JIAS
JOURNAL OF THE
INTERNATIONAL AIDS SOCIETY

Understanding challenges and optimising outcomes of children with perinatal HIV exposure

Guest Editors: Jane Namangolwa Mutanga, Agnes Ronan, Kathleen M. Powis

Supplement Editor: Chloé Zufferey

Volume 26, Supplement 4, October 2023

WILEY

Support

This supplement was organized by IAS – the International AIDS Society. It was supported by a ViiV Healthcare grant, as part of their contribution to the Collaborative Initiative for Paediatric HIV Education and Research (CIPHER). IAS has full control over all the activities and decisions relating to, and forming part of, the IAS Collaborative Initiative for Paediatric HIV Education and Research programme. The content of this supplement is solely the responsibility of the authors and does not necessarily represent the official views of the International AIDS Society or Viiv Healthcare. Viiv Healthcare has not had any input into the content of the supplement.

Disclaimer

The authors alone are responsible for the views expressed in this supplement and they do not necessarily represent the views, decisions or policies of the institutions with which they are affiliated. The opinions expressed in this supplement should not be understood or quoted as being made on behalf of or reflecting the position of the regulatory agencies or organizations with which the author(s) is/are affiliated with or employed by.

Acknowledgements

As the Guest Editors – Jane Namangolwa Mutanga, Agnes Ronan, and Kathleen M. Powis - wish to express their appreciation to all the authors who prepared, submitted, and revised manuscripts in response to this supplement request, even those that were not included. We would also like to thank all the reviewers who invested their time to review and respond, providing feedback on each of the manuscripts. We are grateful to the many research participants who volunteered for studies represented in the supplement. Their willingness to participate in research has highlighted and informed the opportunities that exist to improve health, wellbeing, and developmental outcomes among children and adolescents with perinatal exposure to HIV. We also thank the editors and staff of the Journal of the International AIDS Society, for their thoughtful guidance, rigorous support, and encouragement throughout the process. Finally, we thank the Collaborative Initiative for Paediatric HIV Education and Research (CIPHER), who importantly initiated and championed the advancement of this Supplement.

Understanding challenges and optimising outcomes of children with perinatal HIV exposure

Guest Editors: Jane Namangolwa Mutanga, Agnes Ronan, Kathleen M. Powis
Supplement Editor: Chloé Zufferey

Contents

Volume 26, Supplement 2
October 2023

JIAS
JOURNAL OF THE INTERNATIONAL AIDS SOCIETY

Mutanga JN et al. *Journal of the International AIDS Society* 2023, **26**(S4):e26171
http://onlinelibrary.wiley.com/doi/10.1002/jia2.26171/full | https://doi.org/10.1002/jia2.26171

JIAS JOURNAL OF THE INTERNATIONAL AIDS SOCIETY

EDITORIAL

Achieving equity for children and adolescents with perinatal HIV exposure: an urgent need for a paradigm shift

Jane Namangolwa Mutanga[1,§,#], Agnes Ronan[2,#] and Kathleen M. Powis[3,4,#]

[§]**Corresponding author**: Jane Namangolwa Mutanga, Department of Pediatrics and Child Health, Livingstone Central Hospital, Akapelwa Street, Livingstone, 10101, Zambia. (janemutanga@gmail.com)

Keywords: Adolescents; Children; HIV prevention; Testing; Vertical transmission

Received 21 August 2023; **Accepted** 29 August 2023

One and a half million children (0–14 years) were estimated to be living with HIV globally in 2022 by the Joint United Nations Programme on HIV/AIDS (UNAIDS), with 89% of these children residing in sub-Saharan Africa [1]. It was also estimated that among children living with HIV, only 57% were accessing antiretroviral treatment (ART) compared to 77% of adults aged 15 years and older [2]. The inequity in access to ART between children and adults can be attributed to disproportionately poor uptake of HIV testing, gaps in timely ART initiation, low retention rates and poor adherence rates in the paediatric population compared to adults [3]. Fortunately, remarkable progress in the global scale-up of ART for pregnant and breastfeeding persons living with HIV, along with improved risk-based options for infant antiretroviral (ARV) prophylaxis, and increasing availability of pre-exposure prophylaxis for persons at high risk of HIV acquisition, have led to marked declines in infant HIV acquisition [4]. UNAIDS reported a 58% reduction in the number of new HIV infections among children (0–14 years) between 2010 and 2022, offering hope of achieving sustainable development goal 3.3, targeting an end to AIDS as a public health threat by 2030 [4]. Concomitantly, recent data from the highest HIV burden settings demonstrate marked declines in vertical HIV transmission to as low as 3% in South Africa, 2.4% in Eswatini and 1.8% in Botswana[5].

However, over one million women and girls living with HIV around the world experience pregnancy annually, with 82% estimated to be accessing ART [6]. Therefore, although HIV acquisition in infancy has continued to decline, that decline has almost stalled in recent years, with 130,000 children estimated to have acquired HIV in 2022, compared to 140,000 in 2021 [7]. In addition, the number of children who are HIV-exposed and uninfected (CHEU) has been steadily increasing by at least one million annually. UNAIDS estimates that the cumulative population of CHEU was approximately 16 million globally in 2022, and over 90% of these children reside in sub-Saharan Africa [1, 8]. In South Africa, Eswatini, Botswana and Lesotho, where the prevalence of HIV is high and scale-up of ART access in pregnancy is prioritised, over 20% of all infants born annually have had in utero exposure to HIV, and increasingly to maternal ART [9, 10].

Several studies have demonstrated health outcome disparities among CHEU compared to children without perinatal HIV exposure (children HIV-unexposed and uninfected—CHUU), including high risk of mortality, morbidity, impaired growth and poorer neurodevelopment outcomes [11–17]. These studies demonstrate that in utero exposure to HIV can increase the risk of poor health outcomes across a child's life course, from early infancy into adulthood. Gaps remain in understanding the magnitude of these disparities and their underlying mechanisms, including the relative contributions from biological, social and/or structural processes. Furthermore, there is a lack of consensus on effective interventions to optimise the health and wellbeing of this growing population of children. Public health commitment and programming must go beyond HIV prevention and encompass a holistic approach that includes supporting children with perinatal HIV exposure at the highest risk of poor life course outcomes. Starting life HIV-free is not a sufficiently high enough bar. CHEU at risk for poor outcomes require support to thrive to their fullest potential.

