Our colleagues in Thailand [1] have presented very persuasive evidence that children who are perinatally infected with HIV gain significant benefits from initial antiretroviral therapy (ART) regimens that include 3 drugs—2 nucleoside reverse-transcriptase inhibitors plus 1 nonnucleoside reverse-transcriptase inhibitor. The majority of the children in the study by Puthanakit et al. [1], reported in this issue of *Clinical Infectious Diseases*, were treated with a combination of stavudine, lamivudine, and nevirapine (59%); a smaller percentage were treated with a combination of stavudine, lamivudine, and efavirenz (38%), and only a very small percentage (3%) were treated with zidovudine, lamivudine, and nevirapine. The authors’ characterization of these drug regimens as “HAART,” in spite of the fact that they did not include a protease inhibitor, suggests that the term “HAART” no longer has an agreed-on consensus as to its definition and should be replaced by the more descriptive term “combination ART.”

Similar to data from the United States, both morbidity (as reflected by hospitalization rate) and mortality rates in the Thai study were ameliorated by 3-drug combination ART, and that improvement can be expected when such therapy is started sooner rather than later. In this study, the mean age at the start of ART was 7.6 years, with the threshold for starting ART occurring when the children’s conditions had already progressed to AIDS. Although these data document the benefits of therapy, because of the problem of “confounding by indications” (i.e., the children who are most ill are treated first), the benefit of initiating therapy at an early age before the onset of AIDS-defining illness would be expected to have even greater beneficial effects [2]. This study demonstrates that the strategy of delaying ART in infants and young children to avoid drug toxicity and to preserve future choice may not be as appropriate as it is for adults with stable HIV infection but, rather, may be an example of “too little too late.” In the United States, before 1994, combination ART with 3 drugs in children was the exception; however, by 2001, 98% of perinatally infected children were treated with such regimens [3]. The gain in improved immune function and control of viral replication demonstrated in these US infants, in contrast to that demonstrated in the Thai study [1], usually occurred at a much younger age before the progression to an AIDS-defined clinical stage and, unfortunately, did not occur until 2005 [4]. The number of infants and children in the less-developed world who are presently dying from a disease with a proven therapy is an unacceptable and tragic reality.

The major difference between the experience reported by Puthanakit et al. [1] in Thailand and that in the United States is in the causes listed for hospitalization and death. Puthanakit et al. [1] reported that 23% of hospitalizations and 31% of deaths in their cohort of 192 children were due to immune reactivation syndrome (IRS). This was described in more detail in an earlier report from this group [5]. There is, as yet, no accepted definition of IRS in children; however, similar to the condition in adults, it is generally defined as the occurrence, in an HIV-infected child whose combination ART has led to an increase in CD4 cell count and a decrease in plasma viral load (as defined by HIV RNA titer), of an illness caused by microorganisms that previously defined their AIDS illness, usually occurring within 4–6 months after initiation of combination ART.

Among children followed in the United States as part of the Pediatric AIDS Clinical Trials Group long-term outcomes study (protocol 219/219c), the occurrence of IRS is a rare event as a cause of morbidity and has not been reported as a cause...
of mortality. This discrepancy may be the result of there being less recognition of IRS in the United States, and, when a more accepted definition of IRS is established and applied to US cohorts of infants and children infected with HIV, it may be expected that physicians in the United States will learn from their colleagues in Thailand and elsewhere in the developing world of this unique, newly recognized “toxicity” due to ART in children. However, it is as likely—or even more so—that this marked difference in the occurrence of IRS between the US and Thai cohorts of HIV-infected infants and children is related to the timing and aggressiveness of combination ART. In US cohorts, after 2002, the most preferred recommended combination ART regimen was 2 nucleoside reverse-transcriptase inhibitors plus 1 protease inhibitor rather than 1 non-nucleoside reverse-transcriptase inhibitor, as used in the Thai program, and ART has usually been initiated at a much younger age before progression to an AIDS-defined clinical stage [6]. The initiation of combination ART in infancy or early childhood may prevent IRS by preserving immune function and limiting the development of significant opportunistic infections associated with IRS. This is supported, to some degree, by data from the Strategies for Management of Anti-Retroviral Therapy Study, which demonstrated a greater risk of HIV disease progression, mortality, and major toxicities in patients who had structured interruption of their ART than in patients with continuous ART [7]. If so, this provides further evidence that infants and young children living with HIV infection do better if they are treated early in the course of their illness with currently recommended combination ART.

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References