

were similar between the 2 treatment groups. The difference in HbA1c between treatment groups was highly significant at the closeout of the DCCT, but by the end of the first year of the EDIC study there were no significant differences in HbA1c levels between the two groups. This was the result of both an increase in HbA1c by the intensive therapy group, and a decrease by the conventionally controlled group. These HbA1c values remained stable over the next 3 years (8.38% vs. 8.45%, intensive vs. conventional). In addition, the relative risk of severe hypoglycemia for patients in the former intensive treatment group was < 1 , which was a decrease from the rates during the DCCT, and an increase in hypoglycemic occurrence for the conventionally controlled group. There was no difference in body weight, BMI, or percentage of subjects overweight at year 4 of the EDIC study.

After 4 years of follow-up in the EDIC study, 65% of the original conventionally treated patients showed a 3-step or more progression in retinopathy as compared with 32% of the former intensive group patients. This represents an odds ratio reduction of 74% for those having been in the intensive control group. Thus, the benefits of intensive therapy persisted for an additional 4 years in a significant number despite increased levels of glucose control. Similar findings were observed for the progression of nephrological disease. There was an 85% reduction in the adjusted odds ratio for developing albuminuria in the former intensive treated patients vs. the former conventionally controlled group. Thus, the benefits of previous intensive therapy continued for another 4 years with regard to renal function.

The authors state that these results demonstrate conclusively that the benefits of intensive therapy outweigh any associated risks of hypoglycemia and weight gain, and persist for at least four years. In addition, the data suggest that less than optimal glycemic control during the early years of diabetes (in adolescence) has a long lasting, detrimental effect on

the development of complications even after better glycemic control is established. Thus the recommendation is that intensive therapy be the standard of care for adolescents with type I diabetes mellitus. The DCCT/EDIC study is planned to continue for at least 10 years.

The Diabetes Control and Complications Trial/Epidemiology of Diabetes of Interventions and Complications research group: *J Pediatr* 2001;139:804-812.

Editor's Comment: *The results of the DCCT/EDIC at year 4 in adolescents are not different from those presented for the entire group (New Engl J Med 2000;342:381-389). The findings are important and have significant implications for the treatment of adolescents starting at diagnosis, and perhaps pre-adolescent children with type I diabetes mellitus. Some have assumed that the intensive therapy achieved by the DCCT research group, while important in reducing complications, might not be a reasonable and cost-effective treatment regimen for all adolescents with diabetes. These data prove otherwise. Intensive therapy initiated early in the course of diabetes has prolonged and long-lasting effects of reducing the risks of microvascular complications. Alternatively, diabetes management resulting in poor glucose control during the early adolescent years may be associated with an increased risk of microvascular complications, even after intensive therapy and a reduction in HbA1c has been achieved. Thus, these data support the initiation of intensive diabetes therapy designed to achieve near normal glucose control as early as possible in newly diagnosed adolescents. This must be the standard of care. Patients, their parents, and third-party payers must be educated to understand, demand, and compensate for such treatment.*

William L. Clarke, MD

Growth in Human Immunodeficiency Virus Type 1-Infected Children Treated with Protease Inhibitors

About 33% of children infected with HIV have impaired growth. The extent of such impairment may be regarded as a clinical criterion predicting progression to AIDS. The addition of protease inhibitors (PIs) has been demonstrated to frequently reduce plasma HIV RNA levels, to increase CD4 lymphocyte numbers, and to improve the general condition of children and adults with HIV retrovirus type I infections.

Steiner et al present data on the long-term (72 week) impact of PI treatment on growth of infected children.

Data are reported on 44 children between the ages of 0-17 years with confirmed infection. They were observed for 72 weeks prior to starting PI treatment. Nintavanir or nelfinavir were added to the previous treatment of two nucleoside analogue reverse transcriptase inhibitors. Growth, HIV-1 RNA plasma levels, and CD4 lymphocyte counts were determined at 0, 24, 48, and 72 weeks of treatment. Heights were reported in SD scores as determined from normal aged and gender individuals. Data from 44 children were analyzed in 3 age groups [6

children <3 years of age (group I), 23 children 3-10 years of age (group II), and 15 children >10 years of age (group III)]. All had completed 72 weeks of PI treatment. Multiple regression analyses were used to determine the relationship between parameters of growth and variables such as CD4 cell count and CDC HIV-1 categories. Children in group I were more frequently in the severe CDC clinical category "C" and had higher plasma HIV-1 RNA levels at baseline than those in groups II and III.

