Clinical Infectious Diseases

EDITORIAL COMMENTARY

Widening the Lens to Ensure Children Who Are Human Immunodeficiency Virus (HIV) Exposed Are Alive, HIV Free, and Thriving

Amy L. Slogrove[1,2] and Kathleen M. Powis[3,4,5]

[1]Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Worcester, South Africa, [2]Ukwanda Centre for Rural Health, Department of Global Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Worcester, South Africa, [3]Department of Immunology and Infectious Diseases, Harvard T. H. Chan School of Public Health, Boston, Massachusetts, USA, [4]Departments of Internal Medicine and Pediatrics, Massachusetts General Hospital, Boston, Massachusetts, USA, and [5]Botswana Harvard AIDS Institute Partnership, Gaborone, Botswana

(See the Major Article by Evans et al on pages 586–94.)

Keywords. HIV, children, HIV-exposed, HIV-exposed uninfected, early childhood development, Zimbabwe.

The "Start Free" component of the "Start Free Stay Free AIDS Free" framework, launched in 2016 by the Joint United Nations Programme on HIV/AIDS (UNAIDS) and the US President's Emergency Plan for AIDS Relief (PEPFAR), aims to secure a human immunodeficiency virus (HIV)–free beginning for every child by ending new HIV infections among children [1]. Aligned with this, the Sustainable Development Goals challenge the global community to not only secure child survival, but ensure that children thrive and live transformative lives, contributing to societal transformation [2]. For the 1.3 million children born each year to women with HIV (ie, HIV exposed), this means doing more than ensuring an HIV-free start [3]. Children who are HIV exposed, even when they remain HIV uninfected or HIV free, have not been achieving early childhood outcomes comparable to children born to women without HIV (ie, HIV unexposed) [4]. Prior to widespread availability of antiretroviral therapy (ART), these suboptimal outcomes among children who are HIV exposed and uninfected were associated with advanced maternal HIV disease, maternal mortality, and suboptimal breastfeeding. The Sanitation Hygiene Infant Nutrition Efficacy (SHINE) trial provides us with insights during the ART era as to outcomes for children who are HIV exposed, the majority of whom were also exposed to maternal ART in utero.

SHINE was a 2×2 factorial cluster randomized trial to evaluate improved infant and young child feeding (IYCF) as well as improved water, sanitation, and hygiene (WASH) on stunting and anemia at age 18 months. SHINE recruited >4500 pregnant women from 2 rural Zimbabwean districts between 2012 and 2015, and in the context of 15% maternal HIV prevalence, prespecified all analyses to be stratified by maternal HIV status [5]. In the main trial, IYCF moderately reduced stunting from 35% to 27% and anemia from 14% to 11% in children born to women without HIV, with a slightly stronger effect in children born to women with HIV, reducing stunting from 50% to 40% and anemia from 14% to 7% [6, 7]. WASH had no effect on either of these outcomes regardless of the child's HIV exposure status [6, 7].

The team who conducted the landmark Zimbabwe Vitamin A for Mothers and Babies (ZVITAMBO) trial in Zimbabwe, which heralded the increased mortality and morbidity experienced by children who were HIV exposed and uninfected prior to any antiretroviral drug availability (1997–2001), have now conducted one of the largest and most methodologically rigorous comparisons in the ART era of HIV-exposed and HIV-unexposed children within the SHINE trial. In this issue of *Clinical Infectious Diseases*, Evans and colleagues present results on survival and stunting in HIV-exposed (n = 738) compared to HIV-unexposed (n = 3989) children and describe HIV transmission in HIV-exposed children at age 18 months. While uptake of exclusive breastfeeding was high and breastfeeding was sustained on average beyond the first year of life in both women with and without HIV (mean, 14.8 and 16.4 months, respectively), only 81% of women with HIV were known to be on ART despite its availability through public health facilities across Zimbabwe.

Evans et al observed that overall mortality was 1.41 (95% confidence interval [CI], 1.02–1.93) times higher at age 18 months in children who were HIV exposed (7% mortality) compared to HIV

Received 20 January 2020; editorial decision 20 January 2020; accepted 22 January 2020; published online January 24, 2020.

