was detectable, and it increased by 45 days. (Antibodies from day 45 were tested against day 33 virus because there was no virus growth from the day 45 sample.) ANA continued to be detectable through the remainder of the year following infection (figure 1A). Therefore, the decrease and maintenance of a low level of virus load was associated with the appearance and continued presence of ANA.

Cross-neutralizing antibodies (CNA), defined as antibodies obtained from the health care worker at alternate times from the virus isolate, were also measured (figure 1B). CNA were detectable by 20 days after infection and increased as virus load decreased. The inability to measure ANA at day 20, therefore, was not due to the absence of neutralizing antibody, because there was an effective neutralizing response against viruses isolated on days 33 and 75. In fact, none of the CNA could neutralize the virus isolated on day 20. However, the virus that appeared 13 days later (day 33 after infection) was neutralized by all antibodies tested during the first year of infection. Thus, it is possible that the virus variant isolated at day 20 circulated for too short a period to stimulate neutralizing antibody or was resistant to neutralization.

The switch from syncytial-inducing (SI) to non-SI (NSI) phenotype between days 33 and 75 after infection was preceded by neutralizing antibodies to both viruses (figure 1B). Replication of the SI virus appeared to be restricted by the antibodies, as virus replication was undetectable at 45 days. The NSI virus that appeared following the negative viral culture at 45 days remained the culturable virus phenotype throughout the first year. This occurred even in the presence of neutralizing antibody, implying that NSI but not SI was partially protected from neutralization.

In summary, we have provided evidence that neutralizing antibodies to HIV-1 can be detected as early as 20 days after transmission of the virus. The appearance of neutralizing antibody correlates with the reduction in virus load as measured by HIV-1 plasma RNA and infected PBMC. Thus, ANAs could have a role in the reduction and maintenance of virus load during primary infection. In addition, we have demonstrated that ANA and CNA preceded the switch from SI to NSI phenotype, possibly adding biologic pressure to influence the switch.

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References

By using an experimental rat endocarditis induced with another multidrug-resistant \textit{E. faecium} strain, Whitmann et al. [6] similarly reported that the effect of a ciprofloxacin-rifampicin-gentamicin combination, which provided a spectacular 6 log_{10} cfu/g reduction in vegetation titers after 5 days of treatment, was in part lost in animals held for a relapse study; rifampicin-resistant bacteria were detected in most of them.

These recent data prompt a suggestion that systematic relapse studies or tests for detection of antibiotic resistance be done in evaluating treatments for multidrug-resistant enterococcal in animal models.

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References


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Reply

To the Editor—We appreciate Dr. Caron’s interest in our paper and review of his own prior work in this area [1]. Caron expresses two principal concerns about our paper, namely, that tests for detecting the emergence of resistance were not done and that long-term survivorship studies were not done to detect “relapse.”

First, in contrast to the earlier studies that Caron cites, the strain used in our study was already resistant to all treatment antimicrobials prior to therapy. We fully expect that the strain would remain resistant after therapy as well.

Second, the information provided by experimental infection models of different design (e.g., rate of bacterial clearance vs. rate of cure), in our opinion, is complementary rather than confirmatory. The purpose of our study was to determine whether the more rapid bacterial killing observed in vitro with certain antimicrobial concentrations correlated with outcome in vivo. In the context of the study, the antimicrobial combinations, as noted by Caron, were clearly effective in reducing bacterial density in infections infected with this multidrug-resistant enterococcal strain. We believe the title of the article accurately reflects this finding.

In view of the results from our study, we agree that test-of-cure studies, as suggested by Caron, could provide additional complementary findings (especially in discriminating a possible difference in efficacy between the two- and three-drug regimens). Because test-of-cure studies have dichotomous outcomes, a larger number of animals are required for adequate statistical power. In addition, these studies also require careful specification of study parameters (e.g., treatment duration and time to sacrifice), which differ from those required by bacterial clearance studies. For these reasons (among others), we feel that these additional studies, when done, should be designed in advance, using adequate numbers of animals to test specific a priori hypotheses and should be “stand alone” studies. The recent tendency to study a few animals in one or two selected select treatment regimens should not substitute for well-designed test-of-cure studies.

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