This supplement in the *Journal of the International AIDS Society* features studies and programmes that highlight gaps and describe interventions to improve health outcomes. In addition, opportunities to advocate for programming mitigating health outcome disparities are presented. Collectively, studies in this supplement motivate a more robust policy climate and response to optimizing outcomes of children and adolescents with perinatal HIV exposure with the intent of (1) identifying opportunities for basic science research to identify biological mechanistic pathways for observed health disparities; (2) informing the design of epidemiological studies and interventions investigating social and structural factors associated with increased risk of poor outcomes; (3) highlighting practical interventions to address observed disparities; (4) guiding health and educational policies and programming; and (5) ensuring that parents and caregivers of children affected by HIV have the knowledge needed to identify suboptimal outcomes and advocate for appropriate services.

Failure to diagnose HIV acquisition in a timely manner among infants and children increases the risk of mortality, infectious morbidity, poor growth and neurodevelopmental delays [18–22]. In the maturing HIV epidemic, the importance of client-centred differentiated service delivery has been recognised as a necessary approach towards the goal of eliminating AIDS by 2030 [23]. Following timely diagnoses and initiation of ART, retention in care and achievement of viral suppression are paramount to optimizing the health of all persons living with HIV.

Retention in care has been particularly challenging among adolescents living with HIV [24, 25]. Internalised stigma has been noted as one of the factors associated with discontinuation of HIV care [26]. Harrison and colleagues report on a novel approach involving adolescents and young adults living with HIV in peer support groups comprised of similarly aged individuals living with other chronic illnesses [27]. In their clinic-based pilot intervention called *The Better Together Program*, with peer leaders facilitating peer support group sessions, youth living with HIV reported value in learning about challenges encountered by their peers living with other chronic health conditions. Participation in the peer support groups for five or more sessions, compared to attending fewer sessions, was associated with higher self-reported individual-level resilience, a more positive attitude towards living with HIV, lower internalised stigma and a more positive self-concept, measured using standardised instruments. This pilot provides a unique option for improving the mental wellbeing of adolescents living with HIV that may yield higher retention in care and sustained viral suppression.

de Beer and colleagues evaluated trends in hospitalisations due to infectious causes among children ≤3 years of age between 2008 and 2021. They evaluated perinatal HIV exposure as a surrogate measure of the HIV epidemic's impact on child health services in the Western Cape province of South Africa [28]. The authors analysed over 50,000 eligible hospitalisations and observed that children living with HIV accounted for a decreasing proportion of infectious-cause hospitalisations, with CHEU comprising an increased proportion over time. Importantly, the Western Cape Provincial Health Data Centre's successful automated approach to linking unique maternal and child identifiers and data from various health encounters serves as a powerful model of how harmonised data systems can be leveraged to answer population-level trends [29]. Such real-world data can be useful in identifying implementation gaps and informing knowledge regarding the longer-term health outcomes of CHEU.

Three studies in this supplement offer further insights on neurodevelopment outcomes for CHEU. Bulterys and colleagues report on findings from their Kenya-based observational cohort of mother-infant pairs where the Malawi Developmental Assessment Tool was administered to mothers who provided feedback on their 1-year-old infant's neurodevelopment in the domains of social, language, and fine and gross motor functioning [30]. The study evaluated maternal–infant pairs, half of whom were mothers living with HIV. Interestingly, while comparable social, fine and gross motor scores were found between infants who were HEU and those HIV-unexposed uninfected (HUU), infants who were HEU had higher language scores. The authors also found that infants with in utero exposure to efavirenz had lower gross motor scores compared to infants with in utero exposure to dolutegravir, highlighting the importance of ensuring that registries are in place to monitor short- and long-term health outcomes of in utero ARV exposure in order to identify the safest and most efficacious regimens for use in pregnancy.

A trial in Eswatini conducted by Ruff and colleagues evaluated an intervention delivered by mentor mothers using the WHO's Nurturing Care Framework to improve nurturing care in high HIV burden settings [31]. Mother-child pairs took part in the experiment in which the standard of care was compared to the intervention [31]. The authors found that a Nurturing Care Framework of activities delivered by mentor mothers can viably be integrated into antenatal care clinics and early intervention can reduce neurocognitive disparities. In addition, the authors observed that the mechanisms driving children's early language development occur through modifiable caregiving activities, including reading to infants and children. The provision of nurturing care in early life can positively influence optimal neurodevelopment in CHEU.

Powis and colleagues present educational achievement findings from children attending primary public school in the Botswana-based FLOURISH study [32]. This prospective birth cohort study of children ages 8–12, of whom 75% were CHEU, demonstrated higher odds of lower academic performance, defined as a grade of "C" or less, among CHEU compared to those HUU in mathematics, science, English and overall. The association between being HEU and lower academic performance was attenuated after adjustment for maternal education, breastfeeding, low birth weight and child sex. Biological and socio-demographic factors, including child sex and maternal education, appeared to contribute to this difference.

To better understand possible points of intervention to optimise neurodevelopmental outcomes of children with perinatal HIV exposure, the multifactorial elements associated with these outcomes must be considered. The commentary by Bulterys and colleagues offers insight into the possible biological and behavioural factors associated with neurodevelopmental outcomes among CHEU, from the in utero milieu to household and caregiver-related factors [33]. The authors highlight that CHEU are at disproportionate risk of biological, social and household factors that may threaten their ability to achieve optimal maturation of their brain, immune system, and overall health and wellbeing. The authors advocate for structured early child development training for healthcare workers, equipping these gatekeepers with the ability to conduct rapid neurodevelopmental screening tests to identify children in need of specialised services to address neurodevelopmental delays while also promoting nurturing care among caregivers to mitigate the impact of poorer health outcomes.

The complex social milieu associated with sub-optimal health outcomes among CHEU presents unique challenges for the design of optimal interventions. This is demonstrated in the South African-based prospective cohort study by Le Roux and colleagues where pregnant persons and their children were followed through the child's first year of life, including people living with HIV and their CHEU from 2013 to 2017, with the aim of describing behavioural and socio-economic factors associated with adverse child health outcomes [34]. The authors found that parental alcohol consumption, household intimate partner violence and household food insecurity were associated with poorer child growth and increased infectious morbidity. These risk factors were present at higher prevalence among CHEU compared to those HUU. To our knowledge, this is the first study to systematically evaluate evidence of HIV-related syndemic interactions, at the maternal level or within the household, that potentiate adverse outcomes among CHEU compared to their unexposed peers.

