



The Positive Partners Study of HIV-1 Superinfection

ROBERT M GRANT^{1,2}, ERIC DELWART^{2,3}, JEFF MCCONNELL¹, GREG GREENWOOD^{2,4}

¹Gladstone Institute of Virology and Immunology, San Francisco, CA; ²University of California, San Francisco;

³Blood Centers of the Pacific, San Francisco, CA; ⁴UCSF Center for AIDS Prevention Studies/UCSF

Introduction

The primary goal of this research is to test the hypothesis that a person with an established HIV-1 infection can be re-infected with a second variant of HIV-1 (i.e. superinfection). A case of HIV-1 superinfection after seroconversion has never been documented in the peer-reviewed literature.

Additionally, the Positive Partners study will assess broader virological and epidemiological implications of unprotected sex between partners already infected with HIV. This will eventually include monitoring and testing for the transmission of other viral STDs, and an assessment of how unprotected sex among partners both positive for HIV affects choices about high-risk sex with partners of negative or unknown status.

Specific Objectives for the UARP IDEA Award

1. To develop and evaluate methods of recruitment and retention of anti-HIV-1 seropositive seroconcordant couples who have unprotected intercourse prior to study enrollment and during a one-year follow-up period.
2. To seek evidence of prior superinfection in pilot couples at baseline which could be manifested as dual infection with divergent variants of HIV-1.
3. To determine if HIV-1 superinfection occurs in a small group of sexually exposed couples followed over a 12-month period.
4. To evaluate community interest and support for this research question and project, and the possible effects that the theoretical risk of HIV superinfection has had on the sexual choices of HIV-positive individuals enrolling in the study.

Background

1. Evidence of dual or co-infection with multiple HIV-1 subtypes and recombinant HIV-1 viruses in humans and monkeys have been taken as de facto evidence of superinfection. However, when transmission has been documented, dual infections have resulted from concomitant exposure. Dual infection after sequential exposure has not been reported.
2. Nonhuman primates can be superinfected only in a short window of susceptibility during primary infection, or when immune responses are not fully developed. Published longitudinal studies of viral evolution in humans have provided no evidence of superinfection.
3. The possibility of superinfection with a drug resistant form of the virus and that successful HAART therapy could contribute to susceptibility has heightened the importance of the question.
4. The possibility of HIV-1 superinfection is assumed in prevention messages to deter infected individuals from a course of high-risk sexual intercourse. Little data exists, however, to support a connection between concern about HIV superinfection and sexual choices.

Research Plan

Study Design. This is a one-year prospective feasibility investigation of the occurrence of HIV-1 superinfection among 50 couples of any gender mix. Recruitment for the pilot study was done primarily through the Positive Partners Community Advisory board, local ASOs, and HIV clinics. Couples are deemed eligible through an independent telephone screening of partners. Enrollment and follow-up study visits include interviews and biological specimen collection (blood and semen). Retention strategies include providing clinical test results, follow-up telephone contact every three months, and interim interviews/testing in cases of treatment breakthrough.

Inclusion Criteria:

- HIV-1 seropositive concordant couples.
- Both partners on HAART, or are on STI.
- The couple practices unprotected anal or vaginal intercourse.
- One partner did not infect the other.

Primary Behavioral Measures:

- Sexual networks' characteristics and density including sexual exposure to primary and other partners (past three months).
- Knowledge, attitudes, and beliefs about superinfection.

Virological Measures:

- Viral load, drug resistance genotype, and Complete Blood Count (CBC).
- Baseline assays to distinguish partner's viruses, and follow up analysis to look for evidence of superinfection, include plasma RNA RT-PR sequencing and cellular DNA env V3 and tat Heteroduplex Mobility Assays, env V3, gag p17, and tat cloning and sequencing.

Preliminary Results (18-couple pilot study)

Analysis of preliminary data focused on whether a reasonably diverse sample representing the epidemic in San Francisco enrolled, how appropriate (at risk) enrolling couples were for superinfection research, and what effect participants' beliefs about superinfection had on their sexual choices, if any.

Categorical	N	Percent			
Education					
High school graduate, G.E.D or less	9	24.3%			
Two years of college, AA degree, or college graduate	19	51.4%			
Graduate degree	9	24.3%			
Total	37	100.0%			
Race					
African American/Black	4	10.8%			
Anglo-European/White	27	73.0%			
Asian or Pacific Islander	2	5.4%			
Latino/Hispanic	2	5.4%			
Mixed	2	5.4%			
Total	37	100.0%			
Sexual orientation					
Gay/Lesbian/Homosexual	28	75.7%			
Bisexual	5	13.5%			
Queer	2	5.4%			
Heterosexual/Straight	2	5.4%			
Total	37	100.0%			
Gender					
Female	1	2.7%			
Male	35	94.6%			
Transgender/Transsexual - MTF	1	2.7%			
Total	37	100.0%			
Continuous					
Age	Mean: 40.14	Min: 28	Max: 67	S.D.: 8.09	N: 37
Income	Mean: 36,871	Min: 250	Max: 150,000	S.D.: 39,311	

