

Editorial

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It is Time to Explore the Potential Benefit of Routine Micronutrient Supplementation in Optimizing Bone Health and Growth in HIV Exposed Uninfected Children in the Context of Early Antiretroviral Exposure in Resource Limited Settings

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There is evidence that human immunodeficiency virus (HIV) infected children have decreased bone mineral density (BMD) compared to population norms.^{1,4} Similarly, several studies have shown impaired growth among HIV infected children with several patterns of disrupted growth.⁵⁻⁷ Among other factors, micronutrient deficiencies are believed to contribute significantly to growth failure in HIV infected children, particularly in resource constrained settings with high background rates of micronutrient deficiencies.⁵ Some of the major risk factors of decreased BMD in HIV infected children include antiretroviral therapy (ART) related toxic effects particularly with tenofovir disoproxil fumarate (TDF) containing regimens.^{2,8}

There is some evidence that micronutrient supplementation in HIV infected children improves growth and BMD. In a longitudinal study involving 37 perinatally HIV infected children done in USA, multivitamin use was independently associated with higher BMD Z-scores among multivitamin users compared to non-users.² The provision of multiple micronutrient supplements to ART naïve HIV-infected South African children resulted in improvement in weight-for-height Z-score compared with a placebo.⁹ A systematic review of 11 trials mostly conducted in Africa concluded that multiple micronutrient supplements offer some clinical benefit in HIV infected children.¹⁰ These results have provided a strong rationale for the World Health Organization (WHO) recommendation for multiple micronutrient supplementation for HIV infected children, especially in settings where micronutrient deficiencies are prevalent.¹¹

Whereas, WHO currently recommends multiple micronutrient supplementation for all HIV infected children, supplementation in HIV exposed uninfected children is recommended if they are malnourished and yet this growing population of children in resource limited settings is similarly at risk of impaired growth and bone health.¹² As a result of accelerated scale-up of use of triple ARV combinations for preventing mother-to-child HIV transmission (PMTCT), worldwide, a large number of HIV exposed Uninfected (HEU) infants are exposed to triple ARVs early in life. In resource limited settings where extended breastfeeding for at least 12 months is recommended for infant survival among HIV infected women, these infants are exposed to ARVs (predominantly TDF and Efavirenz (EFV) containing regimens, the current WHO preferred first line triple ART combination for HIV infected pregnant women in PMTCT programmes) for up to 2 years. While lifelong ART greatly minimizes HIV transmission to the baby, prolonged ART exposure both *in utero* and through extended breastfeeding raises safety concerns for the baby, including potential growth impairment and adverse effects on bone health. Additionally, children born to HIV infected women are already prone to under-nutrition related to maternal factors yet nutrition plays a critical role in bone mass formation

and mineralization during the fetal and infancy periods,^{13,14} Some studies have indicated lower Bone Mineral Content (BMC) and lower height-for-age Z-score (HAZ) as well as lower head circumference-for-age Z-score (HCAZ) in infants exposed to TDF *in-utero*.¹⁵⁻¹⁷ More recently, a study that was designed to evaluate the potential bone and kidney toxic effects of TDF among HIV-infected pregnant and breastfeeding women and their infants reported that there were significant decreases in BMC among newborns whose mothers received Protease Inhibitor-based ART during pregnancy compared to those who received only zidovudine (ZDV) during pregnancy.¹⁸ Another first line antiretroviral, EFV is associated with vitamin D deficiency through multiple postulated mechanisms.^{19,20} Vitamin D is critical for calcium absorption and bone mineralization and its deficiency is associated with rickets. Therefore, EFV associated vitamin D deficiency may have potential adverse effects on bone health.²¹⁻²⁴ The growing number of HIV infected pregnant and lactating women on TDF/EFV containing regimens for PMTCT has the potential to have a negative impact on bone health of their infants and young children. Consequently, failure to achieve adequate bone mass during early infancy may predispose these infants to increased risk of childhood fractures and osteoporosis in adulthood.

Although, there is conflicting data on the effect of ART on growth in HIV exposed uninfected infants, a number of studies conducted in Africa have shown that *in utero* ART exposure is associated with lower birth Weight for Age z-scores (WAZ) and length for age z-score (LAZ).^{25,26} Coupled with high background rates of micronutrient deficiencies, prolonged ART exposure in HEU infants raises potential risk for growth impairment in this population. Given these concerns, and background rates of stunting among a third of children in many African settings, it is important to take a closer look at interventions that might counter any added negative effects on bone mineralization and growth caused by prolonged ARV exposure of up to 24-30 months during gestation and extended breast milk ingestion of ARVs among HEU children in resource limited settings.

A number of minerals including calcium, phosphorous, sodium as well as magnesium and vitamins A, B6, B12, C, D, and K, directly or indirectly affect bone mineralization.²⁷ Several studies in both resource rich and resource limited settings have demonstrated some health benefit from micronutrient supplementation in children. In a blinded placebo controlled cluster randomized trial done in India involving 268 HIV uninfected children aged 6-16 years, supplementation with a micronutrient enriched beverage was associated with significantly greater increments for height, weight, whole-body bone mineral content (BMC), whole-body bone area, and BMD at the neck of the femur after 14 months in the supplemented group than in the placebo group ($p < 0.05$).²⁸ A recent randomized placebo controlled trial done in Tanzania revealed small but significant improvements in WAZ with zinc and multivitamin supplements among HIV unexposed infants aged 6 weeks-84 weeks.²⁹

The growing population of HEU may benefit from early multiple micronutrient supplementation given the concerns of effects of prolonged ART exposure on BMD and growth; however, to date, there is very limited published data on effect of multiple micronutrient supplementation on growth and BMC in this population. It is therefore important to evaluate the use of interventions like micronutrient supplementation in HEU infants that could potentially boost bone health and growth in this pediatric population at risk of TDF/EFV adverse drug effects, particularly in Sub-Saharan Africa where micronutrient deficiencies are prevalent. This will build on evidence that would be critical in determining the applicability of such interventions in routine care of the growing population of HEU.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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