LBM declined. Further investigation should be done to determine whether this increase in grip strength is associated with improvements in morbidity or quality of life. Curiously, an increase in grip strength was not seen in the delayed supplementation group although weight and LBM improved at a faster rate than in the early supplementation group.

Ultimately, the investigators saw no effect of supplementation on viral load at any of the time points in their study and similar to the other studies in our systematic review, all groups showed significant declines in viral load 3 months after ART initiation, as would be expected. Although there was some suggestion of an improvement in $CD4^+$ cell counts with whey protein, this effect diminished 3 months after supplementation ended.

Finally, as Olsen et al observe in their article, the scale-up of nutritional supplementation that Ethiopia undertook for all patients with HIV and BMI <18.5 after the study ended did not seem to fare well, with more than 70% of patients defaulting from supplementation. Although the delayed intervention design is one that should be encouraged more widely in research studies of nutritional supplementation to answer some of the remaining scientific questions, it is clear that information from these types of efficacy trials is not enough to translate promising results into policy. A case study or an effectiveness trial of the program in Ethiopia could provide important information on how countries can successfully scale-up nutritional assessment, counseling, and support and avoid some of the challenges that Ethiopia has faced.

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Early Initiation of Antiretroviral Therapy Among Young Children: A Long Way to Go

To the Editors:

The article by Koller et al[1] is a welcome effort to document trends and determinants of immunodeficiency among children living with HIV starting combination antiretroviral therapy (cART) in low-, middle-, and high-income countries and highlights the very modest improvements in the stage at which children begin cART. The article raises several questions which would benefit from further consideration.

Interpreting the findings in this article would be enhanced if there was more information about the sites within each country that contributed data such as how many sites, what level of care were they (clinic or hospital), public or private, nongovernmental or research-based service settings, and rural or urban areas. Without this level of detail on the sites, it is difficult to determine whether these results represent "best case" scenarios, and consequently the situation in "non-international epidemiologic databases to evaluate AIDS (IeDEA)" sites is likely to be much worse. According to the IeDEA Web site (http://www.iedea-sa.org), the main criterion for clinics to participate in the IeDEA collaboration is that a clinic treats people with HIV and prospectively and electronically collects clinical data. In low- and middle-income country (LMIC) settings, this inclusion criterion would likely have limited the sample of facilities to those receiving some donor or research support. Routine health information systems in many LMIC countries have been characterized as weak,[2,3] and it is unlikely that electronic data would be the norm for national health management information systems in these settings.[3,4]

Using the group of upper-middle income countries as an example, 83% of the sample comes from 1 country, South Africa, where all except 1 IeDEA site is situated in the metropolitan areas of Cape Town and Johannesburg, the exception being a clinic in Hlabisa, KwaZulu-Natal, which is a rural demographic surveillance site. The finding that around 63% of children in these research sites in South Africa started cART with severe immunodeficiency is concerning because the situation is likely to be considerably worse in general public health facilities without additional research support and without electronic prospective tracking systems. Similarly, 82% of the sample for the lower middle-income countries comes from Zambia, and within Zambia from 1 nongovernmental organization (Centre for Infectious Disease Research in Zambia), situated in Lusaka. Although the findings are important in improving our knowledge of the progress with access to pediatric cART, having clear information on the source of the data is also critical to improve the utility of the findings for national governments and health managers.

We agree with the conclusion of Koller et al[1] that early diagnosis of HIV in children must remain a global public health priority, and we have shown it is still a major missed opportunity in South Africa.[5] We highlight, though, an important issue affecting initiation of cART among children, which is not discussed in this article, the notion of pediatric HIV disease and treatment as a neglected disease.[6]

Although there is evidence of a worldwide decline in vertical HIV transmission, a high number of children still become infected with HIV.[7] In a country such as South Africa where there have been significant declines in perinatal HIV transmission,[8] The Joint United Nations Programme on HIV/AIDS (UNAIDS) estimates that 16,000 (95% confidence interval: 14,000 to 19,000) children 0–14 years were newly infected in 2013.[7]

Given the complexity of pediatric HIV treatment, it is not surprising that there is late initiation of cART during the first years of life. Treatment options

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are still overlooked, particularly for the youngest children who are unable to take tablet formulations. Unlike for adults where fixed-dose combinations of ARVs are available, children younger than 5 years have to use liquid formulations and caregivers have to measure before administering each dose twice a day.[9] Drugs produced by different companies vary in bottle size and special storage needs. Some carry unpleasant tastes and risks of toxicity.[10] Dosage adjustments depending on weight are needed up to 3 times in the first year of life alone. Procurement of pediatric drugs is complex and forecasting of demand is difficult with a market only a fraction of the size of the adult market. This also leads to prices twice as expensive as the adult equivalents.[11]

We propose that unless more child-friendly formulations are developed, late cART initiation of children is likely to continue. It is also likely that the situation will be even worse in busy nonresearch health settings in LMICs.

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Authors' Reply: Early Initiation of Antiretroviral Therapy Among Young Children: A Long Way to Go

To the Editors:

We thank Doherty and co-workers for their thoughtful and pertinent response to our article describing trends in immunodeficiency at antiretroviral therapy (ART) initiation in children in low, middle, and high income countries.[1] We agree that it is important to know more about the International Epidemiologic Databases to Evaluate AIDS (IeDEA) sites included in the analysis to assess the extent to which they are representative of general public health facilities, and hence whether the finding of improvement in proportion of children with immunosuppression at ART initiation (albeit modest) is generalizable across these countries.

The IeDEA collaboration and the participating sites have therefore been described in dedicated profiles,[2,3] and a survey of the IeDEA sites providing HIV care for children has been published.[4] The survey included 63 sites in Asia (10), Central Africa (4), East Africa (29), Southern Africa (10), and West Africa (10). Nearly 75% of sites were public government-run clinics, 65% were in urban settings, and 57% provided pediatric care in combined adult–pediatric clinics.[4] As pointed out by Doherty and co-workers, many sites received additional financial support from research grants (57%), the US PEPFAR programe (54%) or the Global Fund (24%).[4] We cannot exclude that access to timely pediatric ART at non-IeDEA facilities may be even worse. However, all IeDEA sites followed the relevant national ART guidelines, and the strength of IeDEA data is that it is collected as part of routine care and not from dedicated research cohorts. We believe that the availability of individualized data through the IeDEA collaboration allowed a more nuanced picture of pediatric ART than analyses of program-level aggregate data, while preventing the ecological bias that may affect aggregate data analyses.[5]

We concur with Doherty and co-workers regarding the importance of advocacy for pediatric HIV as a neglected disease with an urgent need for better access to diagnostic tests and effective and safe pediatric-friendly drug formulations.[6] The first barrier to early ART initiation is poor access to early infant diagnosis for which coverage remains low in many settings due to lack of virological diagnostic capacity, delivery services, and low social acceptability.[7,8] Even in IeDEA sites, early infant diagnosis for infants was not universally available throughout the period of data collection, with the diagnosis of HIV being dependent on the presence of clinical symptoms. In the IeDEA site survey, access to certain drugs especially as part of fixed dose combinations was limited in certain regions.[4] Interestingly, Asian sites had poorer access to tenofovir and abacavir, which may reflect more frequent

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