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Incidence of HIV Superinfection Following Primary Infection

To the Editor: Anecdotal reports have suggested that individuals with preexisting human immunodeficiency virus (HIV) infection may be at risk for superinfection by different strains of HIV.¹⁻³ We investigated the incidence of superinfection 6 to 12 months after a first diagnosis of HIV infection.

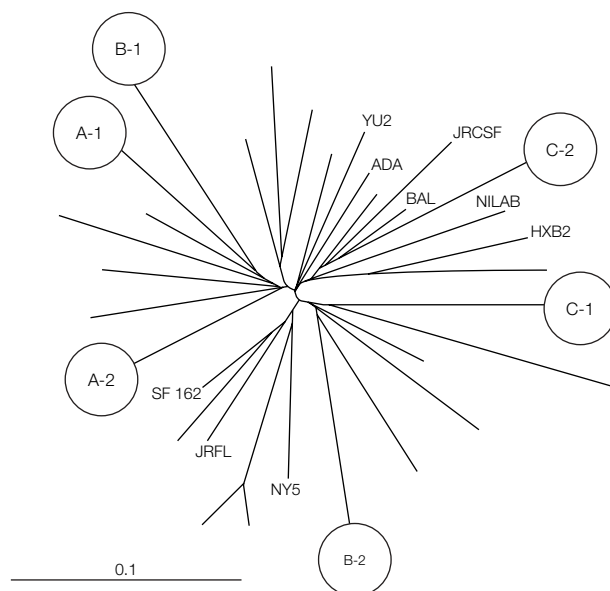
Methods. We included all recently infected antiretroviral-naïve participants (n=78) in the San Diego and Los Angeles Acute Infection and Early Disease Research Programs between December 1997 and June 2003 who had deferred antiretroviral treatment for at least the first 6 months after diagnosis. We retrospectively analyzed blood samples collected at the time of enrollment and then another sample 6 to 12 months later. Superinfection screening was performed on both sets of samples by population-based sequencing of *pol* from plasma HIV RNA using Viroseq version 2.0 (Celera Diagnostics, Foster City, Calif).

Superinfection was suspected when isolates from the same individual shared their most recent common ancestor during phylogenetic analysis with at least 1 other epidemiologically unrelated isolate.⁴ To distinguish these cases from coinfection, dye-primer sequencing of *pol*, length polymorphism analysis of *env*, and clonal sequencing of *env* were also performed and analyzed on samples from multiple time points, as previously described.³ Participants provided written informed consent. These studies were approved by the Human Research Protections Program at the Universities of California at San Diego and Los Angeles.

Results. Standard genotype sequencing of *pol* identified 3 potential cases of superinfection, representing a rate of 5.0% per year (95% confidence interval, 1.7%-13.3%). Further investigations, dye-primer sequencing of *pol*, length polymorphism analysis of *env*, and clonal sequencing of *env* (FIGURE) revealed no evidence of coinfection.^{2,3} We found no evidence of sample contamination or processing error by analyses of *pol* and *env* sequence and HLA antigen on additional samples (data not shown). Within 6 months of detecting the superinfecting strain, plasma viral loads increased (mean, 1.6 log₁₀ copies/mL; range, 0.8-2.2) and CD4 cell counts decreased (mean decrease, 132 cells/μL; range, 150 to 347) in each of the 3 individuals. Furthermore, each was associated with a change in antiretroviral susceptibility. Two individuals, initially infected with drug-resistant HIV, were superinfected with a wild-type strain. The third was initially infected with a wild-type strain and was then superinfected with a drug-resistant strain.

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Figure. Phylogram of 15-20 Clonal Sequences of the V3 Coding Region of *env* From Both Time-Point Samples From Each Individual Suspected of Being Superinfected



Circles indicate 3 individuals (A, B, and C) suspected of being superinfected, each with 2 isolates. Clonal sequences are clustered by time-point sample but not by individual. There was no intermingling of clonal sequences between time points, and sequence clusters differed by >8% homology and were separated by epidemiologically unrelated strains from 15 individuals in San Diego and Los Angeles (unlabeled branches) and laboratory strains (labeled branches).

Comment. We found that 4 independent laboratory approaches each suggested a 5% incidence of HIV-1 clade B superinfection within 6 to 12 months of initial infection. This rate is similar to the initial infection rate reported during a large HIV vaccine trial⁵ that enrolled HIV-negative individuals at risk for seroconversion, and thus may be similar to our cohort. It calls into question any protective effect of initial infection.

We also found that HIV superinfection had significant clinical implications. In 2 of the 3 individuals, the initially transmitted drug resistance would be masked by the wild-type superinfecting virus during routine drug-resistance testing. Antiretroviral therapy could be instituted that would unknowingly be ineffective. The third individual had undergone genotype testing that showed his virus to be susceptible to all antiretroviral medications but subsequently acquired a drug-resistant strain. Thus, he was prescribed an ineffective regimen that failed to suppress his superinfecting virus, as we previously described in an anecdotal report.³

In each of the 3 cases we report, the superinfecting virus had a greater in vivo fitness than the initial virus as evidenced by an increase in serum viral loads and a decrease in CD4 cell counts, similar to previous reports.¹ This scenario of increased viral load and lower CD4 cell count portends a poorer prognosis independent of antiretroviral treatment options.⁶ In-

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dividuals already infected with HIV should thus continue vigilant personal protection through safe-sex practices or clean needle use for injection drugs, even if their risk exposures are with other HIV-infected people.

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Access to Data: Dr Smith had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analyses.

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CORRECTIONS

Incorrect Dosages: In the Original Contribution entitled "Safety and Efficacy of Enoxaparin vs Unfractionated Heparin in Patients With Non-ST-Segment Elevation Acute Coronary Syndromes Who Receive Tirofiban and Aspirin: A Randomized Controlled Trial" published in the July 7, 2004, issue of *JAMA* (2004;292:55-64), there were 2 incorrect dosages on page 56. At the bottom of column 2, the sentence should read, "The dosing regimen for tirofiban in the A to Z trial was a hybrid between the previously proven ACS and percutaneous coronary intervention dosing regimens: a bolus of 10 µg/kg over 3 minutes, followed by a maintenance infusion of 0.1 µg/kg per minute for a suggested minimum of 48 hours (or a minimum of 12 hours after intervention) and a maximum of 120 hours.^{9,13}"

Funding Source Omitted: In the Original Contribution entitled "Association Between Youth-Focused Firearm Laws and Youth Suicides" published in the August 4, 2004, issue of *JAMA* (2004;292:594-601), a funding source was omitted. In addition to the sources cited, the study also received support from the David and Lucile Packard Foundation.