adults who were long-term nonprogressors or those whose conditions continued to progress despite antiretroviral therapy. The subjects with a dominant IL-2 response had very low levels of viremia and had not experienced viral “blips” over the previous 2 years. This pattern was similar to that generally observed in individuals who have cleared the infecting agent. It is important to note that this pattern has not been observed in HIV-infected adults.

CONCLUSIONS. Children with HIV have a higher frequency of HIV-specific CD4+ T cells compared with adults, and their recovery of an IL-2-secreting T-cell pattern indicates a greater capacity for immune restoration in children than adults.

REVIEWER COMMENTS. This elegant study provides a biological rationale for the clinical observation that young children started on antiretroviral therapy have the capacity for remarkable reconstitution of immune functions relative to those reported in adults and older children who have been infected for prolonged periods before antiretroviral therapy. Perhaps it is unfair to compare these results with findings in adults that included patients who were infected for many years before their initiation of therapy. A more appropriate comparative adult group would be those treated within 6 months of their diagnosis. Most importantly, this study demonstrates that children are “different” and that treatment early in infection allows excellent immune reconstitution if viral replication is completely controlled.

Identification of Host Proteins Required for HIV Infection Through a Functional Genomic Screen

PURPOSE OF THE STUDY. The HIV genome encodes only 15 proteins and, therefore, must use multiple host-cell collaborators for successful replication and transmission. Required host-derived proteins include CD4 as the primary virus receptor and chemokine receptors as coreceptors. This study identified multiple other host proteins required for HIV activity.

METHODS. Human cells known to be susceptible to HIV were exposed in vitro to HIV. Using small interfering RNAs able to inhibit each known gene in the human genome 1 at a time, the investigators tested whether HIV could establish an infection and copy itself. HIV dependence on >21 000 human genes was examined.

RESULTS. More than 250 human genes were identified to be required for efficient HIV replication. Termed “HIV-dependency factors,” the products of these genes are known to participate in a broad array of cellular functions and implicate unsuspected pathways in the virus life cycle.

CONCLUSIONS. The extraordinary dependence of HIV on human host proteins for efficient transmission and replication provides many new potential targets for antiretroviral therapy.

REVIEWER COMMENTS. An example of targeting host proteins is the use of chemokine receptor 5 (CCR5) inhibitors. Many people with CCR5 deficiency are very resistant to HIV infection yet have limited if any clinical consequences. Maraviroc CCR5 inhibitor is approved for treatment for HIV infection. This study identified many more such potential targets.

Proteinuria in Children Infected With the Human Immunodeficiency Virus

PURPOSE OF THE STUDY. Proteinuria is a common feature of HIV infection and a potential complication of therapy in adult patients. This study was performed to determine the prevalence of proteinuria in a group of children infected with HIV and to assess this process over time and the impact of antiretroviral therapy on it.

STUDY POPULATION. HIV-infected children (N = 286) were studied from 1998 through 2006.

METHODS. Proteinuria was determined by random urine protein/creatinine ratios, with “normal” defined as <0.2 and “nephrotic” defined as >1.0.

RESULTS. A total of 94 (33%) of the children had proteinuria at baseline. Of these, 32 had urine protein range ratios of ≥1.0. Clinically, the mortality rate was higher in those patients with proteinuria. It is important to note that 55 of the 94 patients with baseline proteinuria showed a good response to antiretroviral therapy, as indicated by a decrease in HIV viral load and a substantial reduction in the number of subjects who had proteinuria.

CONCLUSIONS. Control of HIV viremia with antiretroviral therapy reduces progression of HIV-associated proteinuria and improves the survival rate of infected children.

REVIEWER COMMENTS. Proteinuria is a common feature of HIV infection in children. Two features of this patient popu-
lation may affect the generalizability of the study findings: 85% of the patients were African American or African Caribbean, and the number of individuals with complicating hepatitis B or C was not indicated. Renal disease is more prevalent in HIV-infected black people than white people, particularly with respect to HIV-associated nephropathy. Chronic viral hepatitis may also cause secondary renal disease, likely secondary to an immunocomplex-associated inflammatory process. Regardless of these caveats, the authors’ conclusion is very much warranted: “surveillance of quantitative proteinuria with imaging and chemical indicators of renal dysfunction is very much warranted” for children with HIV infection.

URL: www.pediatrics.org/cgi/doi/10.1542/peds.2008-2139

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Semen-Derived Amyloid Fibrils Drastically Enhance HIV Infection

Seminal Plasma Reduces the Effectiveness of Topical Polyanionic Microbicides

PURPOSE OF THE STUDIES. Heterosexual intercourse is the major route of HIV transmission throughout the world. A variety of factors have been identified that are associated with increased transmission, including virus load, lack of circumcision, and the presence of sexually transmitted diseases. One approach to the reduction of male-to-female transmission has been the use of microbicides, and a major effort has been put forth to identify a safe and effective topical microbicide. The purpose of the Münch et al study was to identify factors in semen that might enhance HIV transmission, and the purpose of the Patel et al study was to examine why one of the most promising microbicides tested has failed thus far to reduce transmission in a large controlled trial.

STUDY POPULATION. Normal human seminal plasma was studied.

METHODS AND RESULTS. In the Münch et al study, investigators screened a complex peptide/protein library derived from human seminal fluid. The authors looked for novel inhibitors and enhancers of HIV infection. They identified fragments of prostatic acidic phosphatase that drastically enhanced HIV infection. Functional and structural analysis showed that these peptides formed amyloid fibrils that captured HIV particles and strongly enhanced the number of productively infected cells in vitro by promoting virion-cell attachment. The authors termed this product “semen-derived enhancer of virus infection” (SEVI). Rats transgenically expressing human CD4 and chemokine receptor 5 (CCR5) are susceptible to HIV infection. In this model, SEVI significantly enhanced the infectivity of HIV in vivo. In the Patel et al study, seminal plasma was shown to dramatically reduce the activity of polyanionic microbicides to reduce infectivity of herpes simplex virus type 2. Further study demonstrated that fibronectin 1 and lactoferrin were the specific factors in seminal plasma that were responsible for this process. In a murine model, this interference in vitro translated to a loss of protection in vivo.

CONCLUSIONS. Components of seminal plasma increase HIV infectivity and reduce the effectiveness of topical polyanionic microbicides.

REVIEWER COMMENTS. That host factors are involved in HIV replication and transmission is not surprising. However, that amyloid fibrils associated with seminal plasma dramatically increase HIV infectivity was not expected. An increased understanding of the mechanism of this enhancement might assist in overcoming the obstacles noted by Patel et al. An extraordinary effort was put forth to identify a safe and effective microbicid that would prevent transmission of HIV. In vitro and in vivo models indicated that the compound, PRO 2000, would dramatically reduce HIV transmission in vivo. The failure of this approach and the finding that seminal plasma directly interferes with this function dramatically illustrate the need to evaluate seminal plasma as a potential interfering agent in the search for effective microbicides.

URL: www.pediatrics.org/cgi/doi/10.1542/peds.2008-2139

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Pediatrics 2008;122;S226
DOI: 10.1542/peds.2008-2139

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*Pediatrics* 2008;122;S226
DOI: 10.1542/peds.2008-2139JJJJ

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