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 P÷C² 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 21.2%; and heart failure or the use of cardiac medications was 28.5%. 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 21-23mer 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 polypeptide 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.
INCIDENCE OF CARDIAC ABNORMALITIES IN CHILDREN WITH HUMAN IMMUNODEFICIENCY VIRUS INFECTION: THE PROSPECTIVE P2C2 HIV STUDY

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Joseph A. Church

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