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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 undernutrition related to maternal factors yet nutrition plays a critical role in bone mass formation

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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-Sahara 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 interet.

REFERENCES

1. Mora S, Zamproni I, Beccio S, Bianchi R, Giacomet V, Viganò A. Longitudinal changes of bone mineral density and metabolism in antiretroviral-treated human immunodeficiency virus-infected children. *J Clin Endocrinol Metab*. 2004. 89(1): 24-28. doi: 10.1210/jc.2003-030767

2. Jacobson DL, Donna S, Christopher D, et al. Predictors of bone mineral density in human immunodeficiency virus-1 infected children. *J Pediatr Gastroenterol Nutr*. 2005; 41(3): 339-346.

3. Eckard AR, Mora S. Bone health in HIV-infected children and adolescents. *Curr Opin HIV AIDS*. 2016.; 11(3): 294-300. doi: 10.1097/COH.0000000000000270

4. Palchetti CZ, Szejnfeld VL, de Menezes Succi RC, et al. Impaired bone mineral accrual in prepubertal HIV-infected children: A cohort study. *Braz J Infect Dis*. 2015. 19(6): 623-630. doi: 10.1016/j.bjid.2015.08.010

5. Arpadi SM. Growth failure in children with HIV infection. *J Acquir Immune Defic Syndr*. 2000; 25: S37-S42.

ISSN 2377-8377 http://dx.doi.org/10.17140/HARTOJ-4-e010

6. McKinney RE Jr, Robertson JW. Effect of human immunodeficiency virus infection on the growth of young children. *J Pediatr*. 1993. 123(4): 579-582. doi: 10.1016/S0022-3476(05)80955-2

7. Chiabi A, Lebela J, Kobela M, Mbuagbaw L, Obama MT, Ekoe T. The frequency and magnitude of growth failure in a group of HIV-infected children in Cameroon. *Pan Afr Med J*. 2012. 11: 15. doi: 10.11604/pamj.2012.11.15.1297

8. Okonkwo RI, Weidmann AE, Effa EE. Renal and bone adverse effects of a tenofovir-based regimen in the treatment of HIV-infected children: A systematic review. *Drug Saf*. 2015; 39(3): 209-218. doi: 10.1007/s40264-015-0371-z

9. Mda S, van Raaij JM, de Villiers FP, Kok FJ. Impact of multi-micronutrient supplementation on growth and morbidity of HIV-infected South African children. *Nutrients*. 2013; 5(10): 4079-4092. doi: 10.3390/nu5104079

10. Irlam JH, Siegfried N, Visser ME, Rollins NC. Micronutrient supplementation for children with HIV infection. *Cochrane Database Syst Rev*. 2013. 10. doi: 10.1002/14651858.CD010666

11. WHO. Guidelines for an Integrated Approach to the Nutritional Care of HIV-Infected Children (6 Months-14 Years). 2009. Web site. http://www.who.int/nutrition/publications/hivaids/9789241597524/en/. Accessed September 24, 2017.

12. WHO. Consolidated guidelines for use of antiretroviral drugs for treating and preventing HIV infection; Recommendations for a public health approach. 2013. doi: http://www.who.int/hiv/pub/arv/arv-2016/en/. Accessed September 24, 2017.

13. Puthanakit T, Siberry GK. Bone health in children and adolescents with perinatal HIV infection. *J Int AIDS Soc*. 2013; 16: 18575. doi: 10.7448/IAS.16.1.18575

14. McDonald CM, Kupka R, Manji KP, et al. Predictors of stunting, wasting and underweight among Tanzanian children born to HIV-infected women. *Eur J Clin Nutr*. 2012; 66(11): 1265-1276. doi: 10.1038/ejcn.2012.136

15. Grigsby IF, Pham L, Mansky LM, Gopalakrishnan R, Mansky KC. Tenofovir-associated bone density loss. *Ther Clin Risk Manag*. 2010; 6: 41.

16. Siberry GK, Williams PL, Mendez H, et al. Safety of tenofovir use during pregnancy: Early growth outcomes in HIV-exposed uninfected infants. *AIDS*. 2012; 26(9): 1151. doi: 10.1097/QAD.0b013e328352d135

17. Siberry GK, Jacobson DL, Kalkwarf HJ, et al. Lower newborn bone mineral content associated with maternal use of tenofovir disoproxil fumarate during pregnancy. *Clin Infect Dis*. 2015; 61(6): 996-1003. doi: 10.1093/cid/civ437

18. Siberry GK, Tierney C, Stranix-Chibanda L, et al; the IMPAACT 1084s Study Team. Impact of maternal tenofovir use on HIV-exposed newborn bone mineral. Conference on Retroviruses and Opportunistic Infections; Feb 22-24, 2016; Boston, MA, USA.

19. Welz T, Childs K, Ibrahim F, et al. Efavirenz is associated with severe vitamin D deficiency and increased alkaline phosphatase. *AIDS*. 2010; 24(12): 1923-1928. doi: 10.1097/QAD.0b013e32833c3281

20. Fabbriciani G, De Socio GV. Efavirenz and bone health. *AIDS*. 2009; 23(9): 1181. doi: 10.1097/QAD.0b013e32832bab0f

21. Brown TT, McComsey GA. Short communications-Association between initiation of antiretroviral therapy with efavirenz and decreases in 25-hydroxyvitamin D. *Antivir Ther*. 2010. 15(3): 425. doi: 10.3851/IMP1502

22. DiMeglio LA, Wang J, Siberry GK, et al. Bone mineral density in children and adolescents with perinatal HIV infection. *AIDS*. 2013; 27(2): 211-220. doi: 10.1097/QAD.0b013e32835a9b80

23. Cazanave C, Dupon M, Lavignolle-Aurillac V, et al. Reduced bone mineral density in HIV-infected patients: Prevalence and associated factors. *AIDS*. 2008. 22(3): 395-402. doi: 10.1097/QAD.0b013e3282f423dd

24. Escota GV, Cross S, Powderly WG. Vitamin D and calcium abnormalities in the HIV-infected population. *Endocrinol Metab Clin North Am*. 2014; 43(3): 743-767. doi: 10.1016/j.ecl.2014.05.005

ISSN 2377-8377 http://dx.doi.org/10.17140/HARTOJ-4-e010

25. Powis KM, Smeaton L, Ogwu A, et al. Effects of in utero antiretroviral exposure on longitudinal growth of HIV-exposed uninfected infants in Botswana. *J Acquir Immune Defic Syndr (1999)*. 2011; 56(2): 131. doi: 10.1097/QAI.0b013e3181ffa4f5

26. Powis KM, Smeaton L, Hughes MD, et al. In-utero triple antiretroviral exposure associated with decreased growth among HIV-exposed uninfected infants in Botswana. *AIDS*. 2016; 30(2): 211-220. doi: 10.1097/QAD.0000000000000895

27. Nieves JW. Osteoporosis: The role of micronutrients. *Am J Clin Nutr*. 2005; 81(5): 1232S-1239S.

28. Shatrugna V, Balakrishna N, Krishnaswamy K. Effect of micronutrient supplement on health and nutritional status of schoolchildren: Bone health and body composition. *Nutrition*. 2006; 22(1): S33-S39. doi: 10.1016/j.nut.2005.07.010

29. Locks LM, Manji KP, McDonald CM, et al. Effect of zinc and multivitamin supplementation on the growth of Tanzanian children aged 6–84 wk: A randomized, placebo-controlled, double-blind trial. *Am J Clin Nutr*. 2016; 103(3): 910-918. doi: 10.3945/ajcn.115.120055