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# HIV Superinfection vs Dual Initial Infection: What Clinicians and Patients Should Know

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## Introduction

HIV-1-infected patients and their clinicians have been asking questions about superinfection -- reinfection with a second strain of HIV after the first infection has been established through seroconversion -- since the early years of the HIV/AIDS epidemic: Does superinfection happen? What is the risk of being superinfected? What will happen to me if I become infected with a second virus? Can I acquire drug resistance through superinfection? Although we continue to ask questions about superinfection -- as well as search for a definitive case -- ongoing research has begun to offer some answers.

## Timing of Superinfection: An Apparent Window of Susceptibility

The first reported evidence of superinfection came from studies of monkeys in 1987.<sup>[1]</sup> More recent research suggests that there may be a window of time in which nonhuman primates are susceptible to superinfection. Otten and colleagues<sup>[2]</sup> found that pig-tailed macaques could be successfully reinfected with a second viral strain up to 4 weeks after initial infection. Attempts to reinfect the macaques were unsuccessful at 8, 12, 14, and 72 weeks after infection. The biological mechanisms that block superinfection after 4 weeks in this animal model are not yet known.

A similar pattern suggesting a "window of susceptibility" has been described in superinfection research in humans. Sixteen cases of apparent superinfection in HIV-1-infected persons have been reported, all since 2002. In 15 of these cases, the second virus appeared within the first 3 years of HIV infection.<sup>[3-10]</sup> In 1 case, the second virus may have appeared after 3 years of infection, but the timing of this event is unknown due to minimal follow-up.<sup>[11]</sup> See [Table 1](#) for a comprehensive list of reported cases.

## Superinfection vs Dual Infection at Baseline

In order to definitively distinguish between infection with 2 or more strains at the time of initial infection vs "superinfection" at a point after the initial infection is established, several demanding criteria must be met. Current superinfection research faces several epidemiologic and virologic limitations that call into question the very use of the term "superinfection" to describe what we have seen so far. At this point, there have been no reported cases of superinfection in which a source partner for the second virus was identified. Until a source partner for superinfection is found, and the timing of exposure confirmed, we cannot be absolutely sure that the second virus was acquired after seroconversion; a patient with a dual infection may express the 2 viruses sequentially, thus appearing to be superinfected. Additionally, technical limitations mean that it cannot be virologically proven that the second virus was not present at baseline. In our own study,<sup>[10]</sup> described in greater detail below, we were unable to detect the divergent virus at baseline using heteroduplex tracking assays (HTA) to detect minor viral variants, but these methods cannot detect minor variants that are present in less than 1.5% to 3.0% of the overall viral population. Many of the other case reports of putative superinfection have not been confirmed using sensitive assays to detect dual infection at baseline. Using HTA, we were also unable to detect the first virus at follow-up even though we assume that it is still present in the body. For these reasons, we prefer to label most "superinfection" cases described thus far as sequentially expressed dual infections (SEDI). Sequential expression of viruses in individuals may reflect sequential acquisition

(superinfection) or nearly concomitant dual infection with sequential expression of viruses due to dynamic immune responses.

In our study, we drew a sample of 104 recently infected patients from The Options Project, the San Francisco site for The Acute Infection and Early Disease Research Program (AIEDRP).<sup>[10]</sup> All patients who remained in the study for at least 6 months and who were untreated at the 6-month visit were included. The last follow-up timepoint with HIV RNA of > 100 copies/mL was selected for comparison to a baseline sample. Superinfection screening involved phylogenetic analysis of protease and reverse transcriptase sequences at baseline and follow-up timepoints using bootstrapped, neighbor-joining trees. After 192 person-years of follow-up, we initially observed 8 cases that appeared to involve the sequential appearance of new viruses over the first few years of infection. However, SEDI could only be confirmed in 4 cases after examination of multiple timepoints. In 3 of these cases, there was evidence of exposure to possible superinfection in the form of self-reported unprotected receptive anal intercourse or treatment for sexually transmitted infections. Using analysis of multiple timepoints and sensitive assays to detect multiple viruses at baseline, we have not been able to rule out superinfection in any of these 4 cases. However, this work is not yet completed. Because source partners are not available to confirm the timing of exposure to the second virus, these cases will not provide definitive proof of superinfection.

