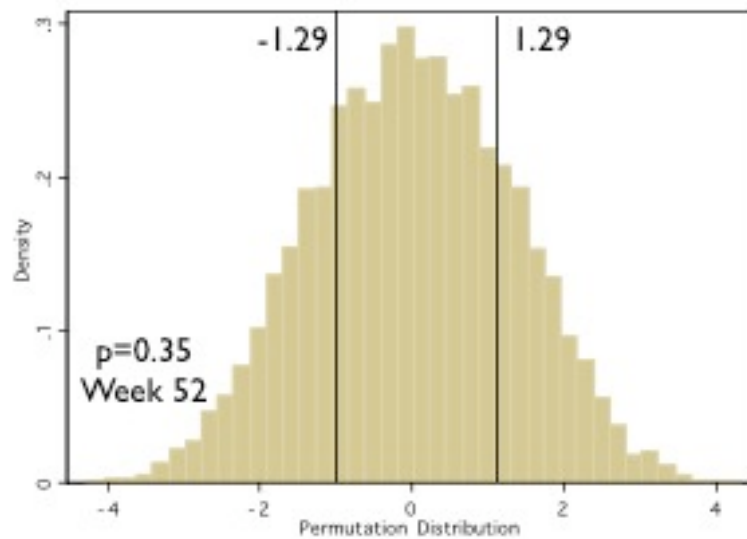
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# Randomization Test

- Rationale: null hypothesis that treatment is not associated with outcome
- Scramble treatment assignments repeatedly
- Compare distribution of treatment effect to observed effect
- p-value: prop of permuted effects more extreme than observed effect

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## Use Differences?

- Take difference between week 52 and baseline value
- Makes use of initial value  
*more direct comparison*
- Very useful if imbalance or missing values

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## Regression on difference

Source	SS	df	MS	
Model	19.2019579	1	19.2019579	Number of obs = 307
Residual	74802.0749	305	245.252705	F( 1, 305) = 0.08
Total	74821.2769	306	244.513977	Prob > F = 0.7798
				R-squared = 0.0003
				Adj R-squared = -0.0030
				Root MSE = 15.461

diff	Coef.	Std. Err.	t	P> t	[95% Conf. Interval]
Sum_rand	-.5002122	1.787675	-0.28	0.780	-4.017949 3.017524
_cons	-1.822368	1.270238	-1.43	0.152	-4.321908 .6771708

Treatment effect: -0.51, p=0.78

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# Baseline as Covariate

- Model: Response depends on rx and baseline
- Use baseline as another covariate
- Doesn't always correct for baseline imbalance!
- Less direct approach

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# Model with baseline as covariate

Source	SS	df	MS			
Model	1731.46748	2	865.73374	Number of obs =	307	
Residual	41508.8778	304	136.542361	F( 2, 304) =	6.34	
Total	43240.3453	306	141.308318	Prob > F =	0.0020	
				R-squared =	0.0400	
				Adj R-squared =	0.0337	
				Root MSE =	11.685	

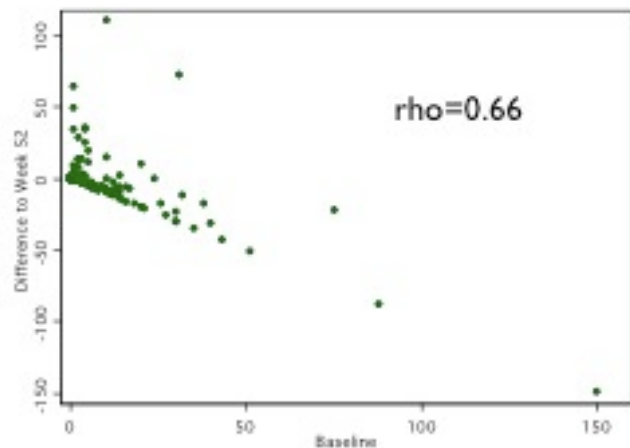
  

hriak52	Coef.	Std. Err.	t	P> t	[95% Conf. Interval]	
_cons	1.854393	.9766	1.90	0.059	-.0473582	3.776145
hriak0	.1805457	.0524784	3.44	0.001	-.0772788	.2838127
hriak52	.9142159	1.336947	0.68	0.495	-1.716627	3.545859

