The advent of highly active antiretroviral treatment (HAART) has affected all age groups of patients with human immunodeficiency virus (HIV). However, its effects in children are clearest when comparing children cared for in the era prior to the availability of HAART with those children treated after HAART became standard of care. In the paper in this month’s issue of the journal by Kapogiannis and colleagues from the perinatal AIDS collaborative transmission study (PACTS) and PACTS-Hope study in the United States, the impact of HAART on mortality is clearly demonstrated [1]. The study was not an easy study to undertake. It involved enrolling infants (both HIV-infected and -exposed) into a long-term follow-up study with no clear direct benefit to the children enrolled. It is a credit to the families and the investigators involved that these children were enrolled in this study before we or their parents knew what the future had in store for them, and that the investigators and the sites were able to follow them for up to 18 years. It is only through a well-designed long-term follow-up study such as this one that we can understand the impact that HIV and its treatment with HAART has had on this unique population.

What do their data show? Simply put, many of the deaths occurred in the pre-HAART and early HAART era, with dramatic reductions in mortality in the post-HAART era. However, they were unable to prove that it was the timing of initiation of HAART that made the biggest impact on the decrease in mortality. What are some of the confounding variables that this and other studies evaluating outcomes based on age at initiation of HAART have had to work with? In the pre-HAART era and even early in the post-HAART era, few medications were available in formulations suitable for infants and children. The problem was further compounded by lack of pharmacokinetic data on these medications in these children. These 2 issues resulted in difficulties administering these potentially lifesaving therapies to those children at highest risk for death. In this study, the lack of data on CD4 and viral load in the pre- and early HAART era in this population has also led to an inability to differentiate between high- and low-risk children enrolled in the study. Thus, the authors are unable to judge whether it was treatment of specific levels of immune suppression and viral replication that were associated with the reported change in mortality noted in their study.

Although it is currently accepted practice to start administering HAART to all HIV-infected children who receive a diagnosis during the first 12 months of life, recommendations on when best to start and what specific antiretrovirals are best to start in children who are identified or who receive a diagnosis at >12 months of age continue to be a complex issue. Decisions to treat in the developed world are based on Centers for Disease Control (CDC) [2] immunologic and clinical categories and include clinical manifestations of HIV (mildly and moderately symptomatic HIV; CDC categories A and B) and the presence of a single serious bacterial infection or lymphoid interstitial pneumonitis [3]. These criteria are different in the developing world, where treatment guidelines for children are based on World Health Organization clinical and immunologic criteria. These include starting HAART for all children aged <2 years, starting HAART for children aged 2–5 years with <25% CD4 cells, and starting HAART for children aged >5 years whose CD4 cell count decreases to <350 cells [4]. The use of guidelines based on moderate or strong recommendations but lacking in evidence continues to be an issue for all care providers. However, hope is on the horizon with new studies underway that will address these issues. These include studies evaluating short- and long-term consequences of different HAART regimens in HIV-infected infants [5], as well as others investigating start and

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**EDITORIAL COMMENTARY**

Highly Active Antiretroviral Treatment and Children

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(See the article by Kapogiannis et al, on pages 1024–34.)
defer strategies [6]. Recent data from a study investigating deferring therapy in children aged >1 year have led to renewed discussion of these issues. In their recent presentation of their PREDICT study, Puthanakit and colleagues revealed that although rates of CDC grade C events or death were 7.6 cases per 1000 person-years in the immediate group and 4.9 cases per 1000 person-years in the deferred group, AIDS-free survival and neuro-developmental issues at 144 weeks did not differ in the deferred as compared with the treatment group. In addition, rates of CDC category B events, hospitalizations, and overall grade 3 or 4 adverse events also did not differ significantly between the 2 study groups [7].

With the ever-increasing impact of programs to prevent mother-to-child transmission, fewer children are being born with perinatal HIV. Gaps in our understanding include identifying those infants at risk for in utero transmission, and issues revolving around when to treat those not treated during the first 1–2 years of postnatal life. Looking ahead to the future, we anticipate that data such as those presented in this journal, as well as data from studies focusing on when is best to start and what is best to start, will help decide the ongoing debate of whom to treat and when to treat in perinatally infected youth.

Note

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