## **Risk for SEDI in Acute, Early, and Chronic HIV Disease**

The risk for appearance of highly divergent viruses may be relatively high in the first year of infection. Also among recently infected persons, Smith and colleagues<sup>[7]</sup> found a 5% incidence rate of HIV-1 clade B superinfection within 6-12 months of initial infection, although dual infections at baseline were not carefully ruled out and exposure data were not reported. Nonetheless, the sequential appearance of second, highly divergent viruses in this case series suggests that the rate of SEDI during the first year of infection may be comparable to -- or, among individuals with documented exposure, higher than -- the overall incidence of new HIV-1 infections.

In the Options substudy, we estimated a SEDI incidence rate of 2.1%, which is comparable to the rate of superinfection reported by Smith and colleagues (5%). However, we further clarified our incidence rate with information about the length of time subjects had been HIV-infected, as well as the amount of exposure (unprotected intercourse) they reported during follow-up ( [Table 2](#) ). Approximately half of the Options cohort reported unprotected intercourse during the first year of infection, indicating that the rate of SEDI among individuals in their first year of infection who reported exposure may be as high as 8%.

The frequency of SEDI in early infection is particularly noteworthy when compared with its rarity during chronic infection. Apparent superinfection cases among untreated, chronically infected individuals have not been published. SEDI was not detected in a clinic cohort after 1072 person-years of observation; however, this case series did not collect data on the subjects' exposure to possible superinfection.<sup>[12]</sup> Another study, which documented high-risk behavior among intravenous-drug users with 215 person-years of observation, also found no evidence of superinfection.<sup>[13]</sup> We found no evidence of superinfection among chronically infected sex partners after 233 person-years of well-characterized exposure to a genetically distinguishable virus (in the San Francisco Positive Partners study).<sup>[14]</sup> This time period involved an estimated 20,859 exposures during unprotected anal or vaginal intercourse. Based on the subjects' self-reported risk behavior, we calculated how many seroconversions would have occurred if the HIV-positive participants were not already HIV-infected. We would have expected to see 89 new infections over this time period, indicating that initial infection provides protective immunity against superinfection in chronically infected individuals.

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 antiviral immune responses to the partner's virus, viral interference, or nonspecific immune responses. Knowledge about these mechanisms may prove to have important implications for HIV vaccine development. We believe that limited superinfection (superinfection that is below the limits of detection by population sequencing) and/or localized superinfection (superinfection of the tissues of the rectal mucosa, for example) occurs, and may be transient. It is important to establish the clinical relevance of these events and the reasons why these types of superinfection do not become systemic. It is also important to determine at what stage of infection patients are susceptible to superinfection. 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. The same models also demonstrate that rampant superinfection is not consistent with the persistent predominance of single viral subtypes in North America and southern African regions despite introduction of divergent subtypes.<sup>[15]</sup>

## **SEDI and Drug Resistance**

Clinicians and HIV-infected patients are perhaps most interested in the question of whether drug resistance can be acquired through superinfection. In 2 of the 16 reported apparent superinfection cases, a wild-type virus was replaced by a drug-resistant or potentially drug-resistant strain ( Table 1 ). The opposite occurred in 4 cases -- a drug-resistant virus was partially replaced by a drug-susceptible strain. Either of these situations is likely to present treatment complications for the patients involved, either due to acquired drug resistance or the masking of drug resistance by a newly acquired, wild-type virus.

## SEDI and Prognosis

On the basis of research among individuals infected with 2 HIV strains, superinfection could lead to a poorer prognosis even when drug resistance is not involved. Two studies among dually infected persons have shown that having more than 1 HIV strain is likely to lead to more rapid disease progression. Gottlieb and colleagues<sup>[16]</sup> found that dually infected individuals progressed from seroconversion to a clinical AIDS-defining event or death faster than did those infected only with 1 strain of HIV-1 (< 3.4 years). Similarly, Grobler and coinvestigators<sup>[17]</sup> found an association between dual HIV strain infection and higher viral load set point. Our own study<sup>[10]</sup> reflected these findings in the short term; in each of the 4 SEDIs we observed, viral load increased and CD4+ count fell after the second virus appeared. Although it is clear that dual HIV infection is associated with poorer prognosis, it remains unclear whether infection with multiple HIV strains causes more rapid progression or is a manifestation of poorer antiviral immune responses. Indeed, susceptibility to superinfection may also indicate a poor antiviral response.