Correspondence: A. L. Slogrove, Stellenbosch University Worcester Campus, 1 Durban St, Worcester, 6850, Western Cape, South Africa (amy@sun.ac.za).

Clinical Infectious Diseases® 2021;72(4):595–7

DOI: 10.1093/cid/ciaa079

unexposed (5% mortality). In both groups, the highest mortality occurred in the neonatal period (first 28 days of life) (57% and 62% of all deaths in HIV-exposed and HIV-unexposed infants, respectively), with the majority of mortality in the first 6 months of life (83% and 81%, respectively). Promisingly, mortality among HIV-exposed children with mothers on ART was similar to children who were HIV unexposed (hazard ratio, 1.11 [95% CI, .75–1.65]). In contrast, mortality among HIV-exposed children whose mothers were not on ART was almost 3-fold higher than among children who were HIV unexposed (hazard ratio, 2.74 [95% CI, 1.69–4.44]), analogous to findings from ZVITAMBO and other studies in the pre-ART era [8, 9]. This underscores the critical importance of going beyond mere ART availability and investing in impactful programs that support mothers to initiate as well as sustain lifelong ART for both maternal and child survival benefit.

Only 81% of HIV-exposed children were confirmed HIV uninfected by age 18 months, 3% were known to be HIV infected, and 16% had unknown HIV status at age 18 months. Among those with known HIV status, vertical HIV transmission at age 18 months was 3% in those born to women on ART and 11% in those born to women not known to be on ART. Yet these are likely underestimates of vertical HIV transmission. Multiple sensitivity analyses were conducted under varying scenarios of HIV transmission in the group with unknown HIV status, estimating vertical HIV transmission to be somewhere between 4.3% and 7.7% overall. This upper estimate from SHINE is in keeping with 2019 UNAIDS-modeled estimates for Zimbabwe that vertical HIV transmission by the end of breastfeeding was ± 8% in 2018 [3]. Tremendous progress has been made in reducing HIV acquisition in children, but this progress has now slowed and 2020 targets for elimination of pediatric HIV are unlikely to be reached amidst unchanged structural factors—poverty, inequality, and interpersonal and community violence—in HIV high-burden countries [1].

Among children in SHINE who were alive and known to be HIV free (HIV exposed and uninfected), growth was compared at 18 months with HIV-unexposed children. Linear growth was poor and stunting prevalence was high in both groups of children. However, HIV-exposed but uninfected children had a mean World Health Organization length-for-age *z* score 0.38 (95% CI, .24–.51) standard deviations lower and stunting prevalence 16 percentage points (95% CI, 10–22) higher (51% vs 34%) than children who were HIV unexposed. Differences in linear growth emerged early, by 1 month of age, with little postnatal recovery in children HIV exposed and uninfected, despite breastfeeding throughout the first year of life. This, along with recent findings from Cape Town, South Africa, suggest an in utero developmental origin to the suboptimal postnatal growth trajectory of children who are HIV exposed but uninfected [10, 11]. In addition to the early vulnerability to mortality in the first 6 months of life, a more nuanced understanding of the impact of HIV and antiretroviral drugs on the in utero environment is required.

Evans and colleagues propose a novel comprehensive measure by which to evaluate the success of vertical HIV transmission prevention programs, by measuring the proportion of HIV-exposed children who are not only HIV free but who are also alive and not stunted, stunting being a simple and feasible proxy indicator of thriving. In the SHINE sample, at age 18 months only 40% of children who were HIV exposed were alive, HIV free, and not stunted compared to 60% of children who were HIV unexposed. There are certainly other measures in addition to stunting by which children who are HIV exposed and uninfected are not thriving, including increased risk for infection-related hospitalizations (predominantly in the first 6 months of life) and delays (particularly in language development) [12, 13]. Evans et al pragmatically propose stunting as an indicator of thriving that is strongly associated with later school and adult functioning and a routinely measured element in well-child visits that could be incorporated into national monitoring programs.

