HIV Superinfection

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Worldwide, 16 cases of HIV-1 superinfection in humans have been reported since 2002. Superinfection is defined as the reinfection of an individual who already has an established infection with a heterologous HIV strain. Controversy exists surrounding superinfection, because it has implications concerning our understanding of worldwide HIV diversity, individual immunity and disease progression, and vaccine development. Here, we review the current understanding of HIV superinfection.

The first case of HIV superinfection was reported in 1987, in a chimpanzee model [1]. Fifteen years later, Ramos et al. described a case in a human [2]. Worldwide, 15 other cases of human superinfection have been reported since then. The initial published reports involved individuals who were reinfected with a virus that belonged to a clade different from that of the initial infecting virus (interclade superinfection) [2, 3]. Because different clades within HIV-1 are >30% different from each other in the env gene, interclade superinfections can be more readily detected than other superinfections. Moreover, immune responses to the initial infection might be less likely to be protective against such a divergent superinfecting virus. Subsequently, however, reinfection with a virus that belonged to the same clade as the initial infecting virus (intrACLade superinfection) started to be reported [4, 5]. Here, we review the growing body of literature on HIV superinfection and discuss its potential implications.

WHAT IS SUPERINFECTION?

Similar to other chronic viral infections, such as those with cytomegalovirus and Epstein-Barr virus, infection of an individual with a second viral strain (dual infection) [6–22] occurs in HIV infection. The terminology related to dual infection is important. The differences between superinfection and coinfection may have significant implications. Dual infection occurs when an individual is infected with strains derived from 2 different individuals. Dual infections can be divided into coinfec tions and superinfections. Coinfection is defined as infection with 2 heterologous strains either simultaneously or within a brief period of time before infection with the first strain has been established and an immune response has developed. Arbitrarily, HIV coinfection would occur within the first month of infection. Superinfection is defined as infection with a second strain after the initial infection and the immune response to it has been established (figure 1) [23, 24]. “Reinfection” is a term that is often used in place of “superinfection,” because some feel that the “super” in “superinfection” may imply that the second infection is stronger, which may or may not be the case. We feel that the term “reinfection” may also be confusing, because it may imply that the first virus had been cleared before the second infection occurred, as happens with influenza virus and various paramyxoviruses. This is not the case with HIV superinfection, in which the initial virus is not cleared before the next virus is acquired.

Discrimination between coinfection and superinfection requires exclusion of a mixed viral population during acute infection [5]. Because it is impossible to prove the absence of a minor population of a second strain (i.e., the coinfecting strain), theoretically, all currently reported cases of superinfection could conceivably be cases of coinfection, with the “superinfecting” virus being present but undetectable early after the initial infection. This could theoretically happen if one virus initially remains localized to a cellular or anatomic compartment, such as the...
lymph nodes, genital tract, or central nervous system, and then appears in the blood later. Another possibility is that the coinfected strain of virus persists at a low level until viral evolution, drug treatment, or host immunity results in a fitness advantage for the minority strain.

Overwhelmingly convincing epidemiologic linkage of the source partner of the superinfection to the recipient will be needed to prove more formally that HIV superinfection, not coinfection, has occurred [25, 26]. Furthermore, a significant amount of quality-control measures should be demonstrated when superinfection is reported. The potential of reporting a false case of superinfection is highlighted by the first reported case of superinfection in humans [27], which was reported in 2000 and was later proved to be the result of a contamination error [27, 28]. However, substantial circumstantial evidence remains that indicates that superinfection does occur, and this evidence will be discussed here.

**WHAT DOES SUPERINFECTION MEAN TO THE GLOBAL EPIDEMIC?**

The global epidemiologic profile of HIV clades represents a formidable pattern of evolution and geographic spread [29]. Nevertheless, the coexistence of almost all of the variants in west-central Africa (Cameroon and the Democratic Republic of the Congo) and the differential radiation of these variants throughout the world suggests that the introduction of HIV into humans occurred in this geographic area, which, not coincidentally, corresponds to the habitat of the chimpanzee, the likely zoonotic source of HIV-1, via simian immunodeficiency virus (SIV)cpz [29–32].

A portion of the worldwide HIV genetic diversity is a result of the error-prone viral reverse transcriptase (RT), coupled with a high viral replication rate [29, 33]. Additional genetic diversity is introduced as a result of recombination that may take place during HIV replication [34]. HIV is diploid; each virion contains 2 strands of RNA genome. If a single cell is infected with 2 different HIV strains, an RNA genome from each strain can be packaged into the same virion. Recombination can then occur when this virion infects the next cell and the viral RT enzyme switches from one viral template to the other, creating a mosaic of the parental viruses in the reverse transcript [35, 36]. This has been demonstrated in nonhuman primate models within 2 weeks of dual infection [37]. Recombination allows for a more rapid increase in viral diversity than does the accumulation of mutations through replication errors [38, 39]. Taken together, this genetic heterogeneity allows for rapid adaptation to host immune responses, target cell availability, and antiretroviral therapy, which can lead to increased viral pathogenicity and infectivity and decreased antiretroviral susceptibility [33, 40].