## Behavioral Implications/Risk

There is some evidence that the risk for superinfection is being weighed against the risk of spreading new infections. We have observed an increase in serosorting -- the selection of sexual practices based on partner's perceived HIV status -- among HIV-positive men who have sex with men (MSM) in San Francisco; many HIV-positive individuals are choosing partners who are also seropositive as a way to prevent the spread of the epidemic. Because people who are HIV-positive have more unprotected sex with other seropositive people, the question of superinfection risk -- and the risk of acquiring other sexually transmitted diseases -- becomes increasingly relevant for HIV-infected patients and their physicians. In terms of sexual health concerns beyond HIV superinfection, HIV-positive persons who have unprotected sex with seroconcordant partners should be counseled about the risks associated with acquisition of sexually transmitted diseases, which can have a more virulent disease course in immunocompromised persons.

So what messages about superinfection should HIV clinicians be giving their patients? It is important for patients -- particularly those who are newly infected and have HIV-positive sex partners -- to know that 15 of 16 apparent superinfections described in the scientific literature occurred during the first 3 years of infection. At this time, there is evidence to suggest that patients who have been infected for over 3 years are not at risk for superinfection. However, these patients should also be informed that superinfection could complicate treatment and lead to more rapid disease progression, and it is not known whether exposure to different viral strains during early infection provides protective immunity against later superinfection. Finally, clinicians and researchers should provide balanced and broad views of the risks of unprotected sex between HIV-1 infected persons, and avoid exaggerated or sensational claims about superinfection that could undermine behaviors such as serosorting and serodisclosure that can help to curtail the spread of HIV.

**Table 1. Case Reports of Sequentially Expressed Dual Infection (Apparent Superinfection)**

Case	Duration of First Infection	Antiviral Treated	Viral Subtypes	Drug Resistance of First Virus	Drug Resistance of Second Virus	Risk Factors	Location	Reference
1	<12 weeks	No	B after AE	Unknown	Unknown	IDU	Thailand	Ramos et al. <sup>[3]</sup>
2	<44	No	AE after	Unknown	Unknown	IDU	Thailand	

	weeks		B					
3	<152 weeks	Yes, intermittent	B after AE	Wild-type	Unknown	MSM	Switzerland	Jost et al. <sup>[4]</sup>
4	<128 weeks	Yes, intermittent	B after A	Unknown	Unknown	MSM	Boston	Altfeld et al. <sup>[5]</sup>
5	<16 weeks	No, initial virus was drug-resistant	B after B	MDR	Wild-type	MSM	San Diego	Koelsch et al. <sup>[6]</sup>
6	<52 weeks	No, initial virus was drug-resistant	B after B	Drug resistance	Wild-type	MSM	San Diego	Smith et al. <sup>[7]</sup>
7	<52 weeks	No	B after B	Wild-type	Drug resistance	MSM	San Diego	
8	<40 weeks	No	B after B	MDR	MDR	MSM	Montreal	Brenner et al. <sup>[8]</sup>
9	84-432 weeks	No	AC after A	Unknown	Unknown	FSW	Nairobi	Fang et al. <sup>[11]</sup>
10	131-177 weeks	No	B after B	Wild-type	Possible NNRTI resistance	MSM	San Francisco	Grant et al. <sup>[10]</sup>
11	16-44 weeks	No	B after B	Wild-type	Wild-type	MSM	San Francisco	
12	29-39 weeks	No	B after B	Wild-type	Wild-type	MSM	San Francisco	
13	43-53 weeks	No	B after B	MDR	Wild-type	MSM	San Francisco	
14	38-55 weeks	No	A after D	Unknown	Unknown	FSW	Kenya	Chohan et al. <sup>[9]</sup>
15	43-84 weeks	No	CA after C	Unknown	Unknown	FSW	Kenya	
16	14-69 weeks	No	A after D	Unknown	Unknown	FSW	Kenya	

*IDU = intravenous-drug use; MSM = men who have sex with men; MDR = multidrug resistance; FSW = female sex workers; NNRTI = nonnucleoside reverse transcriptase inhibitor*

**Table 2. Estimated Rates of Sequentially Expressed Dual Infection (Apparent Superinfection) in the Options Substudy**

Incidence	Estimated rate	If we know...
Incidence of SEDI among recently infected individuals	2.1%	Amount of observation
Incidence of SEDI during first year of	4.3%	Amount of observation and year of infection

infection		
Incidence of SEDI during first year of infection among exposed individuals	~8.0%	Amount of observation, year of infection, and reported exposure through unprotected intercourse

*SEDI=sequentially expressed dual infection*

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