The HIV field has been a champion in progressing global thought, action and capacity-building towards models of healthcare that reflect the lived experiences, needs and preferences of affected individuals and communities [35]. However, infants and children cannot advocate for themselves. It is essential that parents be involved in setting the research agenda and service needs of children with perinatal HIV exposure. A commentary by Bukasa and colleagues discusses the importance of engaging mothers living with HIV in research plans and health communication strategies, and enabling mothers to inform the research agenda and contribute to health policies on behalf of their children [36]. It will be equally important to involve adolescents with perinatal HIV exposure in these conversations. However, adolescents who are HIV exposed and uninfected, when compared to adolescents living with HIV, are less likely to have received disclosure of their exposure status from their parents or caregivers. Davtyan and colleagues evaluated the role of internalised HIV stigma on willingness to disclose HIV status to CHEU. Data were derived from participants of the United States-based Surveillance Monitoring for ART Toxicities (SMARTT) study, a study following outcomes of CHEU [37]. Among mothers living with HIV, disclosure was uncommon and mothers with higher scores for internalised stigma were less likely to disclose. This study demonstrates that internalised stigma must be mitigated among parents living with HIV to remove at least one barrier of HIV exposure disclosure to adolescents who are HIV exposed and uninfected.

Research funders, including the US National Institutes of Health (NIH), are prioritizing research to improve outcomes of children affected by HIV. Lee and colleagues, of the NIH, share current investments in the population of children affected by HIV, highlighting research gaps and outlining future areas of research focus [38]. The authors recommend that research priorities could be achieved more rapidly and sustainably by focusing on data science, data harmonisation and shared efforts between studies. Continued investment is required to expand research commitments that aim to identify biological, social and structural drivers of health outcome disparities. Lastly, given the large and growing population of CHEU, only a portion of whom are at increased risk of suboptimal outcomes, the authors stress that there exists an urgent need for the development of screening tools to identify high-risk CHEU. The Viewpoint by Evans et al. discusses a comprehensive package of HIV-specific and universal interventions that can be delivered throughout the first 1000 days of life [39]. These interventions can be delivered either to the mother or the infant and include early antenatal booking, infant ARV prophylaxis, nurturing care and healthy hygiene practices, among others.

In July 2022, the World Health Organisation, in partnership with UNAIDS and UNICEF, announced the Global Alliance to End AIDS in Children [3]. This strategic vision, designed to end AIDS in the paediatric population by 2030, has four pillars of focus, the first of which calls for optimised comprehensive, high-quality treatment and care for infants, children and adolescents living with and exposed to HIV [3]. While much of this foundation has been laid for children and adolescents living with HIV, the work presented in this supplement highlights that merely celebrating an HIV-free start to life for children and adolescents who are HEU is a short-sighted objective. Collective and collaborative action must be taken to conduct impactful research, identify the multi-faceted biological, social and structural factors that place children with perinatal HIV exposure at risk for poor outcomes, and transform findings into programming with continued monitoring and evaluation components.

AUTHORS' AFFILIATIONS

[1]Department of Pediatrics and Child Health, Livingstone Central Hospital, Livingstone, Zambia; [2]Paediatric Adolescent Treatment Africa, Cape Town, 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

COMPETING INTERESTS

The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

JNM, AR and KMP jointly drafted the editorial. All the authors read and approved the final version.

ACKNOWLEDGEMENTS

As the Guest Editors—Jane Namangolwa Mutanga, Agnes Ronan and Kathleen M. Powis wish to express their appreciation to all the authors who prepared, submitted and revised manuscripts in response to this supplement request, even those who were not included. We would also like to thank all the reviewers who invested their time to review and respond, providing feedback on each of the manuscripts. We are grateful to the many research participants who volunteered for studies represented in the supplement. Their willingness to participate in research has highlighted and informed the opportunities that exist to improve health, wellbeing and developmental outcomes among children and adolescents with perinatal exposure to HIV. We also thank the editors and staff of the Journal of the International AIDS Society, specifically Marlène Bras, Annette Sohn, Chloé Zufferey and Alberto Rossi, for their thoughtful guidance, rigorous support and encouragement throughout the process. Finally, we thank the Collaborative Initiative for Paediatric HIV Education and Research, which initiated and championed the advancement of this Supplement.

DISCLAIMER

The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the regulatory agency/agencies or organisations with which the authors are employed/affiliated.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

