Conclusions. These results demonstrate that siRNA technology can be used to suppress multiple steps of the HIV life cycle and have potential for therapeutic intervention in HIV infection.

Reviewer’s Comments. Advances in molecular biology continue to reveal unique cellular pathways that may be manipulated for therapeutic intervention. That RNA interference can occur in human cells has been recognized for under 2 years. Yet, this remarkable technology has already been harnessed in a model system to demonstrate it’s potential as a treatment for HIV infection. Highly active retroviral drug therapy (HAART) has been extraordinarily successful in reducing HIV-associated morbidity and mortality. However, the rapid emergence and spread of HIV strains that are resistant to current drugs strongly support the development of other avenues of intervention. As with current gene transfer technology, the delivery of therapeutic nucleic acids into specific target cells will be a great challenge.

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SAFETY AND ANTIRETROVIRAL ACTIVITY OF CHRONIC SUBCUTANEOUS ADMINISTRATION OF T-20 IN HUMAN IMMUNODEFICIENCY VIRUS 1-INFECTED CHILDREN


Purpose of the Study. The use of combination antiretroviral therapy has been associated with a substantial decline in morbidity and mortality in human immunodeficiency virus (HIV)-infected individuals. In heavily pretreated subjects, however, the virus often possesses multiple mutations of the reverse transcriptase and protease genes that result in multidrug resistance. Pharmacologic agents effective at alternative stages in the replication cycle of the virus might be useful. The purpose of this study is to evaluate the use of T-20, an inhibitor of virus entry into the target cell, in HIV-infected children.

Methods. Fourteen children, 4 to 12 years of age, with incompletely suppressed HIV were studied. T-20 was administered twice daily by subcutaneous injection. For the first 7 days of the study T-20 was added to the patients’ background antiretroviral therapy, and at day 7 each subject’s failing background therapy was changed to a regimen that was predicted to be virologically active while the T-20 was continued.

Results. T-20 was generally well-tolerated. One child discontinued the drug because of aversion to injections, but no child discontinued because of adverse events. Seventy-nine percent of the children had local injection site reactions at some time during chronic T-20 dosing. Eleven of 14 subjects achieved the protocol-specified milestone of at least 0.7 log reduction in plasma HIV RNA by day seven. Seventy-one percent of subjects had virologic suppression of 1 log or greater by 26 weeks.

Conclusions. A 24-week regimen of twice daily subcutaneous dosing of T-20 in HIV-infected children is safe and tolerable and it is associated with suppression of HIV replication during 24 weeks of administration.

Reviewer’s Comments. Because HIV-infected children often develop resistance to 1 or more classes of antiretroviral therapy, a new class of agents might improve treatment options. Although T-20 administration required twice-daily injections, this should not prevent children from having access to this agent. Treatments requiring daily injections are routinely used in the management of other serious pediatric conditions, and in this study, 13 of 14 subjects enrolled in chronic dosing continued participation throughout the study. In carefully selected and vigorously supported families, T-20 was a tolerable component of an ineffective antiretroviral combination for HIV-infected children.

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ANTIRETROVIRAL-DRUG RESISTANCE AMONG PATIENTS RECENTLY INFECTED WITH HIV


Purpose of the Study. Highly active antiretroviral therapy (HAART) has dramatically reduced the morbidity and mortality associated with human immunodeficiency virus (HIV) in Western countries. A consequence of the widespread availability of these agents is the potential for transmission from an individual carrying resistant virus to uninfected contacts. The purpose of this study was to evaluate the prevalence of HAART-resistant HIV in newly identified and untreated HIV-infected subjects.

Methods. The plasma of 377 adult subjects from 10 North American cities with primary HIV infection who had not been treated and who are identified between May 1995 and June 2000 was evaluated for phenotypic resistance to available antiretroviral agents and the presence of mutations in viral reverse transcriptase and protease genes that would be predictive of drug resistance to various antiretroviral agents (genotypic analysis). Responses to initial treatment was also evaluated in 202 of the subjects.

Results. Over the 5-year study period, the frequency of transmitted drug resistance increased significantly. Phenotypic resistance increased from 3.4% to 12.4% and the frequency of multidrug resistance increased from 1.1% to 6.2%. Resistance mutations by sequence analysis increased from 8% to 22.7% and the frequency of multidrug resistance by sequence analysis increased 3.8% to 10.2%. All of these changes were statistically significant (P < .05). In subjects infected with drug-resistant virus, the time to viral suppression after initiation of treatment was longer and the time to virologic failure was shorter (P = .05).

Conclusions. The proportion of new HIV infections with drug-resistant virus is increasing. Initial antiretroviral therapy is more likely to fail in subjects in patients with drug-resistant virus. Testing for resistance to drugs before therapy initiation is now suggested even for recently infected patients.

Reviewer’s Comments. Although the study population was primarily adult males, a similar prevalence of drug-resistant virus is likely to be present in infected women of childbearing age. This has direct implications for the initiation of treatment during pregnancy and interventions to prevent maternal-infant HIV transmission. A further concern is the tendency of wild type virus to replace drug-resistant virus in the plasma when the virus is no longer under the pressure of drug therapy. Therefore, even if it is no longer detectable in plasma, a drug-resistant variant may persist in the reservoir of latently infective CD4+ T cells. It is currently recommended that all newly identified adult subjects with HIV have resistance testing performed to optimize their initial antiretroviral regimen. Similar approaches should be considered in HIV-infected pregnant women and newly identified HIV-positive infants and children.

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SUPPLEMENT
ANTIRETROVIRAL-DRUG RESISTANCE AMONG PATIENTS RECENTLY INFECTED WITH HIV
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Pediatrics 2003;112;492

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