

No superinfection among seroconcordant couples after well-defined exposure

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Background

Sequential infection with variants of HIV-1, or superinfection, has been described in 5 published case reports involving persons who are recently infected and those who have been intermittently treated with antiretroviral therapy (Ramos 2002, Altfeld 2002, Koelsch 2003).

The frequency of appearance of highly divergent viruses in recent seroconverters has been estimated to be comparable to the overall incidence of new HIV-1 infections (Smith 11th CROI, Hu Barcelona 2002).

In contrast, the detection of highly divergent viruses in chronically infected persons is rare (Gonzales 2003, Tsui 2004).

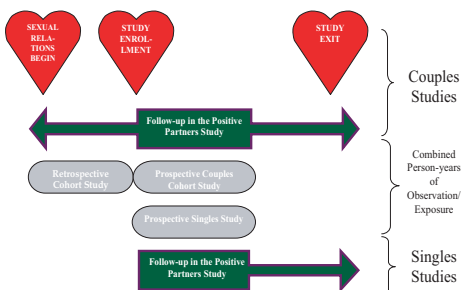
Non-human primate research suggests that there is a window period of susceptibility to superinfection, lasting 4 weeks in pigtailed macaques (Otten 1999).

Mathematical models demonstrate that superinfection restricted to a short window period of susceptibility after initial infection could lead to highly prevalent recombinant infections due to secondary spread from dually infected persons (Gross 2004).

Methods

The Positive Partners study is a prospective cohort of seroconcordant HIV-1 infected couples in San Francisco who practice unprotected anal or vaginal intercourse with each other. Couples were enrolled if they reported that their infections predated their relationship and if viral genetic analysis indicated no evidence of transmission linkage at baseline. Individuals were also enrolled if they reported unprotected intercourse with more than 10 seropositive partners in the past year. Population sequences at the *tat*, *env*, *pro*, and *pol* loci were derived from PBMC DNA and plasma viral RNA.

Study Diagram



Results

- Positive Partners I consisted of 125 enrollments and 106 completions (85% retention) including 46 couples and 34 individuals.
- Data analyzed here include 33 couples and 30 singles assessed either in *tat*, *env*, or *pol*.
- Of 33 couples assessed virologically at baseline 28 had distinguishable viruses in spite of having reported frequent UI with enrollment partners.
- Of the 5 couples with indistinguishable virus at baseline 3 reported infection histories suggesting that transmission occurred within the relationship. In the other two couples superinfection prior to enrollment in our study cannot be ruled out at this time.
- Of 90 individuals who exited the study and who have been assessed so far, evidence of superinfection was not found within any of the couples. One individual, who was a recent seroconverter, developed a highly divergent virus at the followup visit.

Extensive Exposure to Genetically Distinguishable Variants of HIV-1

Couples Analysis		N (Individuals)	Person- years	UAI Exposures
Prospective data	Years observed	58	1.00	58
	UAI with enrollment partner	56	41.58	2,328
	UAI with other partners	58	22.65	1,397
Sub Totals			58	3,725
Retrospective data	Years observed	56	2.86	160
	UAI with enrollment partner		41.58	373,411
Totals			219	377,137
Singles Analysis	Years observed	32	0.80	24
	UAI with positive partners		91.46	2,744
Grand Totals			243	379,880

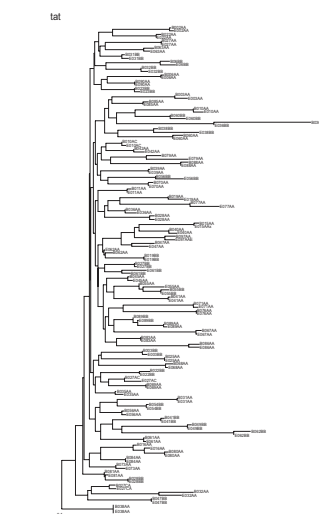
UAI is Unprotected Anal or Vaginal Intercourse

Phylogenetic Analysis

Summary:

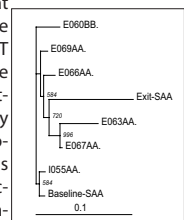
Of 28 couples with genetically distinguishable viruses at baseline, the followup viruses clustered with the baseline viruses in all couples.

Among 32 individuals with more than 10 HIV-1 infected partners per year, one had a highly divergent virus at followup. This one individual entered the study as a recent seroconverter.



A highly divergent virus in one seroconverter

One individual (labeled SAA) is still being evaluated as a possible case of superinfection. He was identified as a recent seroconverter in October 2001 after exposure to multiple partners in sex clubs. At the time of seroconversion, his virus was similar to another participant in our study, who also reported frequent visits to sex clubs. At the followup visit, his virus was highly divergent at the protease locus, and the population sequence of the RT sequence indicated a mixture divergent sequences, suggesting the emergence of a highly divergent variant. His exposure history suggests that this could be a case of superinfection, or it could represent concomitant dual infections with sequential emergence of divergent variants as they escape from immune responses. Clonal analysis of sequences, and assays to detect subsequent viruses in the baseline specimens are being performed.



Conclusions

Seroconcordant couples are uniquely valuable for superinfection research because exposure can be well characterized.

The predominance of superinfection cases among recent seroconverters may reflect a window period of susceptibility to acquiring new infections, as predicted from non-human primate research. Alternatively, recent seroconverters may harbour several viruses that appear sequentially due to viral escape from immune responses.

The one individual with a genetically distinguishable virus at followup suggests that superinfection may have occurred. Additional virological analysis is required. This one individual was a recent seroconverter.

We have found no evidence of superinfection in 58 person years of well-characterized exposure to a genetically distinguishable virus. This period of exposure involved 3725 episodes of unprotected anal or vaginal intercourse. Cases of superinfection among chronically infected individuals have not been published, and case series involving more than 1200 person years of observation did not show evidence of superinfection (Gonzalez *JID* 2003, Tsui *JV* 2004).

Studies of mechanisms blocking HIV-1 superinfection are warranted to better understand why superinfection among chronically infected humans is rare. These mechanisms may include specific anti-viral immune responses, viral interference, or non-specific immune responses.

Acknowledgements

This project is supported by the Centers for Disease Control and the Gladstone Institute of Virology and Immunology. We thank Bernard Branson for project support. We thank Jackie Javier, Timothy Schmidt, Lucy Chow, and Zoila Angeles for genotyping expertise.