REFERENCES

1. UNAIDS. Latest Data on HIV 2023 [cited 2023 July 26]. Available from: https://aidsinfo.unaids.org/.
2. UNAIDS. Global HIV & AIDS Statistics—Fact Sheet. 2023.
3. World Health Organisation, UNICEF. The Global Alliance to End AIDS in Children. 2022.
4. UNAIDS. The Path That Ends AIDS: 2023 UNAIDS Global AIDS Update. Geneva; 2023.
5. UNAIDS. Country Factsheets 2022. 2023. Accessed July 26, 2023. Available from: https://aidsinfo.unaids.org/.
6. World Health Organisation. Global HIV Programme: Mother-to-Child Transmission of HIV. 2023 [cited 2023 Jul 13]. Available from: https://www.who.int/teams/global-hiv-hepatitis-and-stis-programmes/hiv/prevention/mother-to-child-transmission-of-hiv#:~:text=Globally%2C%20an%20estimated%201.3%20million,HIV%20become%20pregnant%20each%20year
7. Dauby N, Goetghebuer T, Kollmann TR, Levy J, Marchant A. Uninfected but not unaffected: chronic maternal infections during pregnancy, fetal immunity, and susceptibility to postnatal infections. Lancet Infect Dis. 2012;12(4):330–40.
8. Slogrove AL, Powis KM, Johnson LF, Stover J, Mahy M. Estimates of the global population of children who are HIV-exposed and uninfected, 2000–18: a modelling study. Lancet Glob Health. 2020;8(1):e67–75.
9. Bulterys MA, Njuguna I, Mahy M, Gulaid LA, Powis KM, Wedderburn CJ, et al. Neurodevelopment among children exposed to HIV and uninfected in sub-Saharan Africa. J Int AIDS Soc. 2023;26(S4):e26159.
10. Slogrove A, Powis KM, J LF, Stover J, Mahy M. Global estimates of children HIV exposed uninfected in the evolving HIV epidemic. Lancet Glob Health. 2019;7:e67–e75.
11. Brennan AT, Bonawitz R, Gill CJ, Thea DM, Kleinman M, Useem J, et al. A meta-analysis assessing all-cause mortality in HIV-exposed uninfected compared with HIV-unexposed uninfected infants and children. AIDS. 2016;30(15):2351–60.
12. Anderson K, Kalk E, Madlala HP, Nyemba DC, Kassanjee R, Jacob N, et al. Increased infectious-cause hospitalization among infants who are HIV-exposed uninfected compared with HIV-unexposed. AIDS. 2021;35(14):2327–39.
13. le Roux SM, Abrams EJ, Donald KA, Brittain K, Phillips TK, Zerbe A, 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;4(3):220–31.
14. Yan H, Peters H, Thorne C. Neonatal deaths among infants born to women living with HIV in the UK and Ireland. AIDS. 2022;36(2):287–96.
15. Nyemba DC, Kalk E, Madlala HP, Malaba TR, Slogrove AL, Davies MA, et al. Lower birth weight-for-age and length-for-age z-scores in infants with in-utero HIV and ART exposure: a prospective study in Cape Town, South Africa. BMC Pregnancy Childbirth. 2021;21(1):354.
16. Fowler MG, Aizire J, Sikorskii A, Atuhaire P, Ogwang LW, Mutebe A, et al. Growth deficits in antiretroviral and HIV-exposed uninfected versus unexposed children in Malawi and Uganda persist through 60 months of age. AIDS. 2022;36(4):573–82.
17. Wedderburn CJ, Evans C, Yeung S, Gibb DM, Donald KA, Prendergast AJ. Growth and neurodevelopment of HIV-exposed uninfected children: a conceptual framework. Curr HIV/AIDS Rep. 2019;16(6):501–13.
18. Newell ML, Coovadia H, Cortina-Borja M, Rollins N, Gaillard P, Dabis F, et al. Mortality of infected and uninfected infants born to HIV-infected mothers in Africa: a pooled analysis. Lancet. 2004;364(9441):1236–43.
19. Violari A, Cotton MF, Gibb DM, Babiker AG, Steyn J, Madhi SA, et al. Early antiretroviral therapy and mortality among HIV-infected infants. N Engl J Med. 2008;359(21):2233–44.
20. Chiappini E, Galli L, Tovo PA, Gabiano C, Gattinara GC, Guarino A, et al. Virologic, immunologic, and clinical benefits from early combined antiretroviral therapy in infants with perinatal HIV-1 infection. AIDS. 2006;20(2):207–15.
21. Schomaker M, Leroy V, Wolfs T, Technau KG, Renner L, Judd A, et al. Optimal timing of antiretroviral treatment initiation in HIV-positive children and adolescents: a multiregional analysis from Southern Africa, West Africa and Europe. Int J Epidemiol. 2017;46(2):453–65.
22. Laughton B, Cornell M, Grove D, Kidd M, Springer PE, Dobbels E, et al. Early antiretroviral therapy improves neurodevelopmental outcomes in infants. AIDS. 2012;26(13):1685–90.
23. Grimsrud A, Bygrave H, Doherty M, Ehrenkranz P, Ellman T, Ferris R, et al. Reimagining HIV service delivery: the role of differentiated care from prevention to suppression. J Int AIDS Soc. 2016;19(1):21484.
24. Haghighat R, Toska E, Bungane N, Cluver L. The HIV care cascade for adolescents initiated on antiretroviral therapy in a health district of South Africa: a retrospective cohort study. BMC Infect Dis. 2021;21(1):60.
25. Ridgeway K, Dulli LS, Murray KR, Silverstein H, Dal Santo L, Olsen P, et al. Interventions to improve antiretroviral therapy adherence among adolescents in low- and middle-income countries: a systematic review of the literature. PLoS One. 2018;13(1):e0189770.
26. Enane LA, Vreeman RC, Foster C. Retention and adherence: global challenges for the long-term care of adolescents and young adults living with HIV. Curr Opin HIV AIDS. 2018;13(3):212–9.
27. Harrison A, Mtukushe B, Kuo C, Wilson-Barthes M, Davidson B, Sher R, et al. Better together: acceptability of chronic illness peer support groups for South African adolescents and young adults. J Int AIDS Soc. 2023;26(S4):e26148.
28. de Beer ST, Slogrove AL, Eley B, Ingle SM, Jones HE, Phelanyane F, et al. Change in HIV-related characteristics of children with infectious disease hospitalizations in Western Cape, South Africa 2008–2021: a time trend analysis. J Int AIDS Soc. 2023;26(S4):e26151.
29. Slogrove AL, de Beer ST, Kalk E, Boulle A, Cotton M, Cupido H, et al. Survival and health of children who are HIV-exposed uninfected: study protocol for the CHERISH (Children HIV-Exposed Uninfected—Research to Inform Survival and Health) dynamic, prospective, maternal–child cohort study. BMJ Open. 2023;13(1):e070465.
30. Bulterys MA, Njuguna I, King'e M, Chebet D, Moraa H, Gomez L, et al. Neurodevelopment of Children who are HIV-Exposed and Uninfected in Kenya. J Int AIDS Soc. 2023;26(S4):e26149.
31. Ruff A, Dlamini X, Nonyane BAS, Simmons N, Kochelani D, Burtt F, et al. A trial of nurturing care among children HIV-exposed and uninfected in eSwatini. J Int AIDS Soc. 2023;26(S4):e26158.
32. Powis KM, Lebanna L, Schenkel S, Masasa Kgole WS, Ngwaca M, et al. Lower academic performance children with perinatal HIV exposure in Botswana. J Int AIDS Soc. 2023;26(S4):e26165
33. Bulterys MA, Njuguna I, Mahy M, Gulaid LA, Powis K, Wedderburn C, John-Stewart G. Neurodevelopment among children exposed to HIV-and uninfected in Sub-Saharan Africa. J Int AIDS Soc. 2023;26(S4):e26159.
34. Le Roux SM, Abrams E, Zerbe A, Philips TK, Myer L. Children of a syndemic: co-occurring and mutually reinforcingadverse child health exposures in a prospective cohort of HIV-affected mother–infant dyads in Cape Town, South Africa. J Int AIDS Soc. 2023;26(S4):e26152.
35. Lazarus JV, Janamnuaysook R, Caswell G. A people-centred health system must be the foundation for person-centred care in the HIV response. J Int AIDS Soc. 2023;26(Suppl1):e26125.
36. Bukasa LL, Namiba A, Brown M, Ndu'ngu E, Nangwala M, Letting G, et al. Setting the research agenda: involving parents in research on children who are HIV-free. J Int AIDS Soc. 2023;26(S4):e26150.
37. Davtyan M, Kacanek D, Lee J, Berman C, Chadwick E, Smith R, et al. The Role of Internalized HIV Stigma in Disclosure of Maternal HIV Serostatus to Children Perinatally HIV-Exposed but uninfected: A Prospective Study in the United States. J Int AIDS Soc. 2023;26(S4):e26167.
38. Lee S, Allison S, Browers P. Strengthening the evidence to improve health outcomes of children with perinatal HIV exposure. J Int AIDS Soc. 2023;26(S4):e26160.
39. Evans C, Prendergast AJ. When and how to intervene to improve the health of children born HIV-free. J Int AIDS Soc. 2023;26(S4):e26157.