Treatment effect: 0.91, p=0.50

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## Difference Highly Correlated with Baseline



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## If use baseline with difference

Source	SS	df	MS			
Model	33312.3991	2	16656.1995	Number of obs =	387	
Residual	41508.8778	384	136.542361	F( 2, 384) =	121.99	
Total	74821.2769	386	244.513977	Prob > F =	0.0000	
				R-squared =	0.4452	
				Adj R-squared =	0.4414	
				Root MSE =	11.685	

diff	Coef.	Std. Err.	t	P> t	[95% Conf. Interval]	
Num_rand	.9142159	1.336947	0.68	0.495	-1.716627	3.545059
hrisk0	-.8194543	.0524784	-15.62	0.000	-.9227212	-.7161873
_cons	1.854393	.9766	1.90	0.059	-.0673582	3.776145

Treatment effect: 0.91,  $p=0.50$ : same

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## Comparing Approaches

- Give similar approaches for randomized trials (baseline similar in two groups)
- Can give big differences for obs data (VGSM, pp 263-265)
- Neither is the ideal approach

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## Repeated Measures Model

- $Y_{ij} = \text{time}_j + rx_i + rx\text{time}_{ij}$
- The treatment effect is now the treatment by time interaction
- Nice because it puts all outcomes on the left side
- Will work for observational and randomized data
- Puts us squarely in the repeated measures framework

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# GEE Results

```
GEE population-averaged model
Group variable:      id      Number of obs   =    756
Link:                identity Number of groups =    449
Family:              Gaussian Obs per group: min =    1
Correlation:         independent          avq =    1.7
Scale parameter:    175.0592          max =    2
Wald chi2(3)       =    8.07
Prob > chi2        =    0.0446

Pearson chi2(756):  132344.77      Deviance         = 132344.77
Dispersion (Pearson): 175.0592      Dispersion        = 175.0592
```

(Std. Err. adjusted for clustering on id)

hrisk	Semi-robust					
	Coef.	Std. Err.	z	P> z	[95% Conf. Interval]	
rx	-.1048387	1.357811	-0.08	0.938	-2.766899	2.556422
week52	-2.925369	1.210538	-2.42	0.016	-5.297979	-.5527583
prod	1.397896	1.753312	0.80	0.425	-2.038533	4.834325
_cons	5.497696	1.007951	5.45	0.000	3.522148	7.473244

Rx effect at week 52: 1.40, p=0.43

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# Repeated Measures

- Is a Gaussian family reasonable?
- How to avoid this? Use a more flexible family?
- Coefficient is unbiased
- Problem is SE, CI and p-value
- Why not just use bootstrap?

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# Bootstrap Results

```
Linear regression                               Number of obs   =    756
                                                Number of clusters =    449
                                                Replications    =    2000
                                                Wald chi2(3)    =    7.94
                                                Prob > chi2     =    0.0473
                                                R-squared       =    0.0079
                                                Adj R-squared   =    0.0039
                                                Root MSE       =    13.2661
```

	Observed Coef.	Bootstrap Std. Err.	z	P> z	[95% Conf. Interval]	
rx	-.1048387	1.339161	-0.08	0.938	-2.729546	2.519868
week52	-2.925369	1.197349	-2.44	0.015	-5.27213	-.5786075
prod	1.397896	1.731649	0.81	0.420	-1.821384	4.915922
_cons	5.497696	1.006152	5.46	0.000	3.525674	7.469717

Results are very close to GEE!

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# Interpretation

*After 1 year, subjects with enhanced counseling had an average of 1.39 more unprotected contacts in the previous 6 months compared with subjects receiving standard counseling, 95% CI (-1.82, 4.92).*

Additive scale awkward, perhaps use log link to get a multiplicative interpretation;

very easy in GEE  
(no need to transform the data)

