relevant nucleoside transporters on antiretroviral action and toxicity is not available. Because most PIs alter tenofovir pharmacokinetics, evaluation of the role of PIs as a drug class on tenofovir-associated kidney dysfunction remains a reasonable approach.

Unfortunately, our data set does not contain the reason for therapy change among the 48 subjects who initiated TDF at baseline and discontinued TDF before study week 48. However, management of toxicity for study participants was based on the grading system and management recommendations used by the AIDS Clinical Trial Group. Because none of these subjects developed a grade 2 or greater serum creatinine clearance rate (defined as a rate 1.4–1.8 times the upper limit of normal), it is unlikely that TDF treatment was discontinued in these subjects because of concerns about renal toxicity.

The National Kidney Foundation [11] and the HIV Medicine Association of the Infectious Diseases Society of America [12] provide similar staging criteria of chronic kidney disease for the clinical management of patients. However, we have come to recognize that these strata of estimated glomerular filtration rates (GFRs) are not appropriate study outcomes for data from clinical trials. For a patient with normal renal function to develop a grade 2 creatinine clearance rate, a GFR change of >48 mL/min would need to occur. Because the follow-up period of most treatment trials is 1–3 years and because real-world HIV therapy is lifelong, even small declines in renal function, if they were to continue throughout the duration of exposure, would have serious clinical implications. Analogous to the slow, progressive natural history of diabetic and hypertensive nephropathy, certain combinations of antiretroviral drugs may also result in a chronic, progressive nephropathy. Therefore, we propose that future studies use a smaller change in GFR, such as 10–15 mL/min per year, as an outcome, because such changes in renal function are more likely to be detected during the relatively brief follow-up period of a clinical trial and are likely to be clinically significant over the long run.

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Pediatric Highly Active Antiretroviral Therapy in Africa: Potential Benefits of a Family-Centered Model

To the Editor—We thank Meyers et al. [1] for their recent review in the Journal, in which the authors elucidated the challenges of delivering pediatric highly active antiretroviral therapy (HAART) in South Africa. More importantly, the authors also suggested practical recommendations to scale-up and improve South African pediatric HAART services. One innovative recommendation proposed was that “family-oriented services should be established at all ART facilities, with at least 1 day/week being assigned for families” [1, p. 5479].

We believe that the family-centered model is an excellent idea. In fact, the Sinikithemba HIV/AIDS clinic in Durban, South Africa, designed and implemented a family-centered model of care in 2003. All adult patients accessing HAART are routinely interviewed about
their children’s health, and those at risk are referred for HIV testing and, if necessary, treatment. Reciprocally, some children receiving HAART at the Sinikithemba clinic have precipitated the diagnosis of HIV/AIDS and the subsequent initiation of treatment for their infected primary caregivers. Referred family members are prioritized for enrollment in the HAART program, and families are given clinic appointments for the same day when possible. The multidisciplinary pediatric HIV team comprises a pediatrician assisted by generalist doctors, nurses, treatment counselors, psychologists, social workers, child care workers, and a pastor, who meet at a weekly pediatric case conference to discuss clinical as well as psychosocial aspects of care.

Outcomes from the Sinikithemba pediatric HAART cohort were recently documented [2]. The data suggested that a pediatric HAART program in a resource-limited setting can be clinically effective and feasible, as demonstrated by improvements in therapeutic responses, survival, patient retention, and regimen durability [2].

At the Sinikithemba clinic, data on the HIV serostatus of the children’s primary caregivers were also collected, with surprising and interesting results [2]. Although half of the children were cared for by at least 1 HIV-positive caregiver, these caregivers showed a protective effect against pediatric mortality, compared with caregivers who were untested or HIV negative [2]. The authors hypothesized that the HIV-positive caregivers receiving HAART at the same treatment site may have been able to provide more-informed treatment support for their children, resulting in better clinical outcomes [2].

Future studies that further investigate the possible benefits of family-centered clinics should be encouraged. These new data may lend support to the theory that a family-centered HAART model not only protects the integrity of caregiving structures by preventing the decline in health or death of primary caregivers but also contributes to better treatment outcomes for pediatric patients [3].

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Protective Effect of HIV-Positive Primary Caregivers on Mortality in Children Receiving Antiretroviral Therapy?

To the Editor—We thank Reddi et al. for their response [1] to our recent review of the challenges of pediatric HIV care and treatment in South Africa [2] and congratulate them on having implemented a family-centered HIV clinic.

Our recommendation to implement family-centered HIV services was to decrease the burden of care associated with caregivers and children receiving HIV services on separate days and to ensure that the caregivers of children in care are not neglected, for the sake of both their own and their children’s health outcomes.

Reddi et al. suggest that, in addition to the benefits described above, children being cared for by HIV-positive caregivers have lower mortality rates [3, 4]. Although we are pleased to have support for the implementation of family-centered models, which is likely to positively influence adherence in children and their caregivers, the data referenced by Reddi et al. need to be interpreted with caution.

In their retrospective study of 13 deaths in a cohort of 151 children started on antiretroviral therapy, there were 3 deaths among the children cared for by HIV-positive caregivers and 10 deaths among those cared for by “HIV-negative or unknown” caregivers [3]. Extrapolation from the presented data suggests that the HIV status of 40.2% of the caregivers was unknown and that only 10.7% of caregivers were known to be HIV negative, with the remaining 49.1% known to be HIV positive. Grouping those of unknown status with those known to be negative is inappropriate. Unfortunately, disaggregated data on caregiver status within the deaths in the HIV-negative or unknown group were not provided. However, if the relative proportion of unknown and negative caregivers in the HIV-negative or unknown group was similar to that in the entire cohort, then nearly 8 of the caregivers in the HIV-negative or unknown group would, in fact, be of unknown status, and 2 would be HIV negative.

The actual status of the unknown group is important. An alternative hypothesis could be formulated—that is, that HIV-positive children receiving antiretroviral therapy and being cared for by an HIV-positive caregiver who is unaware of his or her own status has a deleterious impact on pediatric mortality. This hypothesis is congruent with models of health-seeking behavior and previous meta-analysis of the impact of maternal