By 24 weeks of treatment, there was a significant decrease in mean plasma HIV-1 levels in children of group I vs. those in groups II and III. Twenty-seven of the 44 children showed a sustained reduction of HIV 1 RNA levels. In the 72 weeks before the initiation of PI therapy the differences between Δ -Z scores at 24 week intervals indicated progressive growth retardation which was reversed with a significant increase in growth during the 72 weeks after the PIs were added. This increase was biphasic with a greater increase between weeks 0-24, and a second increase between 48-72 weeks. The greatest increase in growth was in the 6 children in group I, all of whom had significant growth retardation at baseline and in the 4 significantly retarded children in group II. The 19 other children in group II and all 15 in group III had growth rates maintained within 1 SDS of the mean. Growth while receiving PIs was negatively correlated with growth during the preceding period, and positively correlated with an increase in CD4 cells. No correlation was seen between the decrease in plasma HIV-1 levels. Thus, age categories and CDC clinical categories were significantly associated with catch-up growth, but multiple regression analysis revealed that only growth during the preceding period and the age

category were significantly associated with growth during PI therapy.

The authors note that previous studies have shown that stunting has been correlated with higher plasma HIV-1 RNA levels. Of note, the older children in the cohort were not as severely stunted as the younger children, and did not have as significant a growth response to PI therapy. The authors speculate that these findings may be the result of the older children having a slower progression of HIV infection than the younger children, since they survived infancy in the era prior to aggressive therapy. In addition, the authors point out that others have attributed stunting in HIV infected children to sub-clinical hypothyroidism, low IGF-1, or proteolysis of IGF BP3. The authors did not measure these hormone levels.

Steiner F, et al. *Eur J Pediatr* 2001;160: 611-616.

Editor's Comment: *The data reported in this paper by Steiner, et al are important from two aspects. First, treatment with a protease inhibitor can improve growth rates in young HIV infected children. Secondly, those with the greatest catch-up growth are those who are the most stunted initially. Such information is similar to that which has been shown for treatment of nearly every chronic disease of childhood. Unfortunately the authors did not determine biochemical markers of growth, including IGF-1 and IGF BP3. They suggest this be done in future studies. These data might have been useful in helping decide which children could benefit the most from such therapy. The data presented, however, are clinically useful.*

William L. Clarke, MD

Paternal Contribution to Aneuploidy

The relationship of maternal age to chromosomal abnormalities is well established; however, there have been conflicting data with regard to paternal contribution. Of potential pertinence is that 10 – 30% of autosomal trisomies arise during paternal meiosis, 100% of XYYs and 50% of XXYs are paternal in origin, and 80% of Turner syndrome patients are missing the paternal X. Also, an increase in paternal age is associated with the development of uniparental disomy 15, and trisomy 18 is seen with increased paternal age. To further study the relationship of paternal age to diploidy and disomy of sperm, the authors of this paper screened human sperm using four-colour FISH probes. Chromosomes 6, 21, X, and Y were examined to determine the incidence of disomy in sperm related to paternal age where the normal usual sperm are haploid.

Almost 200,000 sperm were examined from 18 healthy donors, ages 24 to 74. The investigators found a significant increase in the level of autosomal disomy and a marginally significant increase in sex chromosome disomy with increasing male age. Significant individual variation was observed. The increase in disomy ranged from 0.3 to 17% for each 10-year period. This suggests that older men have a tendency to show synaptic abnormalities perhaps related to the deterioration of testicular environment with advancing age.

Bosch M, et al. *Euro J Hum Gen* 2001;9:533-538.

Editor's Comment: *There is a growing interest in paternal contributions to congenital anomalies, both potential teratogens and the effect of aging itself. Although triploids are not usually viable, it is interesting*