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# Log Link Results

```

GEE population-averaged model
Group variable:      id      Number of obs   =   1199
Link:                log     Number of groups =    453
Family:              Gaussian Obs per group: min =    1
Correlation:         independent          avg =    2.4
                                      max =    3
Scale parameter:    149.8584      Wald chi2(5)    =   13.43
                                      Prob > chi2     =   0.0196
Pearson chi2(1199): 164844.28      Deviance       = 164844.28
Dispersion (Pearson): 149.8584      Dispersion     = 149.8584
    
```

brisk	b*coef	Bootstrap Std. Err.	z	P> z	[95% Conf. Interval]	
rx	.9809384	.2481136	-0.08	0.937	.6071274	1.584891
week26	.4640374	.1444983	-2.47	0.014	.2520543	.8543024
week52	.4678918	.1715175	-2.07	0.038	.2280952	.9597868
rx26	1.136944	.495007	0.29	0.768	.484344	2.668945
rx52	1.531893	.7181411	0.91	0.363	.6112104	3.839423

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# Interpretation

*After 1 year, subjects with enhanced counseling had an average 53% more unprotected contacts in the previous 6 months compared with subjects receiving standard counseling, 95% CI for relative number of contacts 0.61 to 3.8*

*In the first 6 months subjects with enhanced counseling had an average 13% more unprotected contacts compared with subjects receiving standard counseling, 95% CI for relative number of contacts 0.48 to 2.7*

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## Interpretation

*Both groups had an approximate 54% reduction in the number of unprotected contacts at 6 months and 1 year compared to baseline*

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## Interaction?

- Natural to consider if effect of treatment modified by baseline risk
- Consider two stratum: 0-2 unprotected contacts at baseline v. 2+ unprotected contacts
- Use GEE with treatment by time by stratum interaction

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# 3 way interaction model

```

GEE population-averaged model
Group variable:      id      Number of obs   =   1081
Link:                log     Number of groups =    441
Family:              Gaussian Obs per group: min =    1
Correlation:         independent avg   =    2.5
                                      max   =    3

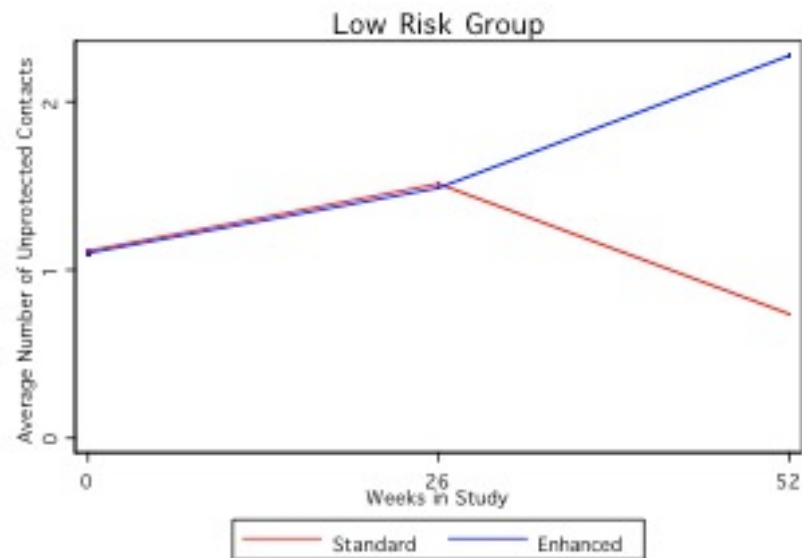
Scale parameter:    134.2375   Wald chi2(10)   =   414.51
                                      Prob > chi2     =   0.0000

Pearson chi2(1081): 145110.75   Deviance        = 145110.75
Dispersion (Pearson): 134.2375   Dispersion      = 134.2375
    
```

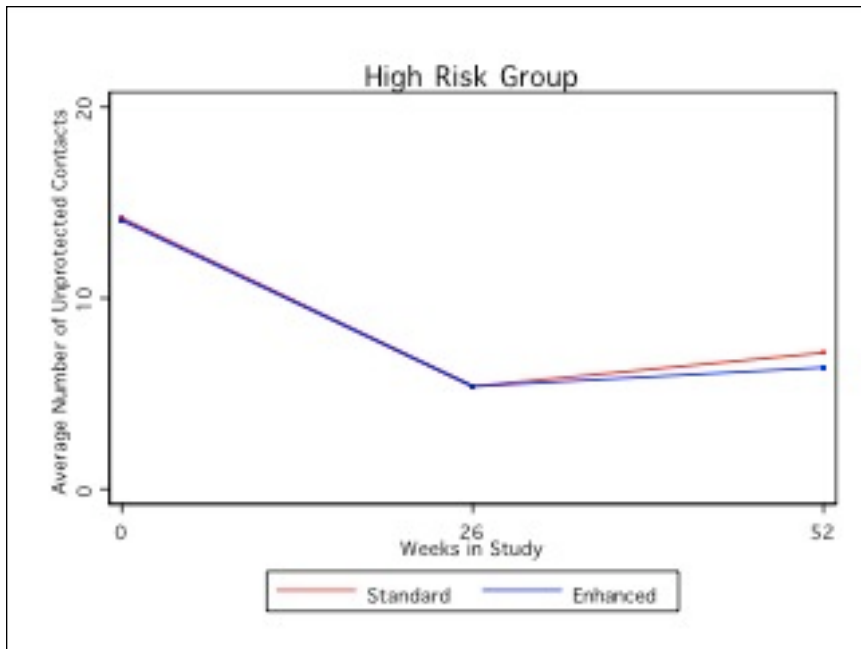
(Std. Err. adjusted for clustering on id)