The best circumstantial evidence for dual infection is the presence of circulating recombinant forms (CRFs) and unique recombinant forms (URFs), both of which can be produced only by the above-described process of recombination. CRFs are mosaic viruses that are propagated from one person to another and spread geographically in one or more locations—for example, CRF02_AG in west-central Africa and South America [29, 41]. It is estimated that, worldwide, 10% of HIV infections involve these recombinant viruses [38]. Currently, there are 15 reported CRFs, which are represented on 4 continents [29, 42]. Additional CRFs are expected to arise in areas where the HIV epidemic is growing and multiple clades intersect, such as Africa, Southeast Asia, and South America [33, 38, 42, 43]. URFs are mosaic viruses that have not spread from their original location [44]. The high prevalence of URFs in certain locales suggests a high frequency of dual infection, but this has been difficult to document.

Presumably, intraclade recombination occurs at least as frequently as does recombination between clades; however, in the context of the genetic diversity of HIV, only interclade recombinant forms are readily discernible by the techniques that are commonly used to identify mosaic viruses [45]. The URFs that have been described are also recognized in dually infected individuals in locations where multiple clades intersect [43]. Recently, a case of superinfection was described in which a URF was generated in a woman who was initially infected with a clade A virus and then was noted 9 years later to have acquired a clade C virus that had recombined with the initial infecting virus. This produced a clade A/C recombinant that fully replaced the initial clade A infection [46].

The magnitude of global HIV diversity, driven in large part by recombination, provides circumstantial but substantial evidence, with no alternative explanation, that dual infection—whether coinfection, superinfection, or both—is widespread. In mathematical models, superinfection during the window of primary infection could account for the proportion of recombinant forms observed in various populations throughout the world [26]. Therefore, given the global frequency of CRFs and URFs, the true incidence of intradual infection—and of superinfection, especially—is probably underestimated in current investigations. Moreover, the rate of intraclade superinfection is even more difficult to assess, given the difficulty of current techniques to distinguish between different viral strains of the same clade [47].

**WHEN DOES SUPERINFECTION OCCUR?**

Recently, a retrospective analysis of a convenience sample of chronically infected individuals receiving antiretroviral therapy was unable to detect HIV superinfection during >1072 person-years of observation [48]. A similar cohort of chronically infected injection drug users showed no evidence of superinfection during >215 person-years of exposure [25]. Currently, most reports of superinfection indicate that it occurred in the setting of primary infec-
HIV superinfection on the basis of the HIV env gene may cause the investigators to screen for an underestimation of the true rate, be-

cause ongoing studies have confirmed and extended in larger populations, to better estimate the true risk of HIV superinfection after initial infection and to determine whether these rates change over time.

In many previous incidence studies, superinfection surveillance relied on population-based sampling for initial screening, a method that may underestimate true incidence rates because it would not detect a superinfecting virus if it remained a minor variant below the level of detection, usually 30% of the circulating viral pop-

ulation [23, 25, 47, 48]. However, this was not the case in 2 studies that screened for superinfection by use of other methods, heteroduplex mobility assays [52] and subtype-specific primers [23]. Superinfection may also have been missed if the superinfecting strain replicated transiently [23] or if it had replaced, through recombi-

nation, some of its genome with the initial infecting strain’s genome by the time of the second sampling and that portion of the original genome was the portion being interrogated [25]. To better evaluate the true incidence of superinfection, large cohorts of newly infected individu-

als will need to be studied longitudinally. These investigations will need to include intensive sampling, epidemiologic partner tracking, and sensitive screening methods to detect minor viral populations and recombinant forms.

WHAT ARE THE INDIVIDUAL CONSEQUENCES OF SUPERINFECTION?

General assumptions that HIV-infected individu-

als cannot be reinfected may have contributed to the increase in risky sexual practices among HIV-infected individuals and, specifically, MSM [33]. Many urban centers have documented increases in rates of syphilis and other sexually transmitted diseases (STDs) among MSM [35] and the high prevalence of transmitted drug-resistant HIV [56]. These riskier sexual practices probably account for the seemingly high incidence of HIV superinfection in southern California [47].

Independent of typical STDs, risky sexual prac-

tices have other consequences, such as HIV superinfection. In most reported cases of superinfection, individuals have experienced a decrease in CD4+ cell count and an increase in HIV load (table 1). The magnitudes of the increase in HIV load and the decrease in CD4+ cell count are similar to those observed during primary infection [52, 60]. Both CD4+ cell count and HIV load are independent prognostic markers for HIV disease pro-

gression [61].

Even studies that could not distinguish
cases of superinfection have not been identified alone [63]. Because most cases of human SIV experienced less disease progression ever, in an animal model, HIV-2–infected cynomolgus macaques superinfected with strains replicating in a single host allows for rapid adaptation and immune escape; alternatively, individuals who are predisposed to dual infection could have an immune system that is incapable of slowing disease progression [62]. Another possibility is that only a more virulent or fit virus is capable of superinfecting in the face of an established infection. However, in an animal model, HIV-2–infected cynomolgus macaques superinfected with SIV experienced less disease progression than did macaques infected with SIV alone [63]. Because most cases of human superinfection have not been identified in systematic prospective studies, a significant bias may exist. In these studies, cases of superinfection were identified only when the second virus emerged as the predominant strain (and, thus, was readily detectable). The virus became the predominant strain because it was more fit than the original strain and, thus, more pathogenic. Future studies that are able to identify cases of superinfection in which the superinfecting virus circulates only as a minority variant may help to clarify the impact that superinfection has on disease progression.

