

Discussion Paper for Educators

Superinfection with HIV

June 2004

Data presented at the 11th Conference of Retroviruses and Opportunistic Infections in San Francisco held in February 2004 documented HIV superinfection occurring at 5% a year in a group of recently infected gay men not on HIV antiviral treatments¹. This follows the publication of a number of documented case reports confirming HIV superinfection.

These case reports show that HIV superinfection can:

- **occur with HIV of both a different subtype and with the same subtype** (there is a common myth that superinfection only occurs with HIV of a different subtype);

and

- have a significant impact on a person health and the ability to control HIV infection with antiviral drugs.

HIV superinfection has only been demonstrated in people who are not on antiviral therapy and there is no evidence that shows superinfection could be the cause of unexplained treatments failure.

Given that HIV superinfection does occur quite frequently and that it can be clinically significant for people with HIV there is a need to inform people with HIV about this so that they can take measures to protect themselves.

For people with HIV superinfection is a concern because they may get super-infected with:

- a more virulent (“nasty”) type of HIV; or
- HIV that is resistant to one or more of the drugs used to treat it.

The confirmation of HIV superinfection as a reality has led to questions and concerns about what the changed information means to people with HIV. The purpose of this paper is to examine the evidence and to pose questions about the sort of advice we should be offering in relation to sex between people with HIV.

SOME DEFINITIONS OF TERMS

(These are not 100% accurate “text book” definitions but they will suffice for the purposes of this article)

Reinfection – refers to getting reinfected with an organism that the body has previously been infected with and where it has cleared the previous infection.



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HIV Superinfection - refers to a second infection with a second and different “type” of HIV after an individual has developed an immune response to the initial “type” of HIV (the terms reinfection and superinfection are often used interchangeably in HIV)

HIV Co-infection – refers to being initially infected with two different “types” of HIV at the same time

Recombinant HIV – refers to a form of HIV that is a “hybrid” of two different types. Such recombinant forms can only occur if at some point the body was infected with two different types of HIV.

DATA ON THE FIRST FIVE CONFIRMED CASE REPORTS OF HIV SUPERINFECTION

Case 1¹ - Involved a 38 year old man who was diagnosed with acute HIV infection in November 1998. He went on HAART that was interrupted in January 2001. He had an initial viral rebound to 80,000 copies that then declined to 21000 copies. He then had a “second rebound” in April 2001 to between 200,000 and 400,000 copies. A detailed analysis of samples revealed he was originally infected with virus of subtype AE and subsequently infected with subtype B during a holiday in Brazil.

Case 2²: Was presented at the 14th International AIDS Conference in Barcelona in 2002. This person, originally infected with HIV subtype B, was in a treatment interruptions study and had achieved virological control after three interruptions when viral breakthrough occurred. Detailed investigation revealed that the man was reinfected with a different virus of subtype B that was only 12% different to the original virus. Despite this the man was unable to control the second infection.

Cases 3 and 4³: Involve two IDUs from Thailand who were participants in a cohort study and the superinfections were detected from analysing stored samples. Case 3 involves a 30 year old Thai woman who was initially HIV-negative in June 1996, then HIV-positive to subtype AE in December 1996 and then was identified with subtype B in January 1997. Case 4 involved a 32 year old Thai male who was initially infected with subtype B and then super-infected with subtype AE seven months after seroconversion.

Case 5⁴ : Involves a person who was initially infected with drug-resistant HIV of subtype B. They achieved a viral load set point of 6000 after primary infection. Then in month 4 the viral load jumped to 34000 and then subsequently to 200,000. Detailed investigation revealed they had been super-infected with HIV of subtype B that was wild-type virus (that is not drug resistant). He was much less able to control the super-infection. (It’s worth noting that in this case superinfection with non-resistant virus had negative implications for HIV progression – this particular drug resistant virus may be harder to treat – but it is less “virulent” or than the wild-type virus)

From these five case reports we can conclude:

1. That superinfection does occur **but we do not know how often it occurs.**
2. That superinfection occurs both within the same subtype (clade) and between different subtypes. (This has implications for HIV vaccine development)
3. That when superinfection occurs it may have big implications for the person’s health and for HIV disease progression

The case reports mostly relate to people with recent primary infection. None of the superinfections occurred while people were currently on treatments and none involved superinfection with resistant strains (but this does not mean this cannot occur).

It needs to be noted that demonstrating superinfection requires very sophisticated methodologies, some of which have only been recently developed and are only available in highly resourced research laboratories. Further, the over representation of acutely infected patients in the case reports may be an artefact because identification of superinfection may be easier in people with robust immune systems and there have been more people with recent primary infection that have been part of intensely monitored cohorts that are likely to lead to the identification of superinfection.