Harrison A et al. *Journal of the International AIDS Society* 2023, **26**(S4):e26148
http://onlinelibrary.wiley.com/doi/10.1002/jia2.26148/full | https://doi.org/10.1002/jia2.26148

JIAS JOURNAL OF THE INTERNATIONAL AIDS SOCIETY

RESEARCH ARTICLE

Better Together: acceptability, feasibility and preliminary impact of chronic illness peer support groups for South African adolescents and young adults

Abigail Harrison[1,2,§], Bulelwa Mtukushe[3], Caroline Kuo[3,4], Marta Wilson-Barthes[1], Bianca Davidson[3], Rebecca Sher[3], Omar Galárraga[1,†] and Jacqueline Hoare[3,†]

[§]**Corresponding author**: Abigail Harrison, International Health Institute, Brown University School of Public Health, 121 South Main St, GS 121–2, Providence, RI 02912, USA. Tel: +401 863 6201. (abigail_harrison@brown.edu)
[†]Jaqueline Hoare and Omar Galarraga are co-senior authors. Both authors contributed equally to this work.

Abstract

Introduction: Peer support can help navigate the isolation and psychological strain frequently experienced by youth living with chronic illness. Yet, data are lacking on the impact of providing support for youth living with mixed chronic conditions. We assessed the acceptability, feasibility and preliminary mental health impacts of a clinic-based peer support group for South African youth living with chronic illnesses, including HIV.

Methods: This mixed-methods pilot study (September 2021–June 2022) enrolled 58 young patients, ages 13–24, at an urban hospital in Cape Town, South Africa. In-depth interviews elicited the perspectives of 20 young people in relation to their participation in the *Better Together* programme, a recurring clinic-based peer support group for patients with mixed chronic illnesses. Self-reported resilience, attitudes towards illness, stigma and mental health were captured via established measures. *T*-tests and multivariate analysis of variance compared psychosocial outcomes for 20 group participants and 38 control patients, controlling for socio-demographic characteristics at enrolment. Logistic regression analyses estimated the predicted probability of a positive depression or anxiety screening given peer group participation.

Results: All interviewees valued being able to compare treatment regimens and disease management habits with peers living with different conditions. Adolescents living with HIV stated that understanding the hardships faced by those with other conditions helped them accept their own illness and lessened feelings of isolation. Compared to patients who did not participate in *Better Together*, those who attended ≥5 groups had statistically significantly higher individual-level resilience, a more positive attitude towards their illness(es), lower internalised stigma and a more positive self-concept. The probability of being screened positive for depression was 23.4 percentage points lower (95% CI: 1.5, 45.3) for *Better Together* participants compared to controls; the probability of a positive anxiety screening was 45.8 percentage points lower (95% CI: 18.1, 73.6).

Conclusions: Recurring, clinic-based peer support groups that integrate youth living with HIV and other chronic diseases are novel. Group sustainability will depend on the commitment of experienced peer leaders and providers, routine scheduling and transportation support. A fully powered randomised trial is needed to test the optimal implementation and causal mental health effects of the *Better Together* model.

Keywords: adolescents; HIV care continuum; social support; Africa; coinfection; stigma

Additional information may be found under the Supporting Information tab of this article.

Received 16 February 2023; **Accepted** 14 August 2023

1 | INTRODUCTION

Sub-Saharan Africa (SSA) has some of the worst health profiles for young people in the world [1]. Ninety percent of the 2.1 million young people living with HIV reside in SSA [2, 3], and AIDS remains the leading cause of death among young people in the region [4]. Chronic kidney disease is increasing among young people in SSA [5–7] and the annual incidence of type 1 diabetes is 3.9% in this population [8]. Chronic illness, including HIV, is a leading risk factor for depression and other psychological disorders in youth [5, 8–11], with young people with chronic conditions feeling isolated and misunderstood by their healthy peers [12–15]. As demonstrated in the HIV and AIDS literature, feelings of social isolation are further compounded by reduced access to care [16, 17] and disease-related stigma [18, 19], which can undermine treatment adherence [5, 12, 16, 20–24] and contribute to poorer outcomes [12, 14, 16, 25–28].

Adolescence is a time of rapid growth and physiological change, accompanied by important individuation and socialisation processes [29]. Managing a chronic disease during this developmental stage often presents challenges for the patient as well as their family and care providers; medication adherence and retention in chronic disease care are frequently worse for adolescents than for adults [30–34]. Similar to studies of adolescents living with HIV (ALHIV), studies of treatment adherence in adolescents with chronic renal disease find non-compliance rates in the range of 32% [17] to 38.2% [15], with an average of 11% of doses missed and nearly a quarter of individuals taking medications late [15]. Rates of treatment non-adherence for adolescent and young adult cancer cohorts range from 27% to 60% [33]. Adolescents who view themselves as different and less worthy than their peers because of their illness are likely to become socially isolated, have a poorer self-concept, lowered academic functioning and behavioural problems [35]. At the same time, young people who are able to focus on the positive aspects of their condition have more favourable treatment outcomes and recovery from an illness compared to those who do not [32, 36, 37]. The bi-directional relationship(s) between mental health and chronic disease outcomes, including HIV, necessitate evidence-based models that address the unique physical and mental health needs of patients during adolescence and emerging adulthood [38–41].

In addition to clinical determinants (e.g. disease severity, access to treatment), psychosocial factors play a critical role in determining chronic disease outcomes among adolescents. Many young people have difficulty adhering to tailored treatment regimens due to poorly developed abstract thinking, poor ability to plan, an immature ability to imagine future consequences and a concept of themselves as "bulletproof" or not vulnerable [11, 34, 42–44]. These issues indicate that preventing long-term disease-related complications is—on its own—an insufficient motivator for treatment compliance among chronically ill adolescents; developing greater autonomy of disease management habits and cultivating stronger relationships with peers and social networks are also needed to improve clinical and mental health outcomes for this population.

This paper reports findings from an implementation research project evaluating the impact of a recurring, clinic-based peer support group for young people living with chronic illness in Cape Town, South Africa. Based on extensive evidence that group support offers psychological benefit for young people living with the same chronic condition [44–47], this pilot study uses a mixed-methods design to examine the acceptability, feasibility and preliminary impact of a peer support group for youth who are living with a range of chronic illnesses (including HIV) and participating in one group together. Young people managing chronic illnesses other than HIV frequently experience similar stigma, in relation to medication and daily pill taking, and frequent illness episodes or hospitalisations. Preliminary effectiveness evidence of mixed-condition peer support groups can inform future randomised trials, and the optimal design of adolescent peer support groups in similar settings.

