EFFECTIVENESS OF COL-1492, A NONOXYNOL-9 VAGINAL GEL, ON HIV-1 TRANSMISSION IN FEMALE SEX WORKERS: A RANDOMISED, CONTROLLED TRIAL


**Purpose of the Study.** Nonoxynol-9, marketed as a spermicidal contraceptive, has in vitro anti-human immunodeficiency virus (HIV) activity. This study was designed to assess the effectiveness of COL-1492, a nonoxynol-9 vaginal gel, in the prevention of HIV infection in women with a high risk of HIV exposure.

**Methods.** This was a randomized, placebo-controlled, fully masked phase II/III trial with COL-1492. Eight hundred ninety-two female sex workers in 4 developing countries were assigned to receive the nonoxynol-9 gel (449 women) or a placebo gel (443 women). The primary endpoint was incident HIV infection; secondary endpoints included *Neisseria gonorrhoeae* and *Chlamydia trachomatis* infections.

**Results.** Thirty-two percent of the women reported using >3 applicators per working day. In these women, the risk of HIV infection in nonoxynol-9 users was almost twice that in placebo users. In the 68% of women who used the applicators less frequently, there was no difference in HIV infection incidence. There were no significant effects on nonoxynol-9 on *N. gonorrhoeae* or *C. trachomatis* infections.

**Conclusions.** COL-1492, a nonoxynol-9 containing vaginal gel does not protect high-risk women from HIV infection. Further, multiple applications of nonoxynol-9 appear to enhance the risk of HIV infection likely by causing local toxic effects on the vaginal mucosa.

**Reviewer’s Comments.** This report is consistent with other trials that demonstrated that nonoxynol-9 was not effective in preventing sexually transmitted diseases including HIV and that it might actually increase the risk for HIV transmission. Because of these findings, the World Health Organization has concluded that nonoxynol-9 should not be used or promoted for the prevention of HIV or sexually acquired infections. For sexually active adolescents, only abstinence and condoms should be recommended for the prevention of HIV or other sexually acquired infections.

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INCIDENCE OF CARDIAC ABNORMALITIES IN CHILDREN WITH HUMAN IMMUNODEFICIENCY VIRUS INFECTION: THE PROSPECTIVE P2C2 HIV STUDY


**Purpose of the Study.** Human immunodeficiency virus (HIV) infection may be associated with severe cardiac complications. The objective of this study was to describe the 5-year cumulative incidence of cardiac abnormalities in HIV-infected children.

**Methods.** A prospective cohort was developed involving children from 10 hospitals throughout the United States. Group I included 205 HIV-infected children enrolled at a median age of 1.9 years and group II consisted of 600 HIV-exposed children enrolled prenatally or as neonates. Of this group, 93 were ultimately shown to be HIV-infected. Echocardiographic indices of left ventricular function were measured every 4 to 6 months.

**Results.** In group I (retrospectively identified HIV-infected children), the 5-year incidence of left ventricular fractional shortening of ≤25% was 28%; left ventricular end-diastolic dilatation was 21.7%; and heart failure or the use of cardiac medications was 28.8%. The mortality rate 1 year after the diagnosis of heart failure was >50%. Within group II (at-risk infants), the 5-year incidence of decreased fractional shortening was 10.7% in the HIV-infected compared with 3.1% in the HIV-uninfected children. Left ventricular dilatation, heart failure, or the use of cardiac medications were more common in infected children.

**Conclusions.** During the 5 years of this study, cardiac dysfunction occurred in up to 39% of HIV-infected children and was associated with an increased risk of death. The authors recommended that HIV-infected children undergo routine echocardiographic surveillance for cardiac abnormalities.

**Reviewer’s Comments.** Prospective natural history studies are particularly useful as a tool to understand disease progression. The Pediatric Pulmonary and Cardiovascular Complications of Vertically Transmitted HIV Infection Study (P2C2) was initiated in 1990 and enrollment was concluded in 1994. At that time, very limited antiretroviral therapies were available and there were no potent combination therapies, currently referred to as highly active antiretroviral therapy (HAART). The remarkably high incidence of cardiac disease in this patient population largely represents the natural history of untreated or marginally treated HIV in perinatally infected children. The current incidence of heart disease in HIV-infected children is likely to be much less, and patients with previously demonstrated profound cardiac compromise have been noted to have normalized their echocardiographic measurements. It is not clear that routine echocardiographic surveillance of all HIV-infected children is indicated currently. In the HAART era, the best strategy for heart monitoring requires additional investigation.

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siRNA-DIRECTED INHIBITION OF HIV-1 INFECTION


**Purpose of the Study.** In mammalian cells, DNA is transcribed into RNA. “RNA interference” is a mechanism of posttranscriptional gene silencing. Short interfering 21-23-mer double-stranded RNA segments guide messenger RNA (mRNA) degradation in a sequence-specific fashion. The purpose of this study was to investigate the feasibility of using siRNA to suppress the expression of human immunodeficiency virus (HIV) receptors (CD4), a viral structural protein (Gag) and green fluorescent protein substituted for an HIV regulatory protein (Nef).

**Methods.** siRNAs specific for CD4, p24 (gag) and green fluorescent protein mRNAs were prepared. These were transfected in vitro into cell lines that were permissive for HIV infection. These cell lines were then infected in vitro and the degree of suppression of target proteins was measured.

**Results.** Silencing the expression of CD4 on target cells decreased HIV entry into target cells. Silencing of Gag polyprotein production inhibited HIV RNA replication. Silencing of viral regulatory gene expression (green fluorescent protein as a substitute for Nef) reduced viral gene expression in target T-cells.
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 <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.

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.

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 infective antiretroviral combination for HIV-infected children.

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Pediatrics 2003;112;491

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Pediatrics 2003;112;491

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