	Mean	Min.	Max.	S.D.	N
Years since first tested HIV-positive	7.91	0.42	15.74	4.63	37
Number of different ARVs ever taken	5	2	12	3.01	19
Total years on any/all ARVs	5.0	0.3	13.3	3.8	37
Lowest CD4+ count	201	0	620	148	37
Recent CD4+ count	469	65	800	195	37
Recent Viral Load	22,294	<50 (25)	270,000	66,468	37
CD4+ count at enrollment	536	110	1,600	331.2	36
Viral load at enrollment	25,075	<50 (13)	367,658	70,217	37

Participants reported high rates of exposure to potential superinfection:

- Participants reported almost nine episodes of intercourse over the past 30 days with their primary partners.
- Less than half of the couples were monogamous, nonmonogamous individuals reported an average of over two other HIV-positive partners in the past six months.

Measures of Sexual Exposure	Mean	Min.	Max.	S.D.	N
Length of sexual relationship (years)	3.8	0.08	13	4.44	37
Intercourse with primary partner (past 30 days)					
Receptive anal intercourse	4.26	0	35	7.48	35
Insertive anal intercourse	4.30	0	31	7.08	33
All intercourse	8.72	0	35	8.78	33
Intercourse with condoms (4 couples)	0.3	0	6	1.1	33
Couples and their outside partners (last 6 months)					
		N		Percent	
Monogamous couples		8		44.4%	18
Monogamous singles		18		48.6%	37
Individuals' and their outside partners (last 6 months)					
	Mean	Min.	Max.	S.D.	N
Number of outside partners	10.16*	1	90	20.56	19
Number involving unprotected intercourse	6.15	1	32	8.32	13
Number HIV-negative or of unknown status	3.91	1	12	2.98	11
*Median: 4.72					

Virological Summary:

- Exactly half of participants were virally suppressed on H.A.A.R.T.
- Because successful viral suppression might create a window for superinfection to occur during chronic infection we looked at whether couples included one partner who was suppressed and one with viremia—50% of couples met these high-risk criteria.
- In one-half of twelve couples analyzed at baseline partners' viruses were genetically unlinked.

Individual Level Analysis		
Treatment	N (36)	%
Interruption	4	11.10%
On treatment	32	88.90%
Viral Load (VL)		
<100 copies/ml	18	50.00%
>100 copies/ml	18	50.00%
Drug resistance		
Viral responder	18	50.00%
Any drug resistance	12	33.30%
Nucleoside resistance	10	27.80%
Non-nucleoside resistance	8	22.20%
Protease Inhibitor resistance	7	19.40%
Couples' Level Analysis		
Virological Risk	N (18)	%
Concordant VL suppression	5	27.80%
Concordant viremia	4	22.20%
Discordant viremia	9	50.00%
Viral Linkage within couples		
Unlinked viruses	6	54.50%
Linked viruses	5	45.50%

Concern about superinfection was associated with sexual practices:

- Participants who believed superinfection poses a "serious problem" were less likely to have outside partners, more likely to practice early withdrawal, and tried to protect themselves from superinfection.
- Those who tried to protect themselves from superinfection had more outside partners who were HIV-negative or of unknown status.

	Mean	r	p
Had heard of superinfection before the study	94.60%		
Years knew about the possible risk	4.8		
Concerns experienced about superinfection when having intercourse (4-point scale):			
receptive to ejaculation	2.38		
insertive to ejaculation	2.33		
receptive with withdrawal	1.69		
insertive with withdrawal	1.74		
Beliefs about superinfection and sexual practices			
Superinfection concerns (index) and number of outside partners	0.66	0.03	
Believed superinfection posed a "serious problem" associated with:			
more intercourse with early withdrawal	0.32	0.08	
having outside partners (less likely)	-0.40	0.02	
intent to protect oneself from superinfection	0.41	0.02	
Intent to protect oneself from superinfection and number of HIV-negative or unknown status partners			
	0.45	0.06	

Conclusions

1. Community reaction to the study, including our Community Advisory Board, was quite positive and supportive. Couples appropriate to an investigation of HIV-1 superinfection were willing to enroll in the study. A few couples have separated during the follow-up period, but no individuals are known to be lost to the study.
2. The telephone screening procedure effectively identified couples that had genetically distinguishable viruses at baseline in about 75% of cases. Superinfection, if it occurs during follow-up, should be detectable in these couples.
3. No evidence of prior superinfection (dual infections or recombinant viruses) has been found in the baseline analysis of 12 pilot couples.
4. Beliefs about superinfection apparently fostered harm reduction strategies that may have reduced the risk of superinfection for all partners (i.e. withdrawal), or shifted risk to partners willing to practice more frequent receptive intercourse and to HIV-1 uninfected partners. Concerns about superinfection may disrupt primary relationships and increase risk of new HIV-1 infections.

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