2 | METHODS

This pilot study used a mixed methods approach to investigate the acceptability, feasibility and preliminary mental health impacts of the *Better Together* programme.

2.1 | The Better Together programme

The *Better Together* programme [48] provides a weekly facilitated group session open to all adolescents, ages 13–24, who are living with a chronic illness and receiving care at Groote Schuur Hospital (GSH) in Cape Town, South Africa. GSH is a large public health sector hospital where care is provided free to patients through South African governmental health services. Since 2017, *Better Together* has helped adolescents with a range of chronic conditions (including HIV, renal disease and psychiatric conditions) to (1) build social networks that enhance psychosocial support; (2) develop a sense of belonging with peers; (3) create a space where adolescents can share their experience(s) living with and managing chronic illness; and (4) build empathy among ALHIV and other conditions. Groups are facilitated by a volunteer peer mentor who is also living with a chronic condition, and overseen by clinicians from the hospital's Adolescent Clinicians Group.

Volunteer peer mentors approach patients in the GSH waiting room and invite them to participate in the group sessions. Some adolescents attending GSH also participate in disease-specific support groups at their individual clinics; every adolescent enrolled in care at GSH is invited to join the *Better Together* groups regardless of whether they are also participating in another group.

Group participants are not required to disclose their disease within the groups, but may choose to do so. Confidentiality is discussed at the beginning and end of every session. A peer mentor supervisor (either a psychologist or a social worker) is present to observe all groups and provide additional support to mentors and group participants where necessary. Groups are divided into structured topics related to general adolescent health and development (e.g. sexual and reproductive health, mental health) and less structured "social" groups. Peer mentors are trained to adjust their topics to the age and cognitive maturity of the group members.

2.2 | Eligibility, enrolment and informed consent

Enrolment and data collection were conducted at GSH from September 2021 through July 2022. Qualitative data collection included in-depth interviews (IDIs) with $n = 20$ young people who were living with chronic illnesses and who had participated in at least five *Better Together* peer group sessions prior to study enrolment. Quantitative data on resilience, attitudes towards illness, stigma and mental health were ascertained via self-report from the $n = 20$ individuals who participated in the qualitative interviews and from an additional $n = 38$ adolescent patients at GSH who had not participated in the *Better Together* program. The research team obtained written parental consent and adolescent assent for participants <18 years, and informed consent from those ≥18 years. Participants for whom the team was unable to gain parental consent and/or adolescent assent were excluded. Disclosure of disease status was not required for study enrolment. Participants were informed via the informed consent/assent forms that all of their personal information, including their history of chronic illness(es), would be kept confidential during and after the study.

2.3 | Quantitative data collection

Self-reported demographic and clinical data were obtained at study enrolment. Medical history was extracted from electronic medical records and during GSH clinic visits. Additionally, established measures were administered to all study participants at enrolment to quantitatively assess the psychosocial impact(s) of the peer group intervention. Specifically, we administered the Connor-Davidson Resilience Scale (CD-RISC 10) [49, 50], Child Attitude Toward Illness Scale (CATIS) [51–53], Revised Berger scale of disease-related stigma [54, 55], HIV-stigma scale for South African adolescents living with HIV [56] and Beck Youth Inventories Second Edition (BYI-II) [57, 58]. We have previously administered these measures among adolescents and young adults in South Africa, with evidence of good reliability in isiXhosa-speaking populations [59, 60]. Appendix S1 includes a description of each psychosocial measure.

2.4 | Qualitative data collection

IDIs were conducted with $n = 20$ adolescents living with chronic illness who were regular attendees at the *Better Together* peer support group. The IDIs explored adolescents' acceptability and willingness to participate in the programme, as well as their chronic illness narratives and life experiences. Conducting IDIs is consistent with best practice recommendations for sensitive topics; all qualitative procedures followed best practice guidelines [61, 62]. All participants were recruited from hospital-based peer support groups using convenience sampling. Adolescents were eligible for the IDIs if they met the following inclusion criteria: (1) 13–24 years of age, had attended at least five *Better Together* peer group sessions; (2) aware of their chronic illness as confirmed through self-report; and (3) currently or previously on treatment for their chronic illness as confirmed through self-report.

Interviews were conducted using a semi-structured interview protocol that was adapted from similar qualitative research with adolescents in South Africa. The protocol explored the following aspects of the *Better Together* programme: (1) barriers and facilitators to participation; (2) acceptability of the programme as a chronic illness management strategy; (3) predicted behavioural impacts of the programme, including coping with a chronic illness and medication adherence; and (4) preferred programme format. Interviews were conducted in the participant's language of preference (English or isiXhosa). Interviews lasted approximately 1–1.5 hours and were digitally audiotaped. Interviewees received R250 Rand (~$15) for their time and transport.

2.5 | Analytic approach

Quantitative analyses were conducted using StataSE 16 software (Stat Corp.). We first report mean values and standard deviations for continuous characteristics or frequencies and percentages for categorical characteristics overall and by peer group participation. Second, a one-way multivariate analysis of variance (MANOVA) was used to estimate associations between peer group participation and psychosocial wellbeing (i.e. on total scores for the CD-RISC 10, CATIS, Revised Berger Scale and on BYI-II T-scores). MANOVA is appropriate for evaluating mean differences on multiple dependent variables simultaneously while adjusting for intercorrelations among them [63]. ALHIV-SS data were excluded from the MANOVA because not all participants were living with HIV. Third, multivariate logistic regression models estimated the odds of being screened positive for depression or anxiety given *Better Together* participation (= 1 if attended ≥5 peer groups prior to study enrolment or = 0 if attended 0 peer groups). Models were adjusted for potential sources of confounding at enrolment, specifically age (in years), sex (male/female), household size, housing type (formal or informal), living status of biological mother (alive/deceased) and participation in one or more government social protection programme(s) (yes/no). Stata's margins command was run after logistic regressions to estimate the predictive probability of being screened positive for depression or anxiety given peer group participation. A cut point of ≥19 for the Beck Youth Depression Inventory (BDI-Y) raw score was considered a positive screening for moderate to severe depression [64]. A cut point of ≥20 for the Beck Youth Anxiety Inventory (BAI-Y) raw score was considered a positive anxiety screening [65]. Quantitative results were interpreted using point estimates, confidence intervals (CIs), and *p*-values; we did not consider an association to be statistically significant based solely on whether *p*-values were below a given threshold [66, 67]. For all models, alpha was set at 0.10 following literature which suggests that less stringent *p*-values may be more relevant for identifying meaningful associations in smaller studies [68, 69].