Almost 2 decades after ZVITAMBO, following major advances in HIV programs, ART availability, and vertical HIV transmission strategies, substantial progress has been made to reduce vertical HIV transmission and improve survival in children who are HIV exposed. Evans et al rightly challenge us to now widen the lens by which we evaluate HIV program progress and success, and to set the goal of achieving a population of HIV-free children born to women with HIV who not just survive, but rather thrive.

Notes

Disclaimer. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health (NIH).

Financial support. This work was supported by the Fogarty International Center of the NIH (award number 1K43TW010683 to A. L. S.) and the Eunice Kennedy Shriver National Institute of Child Health and Human Development (award number 1R21HD093531 to K. M. P.). A. L. S. receives salary support through the Collaborative Initiative for Pediatric HIV Education and Research Grantee Program of the International AIDS Society (2017/518-SLO).

Potential conflicts of interest. The authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

References

1. Joint United Nations Programme on HIV/AIDS. Start Free Stay Free AIDS Free 2019 report. **2019**. Available at: https://www.unaids.org/en/resources/documents/2019/20190722_UNAIDS_SFSFAF_2019. Accessed 31 July 2019.
2. United Nations. Transforming our world: the 2030 Agenda for Sustainable Development. **2015**. Available at: https://sustainabledevelopment.un.org/post2015/transformingourworld. Accessed 3 September 2018.
3. Joint United Nations Programme on HIV/AIDS. 2019 UNAIDS estimates. **2019**. Available at: http://aidsinfo.unaids.org. 16 July 2019.
4. Evans C, Jones CE, Prendergast AJ. HIV-exposed, uninfected infants: new global challenges in the era of paediatric HIV elimination. Lancet Infect Dis **2016**; 3099:1–16.
5. The Sanitation Hygiene Infant Nutrition Efficacy (SHINE) Trial Team. The Sanitation Hygiene Infant Nutrition Efficacy (SHINE) trial: rationale, design, and methods. Clin Infect Dis **2015**; 61(Suppl 7):685–702.
6. Humphrey JH, Mbuya MNN, Ntozini R, et al; Sanitation Hygiene Infant Nutrition Efficacy

(SHINE) Trial Team. Independent and combined effects of improved water, sanitation, and hygiene, and improved complementary feeding, on child stunting and anaemia in rural Zimbabwe: a cluster-randomised trial. Lancet Glob Health **2019**; 7:e132–47.
7. Prendergast AJ, Chasekwa B, Evans C, et al; SHINE Trial Team. Independent and combined effects of improved water, sanitation, and hygiene, and improved complementary feeding, on stunting and anaemia among HIV-exposed children in rural Zimbabwe: a cluster-randomised controlled trial. Lancet Child Adolesc Health **2019**; 3:77–90.
8. Marinda E, Humphrey JH, Iliff PJ, et al; ZVITAMBO Study Group. Child mortality according to maternal and infant HIV status in Zimbabwe. Pediatr Infect Dis J **2007**; 26:519–26.
9. Brennan AT, Bonawitz R, Gill CJ, et al. A meta-analysis assessing all-cause mortality in HIV-exposed uninfected compared with HIV-unexposed uninfected infants and children. AIDS **2016**; 30:2351–60.
10. le Roux SM, Abrams EJ, Donald KA, et al. Growth trajectories of breastfed HIV-exposed uninfected and HIV-unexposed children under conditions of universal maternal antiretroviral therapy: a prospective study. Lancet Child Adolesc Health **2019**; 4642:1–12.
11. Slogrove AL, Powis KM. Fetal origins of postnatal growth faltering in HIV-exposed uninfected children. Lancet Child Adolesc Health **2019**; 3:201–3.
12. le Roux S, Abrams E, Donald K, et al. Infectious morbidity of breastfed, HIV-exposed uninfected infants under conditions of universal antiretroviral therapy in South Africa: a prospective cohort study. Lancet Child Adolesc Health **2020**. doi:10.1016/S2352-4642(19)30375-X.
13. Wedderburn CJ, Yeung S, Rehman AM, et al. Neurodevelopment of HIV-exposed uninfected children in South Africa: outcomes from an observational birth cohort study. Lancet Child Adolesc Health **2019**; 4642:4–6.