Superinfection Case Report Summary				
Source : Treatments Roadshow PowerPoint, ATPA				
Case	Timing Months	Clade	Immune response	Deleterious VL/CD4 changes
1	30	AE/B	-	Yes
2		B/B	Strong	Yes
3/4	3/11	AE/B B/AE	Present only to initial strain	No
5	4	B/B R/WT	-	Yes
No superinfected patient was on HAART				

SO NOW WE KNOW SUPERINFECTION DOES OCCUR, DO WE KNOW HOW OFTEN IT OCCURS?

There are some studies that have attempted to answer this question – but where they are not studies based on positive couples they depend on HIV seroprevalence (including the patterns of different HIV types) and individual rates of risk behaviour and they are difficult to interpret.

Some of the studies that have attempted to offer insight into how often superinfection occurs include:

- a) A study that followed 15 HIV-positive couples for at least two years with sampling every six months. No evidence of superinfection was found.⁵ (But no data on rates of unprotected sex was given and if there are protective immunological responses this group may be expected to have them).
- b) A large study of people with HIV in California that examined the protease and reverse transcriptase sequences over time and looked for changes in the sequences that could be due to superinfection. Over 1072 person-years of observation they found no evidence of superinfection.⁶ (Once again there is no data on risk behaviour and people in this study were on HAART)

- c) An African study reported on at the 2nd International AIDS Society Conference in Paris in 2003 examined the frequency of recombinant HIV in 147 commercial sex workers on Burkina Faso over time. They identified the appearance of recombinant forms in 4 cases over 2 years that coincided with increases in plasma viremia. Their conclusion was that superinfection was not an “uncommon event” (although this is a high risk population with multiple exposures so others may conclude from the same data that superinfection is still uncommon) 7.

It is not possible to be confident from the limited evidence currently available to make any conclusions about how often superinfection occurs.

SO WHAT DO WE SAY AS HIV EDUCATORS?

Originally when safe sex guidelines were framed in the mid 1980s – often based on knowledge of biology rather than firm evidence – the recommendation to people with HIV was to practice safe behaviours with other people with HIV. Partly this was because of a desire to have one ‘gay community’ guideline – safe sex for all – and partly it was based on a belief that reinfection (as it was then called) was possible and may have consequences for HIV disease progression.

In the late 1980s both HIV-negative gay men and HIV-positive gay men challenged the ‘safe sex for all in all contexts’ guidelines. Many HIV-negative gay men in established relationships practised negotiated safety, and many HIV-positive men practised unprotected sex with each other – both in and outside established relationships. There were concerns about both of these strategies but gay men were negotiating long term ways of living with a deadly virus. No firm evidence had emerged confirming superinfection – and even if it did occur – there was no evidence that it did a great deal of harm.

The only hint of any evidence that did exist was indirect - from dozens of prospective studies of people with HIV that looked for any factors associated with progression of HIV disease. A huge range of factors was examined – from sniffing amyl nitrate to moving house. The only factors that consistently appeared to be associated with disease progression in non-treated populations were age and frequency of risk behaviours. Other factors such as ‘stress’, ‘having support’, ‘smoking’ and ‘having a partner’ also were associated in some studies – but not others. Frequent risk behaviour could result in superinfection or in repeated exposure to other infections. Some have also postulated some immunosuppressive effect of semen.

The consensus of scientific opinion for a brief period in the early 1990s became that superinfection did not occur, or if it did occur, it occurred rarely and it was unlikely to have major impacts on an individual’s health. However, that consensus began changing in the mid 1990s – except by and large it was only ‘opinion’ until more recently. There has always been firm evidence of the impact of other infections and STIs on HIV disease progression in untreated populations.

Now that we know that superinfection does occur – but we don’t know how often do we give priority to this changed information? When it became clear in the late 1980s that oral sex could transmit HIV we didn’t rush out and say ‘use condoms for oral sex’. We knew that this was never going to happen – and we had concerns that overstating the risk of oral sex may undermine motivation to sticking to protected anal sex (and indeed there was social science supporting this contention). It is probably similar concerns that have led to some caution emphasising this changed information. However, we have a fundamental obligation to provide positive people with this information so that can choose to protect themselves.

We know superinfection occurs. We know it can have a big impact on an individual's health. But we do not know how often it occurs – and while the consensus may have been that it occurs rarely the availability of better detection methods means that the consensus is shifting to 'it occurs more often than we previously thought'.

In summary:

1. Superinfection happens.
2. When it does happen it may have a large impact on an individual's HIV disease progression and additionally it may have an impact on the ability to treat HIV disease.
3. We do not know how often it happens. The original scientific consensus was superinfection occurred "rarely – if at all". With better detection methods and research tools that consensus no longer exists – but there is not yet firm data (and there may never be) on how often it occurs.

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