Qualitative data were transcribed verbatim and translated into English as needed. All transcripts were double-coded. We use a general inductive approach to analyse the qualitative data. Common words, phrases, sentences and ideas were clustered to develop a codebook. Data were analysed using open-coding, axial coding, and coding of marginal remarks and comparisons [56] using NVivo (QSR International, 2012), followed by thematic analysis of specific codes and sub-codes. Meaning from these codes was formulated to produce clusters of themes, which were then discussed and agreed on in the coding team.

2.6 | Ethical approval

All study procedures were approved by the University of Cape Town Human Research Ethics Committee (HREC Approval Number: 075/2020). Written parental consent and written adolescent assent were obtained for participants <18

Table 1. Characteristics of adolescent participants enrolled in the pilot study, overall and by *Better Together* peer group participation

	Total participants ***N* = 58**	**No Better Together group participation** ***n* = 38**	**Has attended at ≥5 Better Together group sessions** ***n* = 20**	***p*-value[a]**
Age	18.74 (2.84)	17.26 (2.20)	21.55 (1.43)	<0.001
Biological sex[b]				1.00
Female	50% (29)	50% (19)	50% (10)	
Male	48% (28)	47% (18)	50% (10)	
Other	2% (1)	3% (1)	0% (0)	
Race				0.40
Black African	71% (41)	74% (28)	65% (13)	
Coloured[c]	28% (16)	26% (10)	30% (6)	
Indian or Asian	2% (1)	0% (0)	5% (1)	
Language				0.22
IsiXhosa	57% (33)	58% (22)	55% (11)	
Afrikaans	9% (5)	13% (5)	0% (0)	
English	33% (19)	26% (10)	45% (9)	
Other	2% (1)	3% (1)	0% (0)	
Highest level of education completed				0.15
Primary (< grade 8)	9% (5)	13% (5)	0% (0)	
Secondary (≥ grade 8)	91% (53)	87% (33)	100% (20)	
Household size (adults and children)	5.72 (2.39)	6.05 (2.43)	5.10 (2.25)	0.15
Housing type				0.49
Formal	81% (47)	84% (32)	75% (15)	
Informal	19% (11)	16% (6)	25% (5)	
Is biological mother alive?				0.77
No	34% (20)	37% (14)	30% (6)	
Yes	66% (38)	63% (24)	70% (14)	
Is biological father alive?				0.77
No	40% (23)	39% (15)	40% (8)	
Yes	53% (31)	58% (22)	45% (9)	
Unknown	7% (4)	3% (1)	15% (3)	
Currently accessing a government social grant				0.089
No	55% (32)	47% (18)	70% (14)	
Yes	43% (25)	53% (20)	25% (5)	
Missing	2% (1)	0% (0)	5% (1)	

Note: Data in Table 1 are presented as mean (SD) for continuous variables and % (*n*) for categorical variables.
[a]Differences between peer group participants and control patients were assessed using a two sample *t*-test and a Fisher's exact test for continuous and categorical variables, respectively.
[b]Survey respondents self-reported their biological sex as "Male," "Female" or "Other" in response to "Would you define your sex as?".
[c]Coloured is an official, socially acceptable racial classification defined by South Africa's Population Registration Act of 1950.

years of age, and written informed consent was obtained from at least 18 years of age. All human subjects research was conducted by Investigators at GSH. All data that Brown University Investigators received from the University of Cape Town excluded identifiable private information, identifiable biospecimen and coded information, and thus did not meet the definition of human subjects research as defined by *45 CFR 46*.

3 | RESULTS

3.1 | Quantitative findings

Fifty-eight total patients enrolled in the quantitative portion of this pilot study, 20 of whom had attended ≥5 *Better Together* peer support groups prior to enrolment (Table 1). Participants were 18 years of age on average and

Table 2. Mean total scores on psychosocial measures among adolescent patients with and without exposure to the *Better Together* peer group intervention

	Summary score interpretation	Non-peer group patients (Control group)	Peer group participants (Intervention arm)	*p*-value[a]
10-item Connor-Davidson Resilience Scale (CDRISC-10)	Higher score indicates greater individual resilience	26.47 (6.79)	31.40 (4.03)	0.004
13-item Child Attitude Towards Illness Scale (CATIS)	Higher score indicates a more positive attitude towards chronic illness	45.37 (8.52)	53.50 (6.92)	<0.001
Revised Berger Scale of Chronic Disease-Related Stigma	Higher score indicates more frequent chronic disease-related stigma	37.84 (7.73)	31.75 (7.61)	0.006
10-item HIV Stigma Scale for South African Adolescents Living with HIV (ALHIV-SS)	Higher score indicates more frequent HIV-related stigma	7.31 (3.35)	6.17 (2.12)	0.28
Beck Self-Concept Inventory for Youth	Higher score indicates elevated (more positive) self-concept symptoms	51.53 (11.16)	57.20 (5.93)	0.039
Beck Anxiety Inventory for Youth	Higher score indicates elevated anxiety symptoms	56.53 (12.91)	53.60 (9.58)	0.38
Beck Depression Inventory for Youth	Higher score indicates elevated depressive symptoms	52.37 (10.78)	47.65 (5.26)	0.071
Beck Anger Inventory for Youth	Higher score indicates elevated anger symptoms	51.29 (9.75)	48.85 (4.79)	0.30
Beck Disruptive Inventory for Youth	Higher score indicates elevated disruptive symptoms	49.34 (8.05)	47.70 (5.21)	0.41

Note: Scores are presented as mean scores with standard deviations in parentheses.
[a]Differences in mean measure scores between peer group participants and control patients were assessed using a two sample *t*-test.
For all measures other than the ALHIV-SS, $n = 58$ (20 peer group participants and 38 control group patients). For the ALHIV-SS, $n = 44$ (12 peer group participants and 32 control group patients).
Patients were required to have attended ≥ 5 peer groups at study enrolment to be included in the treatment arm. Control patients had never participated in the *Better Together* peer group intervention.
Scores for the Becky Youth Inventories (BYI-II) represent T-scores assigned by age and gender. On each of the BYI-II subscales, a T-score of ≤55 = average symptoms, 55–59 = mildly elevated symptoms, 60–69 = moderately elevated symptoms and ≥70 = extremely elevated symptoms.

predominately (71%) Black African. Half (50%) self-reported their biological sex as female, most (91%) had completed at least some secondary schooling, and 43% were enrolled in a government social programme. On average, participants came from a six-person household, and 66% and 53% had a biological mother and biological father who was still living, respectively. Peer group participants were older than non-peer group patients on average ($p < 0.001$). Twelve of the 20 peer group participants and 32 of the 38 control group patients were living with HIV at study enrolment.