Superinfection has also been reported to complicate antiretroviral therapy [57] and, potentially, drug resistance testing [5, 49, 58]. Probably because of the relatively high prevalence of HIV drug resistance and drug-resistance testing in the United States, many reported cases of HIV superinfection have occurred in the setting of transmitted drug resistance [47, 59]. Another possibility is that drug-resistant strains have an impaired replicative fitness in the setting of no antiretroviral therapy, which may allow a drug-sensitive strain to superinfect [5, 49]. However, there is a report of an individual who was first infected with a drug-sensitive strain and then superinfected with a drug-resistant strain, which was unrelated to the replicative capacity of pol [57]. There is also a report of an individual who was infected and then superinfected with heterologous strains that both harbored multiple drug resistance–associated mutations [59]. Superinfection involving drug resistance can have serious clinical consequences. When the drug-sensitive strain is the superinfecting strain and becomes the predominant virus, the drug-sensitive strain may mask the underlying drug-resistant strain, making drug-resistance testing unreliable [5]. When the superinfecting virus harbors drug resistance, the effective antiretroviral options available to the individual are reduced [57].

Because the frequency of superinfection is poorly characterized—as are its clinical consequences—how to counsel individuals already infected with HIV has been debated. Many believe that clinicians must counsel patients already infected with HIV to continue vigilant personal protection,
perinfection for which CD8+ T cell re-
in training the cytotoxic T lymphocyte re-
ponent of an effective HIV-1 vaccine [2,
fection were evaluated, the superinfecting
infection is not reflective of the situation
vaccine studies in animals have shown that
vaccinated animals are hypersusceptible to
virus when challenged shortly af-
immune response to the initial infecting vi-
immune control of the second infecting virus [3, 5,
un from then on toward the second infecting virus
sponses to the superinfecting virus have
hypothesis is supported by the cases of superinfection
occuring in individuals who had good
control of the initial infecting virus—
high CD4+ cell counts—and then less immune
control of the second infecting virus [3, 5, 47, 49].
Furthermore, superinfection seems
to occur in individuals who have a ma-
ture immune response to the initial in-
fecting virus, even when both strains be-
ong to the same clade [4, 49]. This may
not bode well for the development of a
cross-protective vaccine [66].

On the other hand, it could be argued
that superinfection is not reflective of the
situation where an uninfected host is
vaccinated. Unlike vaccination, infection highly
activates the immune system, and activ-
vated CD4+ T cells are the primary host
cells for HIV replication [67]. Two vac-
cine studies in animals have shown that
vaccinated animals are hypersusceptible to
lentivirus when challenged shortly af-
ner a vaccine boost, when the immune
system may have been activated [68, 69].
Furthermore, the antibody responses to
vaccination and superinfection also may
not be the same—and although antibody
responses to the superinfecting virus have
been documented [2], neutralizing re-
sponses have not been investigated in de-
tail in either animal models or humans.
Future studies that are able to identify both
incident cases of superinfection and un-
successful superinfection challenges may be
necessary to better understand the immu-
nologic correlates of protection.

**FUTURE STUDIES**

Lentiviral superinfection has been de-
scribed with feline immunodeficiency vi-
rus in cats, SIV in macaques, and HIV-1
in chimpanzees [1, 51, 70], so it is not
surprising that HIV superinfection occurs
in humans. The mysteries of HIV super-
infection are beginning to be unraveled,
but continued collaboration between the
HIV-research community and the HIV-
affected community is required to make
further progress. We propose that the fol-
lowing questions be addressed by future
research.

1. What is the incidence of HIV su-
perinfection and coinfecion in various
groups at risk for HIV acquisition?
2. What is the natural history of HIV
dual infection with regard to disease pro-
gression and drug resistance?
3. How does dual infection and, spe-
cifically, superinfection influence global
HIV diversity?

4. What is the window of suscep-
tibility to HIV superinfection? Does it
vary among HIV subtypes and routes of
exposure?

5. Which immunologic correlates
(i.e., cell-mediated and neutralizing an-
tibody responses) are associated with
HIV superinfection and unsuccessful su-
perinfection challenges? How do these re-
late to vaccine development?

6. Does superinfection occur more
readily with a virus that belongs to the
same clade as that of the initial infecting
virus (interclade superinfection) or with
a virus that belongs to a different clade
(intraclade superinfection)? How might
this affect the selection of viral strains for
vaccine development in given regions?

7. What are the psychological and
behavioral consequences of HIV superin-
fecion in HIV-affected communities, and
how can HIV-prevention strategies be
improved to incorporate this new paradigm?
References