hrisk	Semi-robust		z	P> z	[95% Conf. Interval]	
	a*coef	Std. Err.				
rx	.9907393	.2544728	-0.84	0.971	-.5988827	1.639047
_Intrat_1	12.68528	1.898027	19.87	0.000	9.770848	14.47037
week26	1.361164	.8698124	0.49	0.629	-.3890226	4.762622
_IntrXwe-1_1	-.2824122	.1913214	-1.87	0.862	-.0749572	1.065451
week52	-.6585179	.3211938	-0.86	0.392	-.2531591	1.712945
_IntrXwe-5_1	-.7815547	.474424	-0.44	0.662	-.2246105	2.582095
rx26	-.9891456	.9121687	-0.81	0.989	-.1978585	4.944993
_IntrXrx26_1	1.815895	.9835124	0.82	0.986	-.1846447	5.58714
rx52	3.133199	2.118047	1.70	0.890	-.8370432	11.72811
_IntrXrx52_1	-.2915404	.2347489	-1.53	0.126	-.0681603	1.413923

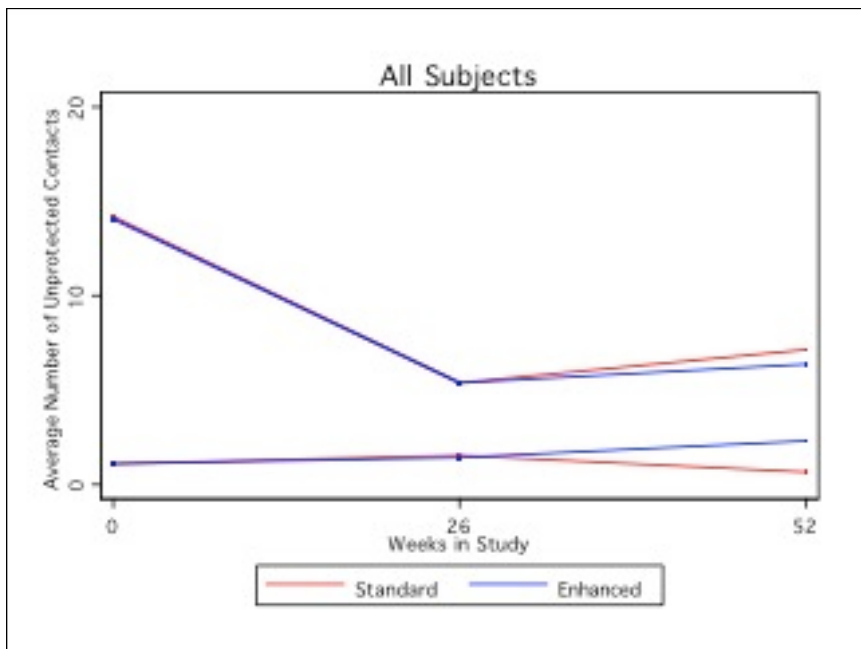
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## Summary of Results

- High risk subjects reduced their contacts during the study
- Low risk subjects didn't change much
- No evidence of an effect of enhanced counseling in either stratum

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## General Advice

- Could simply do a series of t-tests  
analysis using all data can be more efficient
- Using differences and adjusting baseline less desirable  
*especially for observational data*
- Repeated measures gives unified analysis
- Resampling methods can make analysis less sensitive to distributional assumptions

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