Table 2 shows the average total score on each psychosocial measure for the two study groups. Compared to youth patients who did not participate in any *Better Together* peer groups, those who had attended at least five peer group sessions had higher self-reported individual-level resilience ($p = 0.004$), a more positive attitude towards their chronic illness(es) ($p < 0.001$), lower internalised stigma related to their chronic disease ($p = 0.006$), stronger self-concept (e.g. confidence in self, positive body image, relatability to others) ($p = 0.039$) and lower depressive symptoms ($p < 0.10$). At $\alpha = 0.10$, average total or T-scores on the ALHIV-SS HIV stigma scale, Beck Anxiety Inventory for Youth, Beck Anger Inventory for Youth and Beck Disruptive Inventory for Youth did not statistically significantly differ between peer group and non-peer group patients. Results of the one-way MANOVA confirmed the aforementioned associations, showing a statistically significant association between mental health improvements as a function of peer group participation overall, (Wilks' Lambda = 0.7349, F (8,49) = 2.21, $p = 0.043$), and specifically for the individual domains of resilience, attitude towards illness, chronic disease stigma, self-concept and depression.

Table 3 presents the results of logistic regression models estimating associations between peer group participation and depression or anxiety. In all models, attending ≥5 group

Table 3. Results of logistic regression analyses estimating associations between participation in peer support groups and being screened positive for depression or anxiety (*N* = 58 adolescents living with chronic illness)

		(1) Positive depression screening OR (95% CI)	(2) Positive depression screening aOR (95% CI)	(3) Positive anxiety screening OR (95% CI)	(4) Positive anxiety screening aOR (95% CI)
Participation in ≥ 5 peer group sessions	No	(ref)	(ref)	(ref)	(ref)
	Yes	0.13*	0.08*	0.38	0.05**
		(0.02, 1.09)	(0.00, 1.50)	(0.11, 1.37)	(0.01, 0.57)
Age in years			1.04		1.41*
			(0.70, 154)		(0.96, 2.07)
Biological sex	Female		(ref)		(ref)
	Male		0.60		0.30*
			(0.12, 2.94)		(0.07, 1.25)
Household size (adults and children)			1.00		1.00
			(0.69, 1.41)		(0.72, 1.38)
Housing type	Formal		(ref)		(ref)
	Informal		0.41		0.43
			(0.03, 5.16)		(0.06, 3.19)
Status of biological mother	Deceased		(ref)		(ref)
	Alive		0.18**		0.41
			(0.03, 0.91)		(0.09, 1.80)
Participating in government social protection programme	No		(ref)		(ref)
	Yes		0.36		0.21**
			(0.08, 1.79)		(0.05, 0.97)

Note: A cut point of ≥ 19 on the Beck Youth Depression Inventory (BDI-Y) raw score was considered indicative of a positive depression screening [64]. A cut point of ≥ 20 on the Beck Youth Anxiety Inventory (BAI-Y) raw score was considered indicative of a positive anxiety screening [65].
Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; OR, odds ratio.
*$p < 0.10$; **$p < 0.05$; ***$p < 0.010$.

sessions was positively associated with a reduced odds of being screened positive for depression or anxiety. In adjusted models, relative to adolescent patients who did not participate in peer groups, the odds of being screened positive for moderate to severe depression was 0.08 times lower among peer group participants (95% CI: 0.00, 1.50), and the odds of being screened positive for anxiety was 0.053 lower among peer group participants (95% CI: 0.01, 0.57). The predicted probability of being screened positive for moderate to severe depression was 23.4 percentage points lower for young adults participating in the *Better Together* programme compared to non-peer group patients (95% CI: 1.5, 45.3; $p = 0.036$); the probability of a positive anxiety screening was 45.8 percentage points lower among peer group participants (95% CI: 18.1, 73.6; $p = 0.001$).

3.2 | Qualitative findings

Across interviews, all participants emphasised the value of being able to compare treatment regimens and personal stories with peers living with different conditions. ALHIV stated frequently that understanding the hardships faced by those with other conditions helped with acceptance of their own illness and lessened feelings of isolation. Similarly, youth living with other chronic conditions experienced increased social support and reduced isolation. Although disclosure was not required within the groups, many participants described the process of becoming comfortable discussing their illness with peers.

Theme 1 Meeting young people with different illnesses was an eye-opening and powerful experience for most young people.

The participants found support from youth living with different illnesses, and learned about the common challenges faced by people with HIV, diabetes or chronic conditions, such as kidney disease. When asked about attending the peer support group with other youth living with different illnesses, one participant responded that the experience helped to combat the feeling of isolation by connecting around challenging aspects of living with a chronic illness:

> That was a very powerful move. I don't know who thought about it, but it was so powerful. We started meeting with other groups. We are told that we're going to say what we really have. And when we got the group, we started looking at each other there and there was a bit of fear. And then I said, guys, 'I'm… thought I

> should put it out there guys. I'm positive.' And then the next fellow… And then other people asked, how does it feel to be positive? And then we got information upon information. (PID00009; Male aged 24, living with HIV)

The same participant continued:

> I remember one person who said I wish I was positive, and then I asked why …? And then they said having a kidney failure is the worst. … then they mentioned that they take 21 tablets a day; by saying that the whole group said, Wow, 21 tablets. And then they asked how many tablets do you guys take? Some people said three tablets, you only take three tablets and there are people who find it hard to take three tablets. That kind of made me feel that maybe I'm not having the worst. So I am just overreacting, let me take my medication. (PID00009; Male age 24, living with HIV)

Another participant agreed, comparing his concerns with adherence to HIV medication as easy, compared to a diabetes patient, "someone who pricks him or herself every hour." Others reflected on the benefits of meeting peers with different chronic illnesses:

> To be honest, I am enjoying much more than the group I had whereby it's just people with my chronic illness. I mean, it is nice to have a group of people with the same illness, but to me I feel like it is nice to get to chat with people with different illnesses because you hear different experiences from them and even though we may think that it is different, but we have many similarities and things that we go through. (PID 00001, Male age 20, living with renal disease)

Overall, youth were positive about their participation in the peer support groups, and saw added benefits from meeting and interacting with other young people, sharing the common experience of living with chronic illness and the challenges this poses for a young person, including frequent feelings of isolation.

Theme 2 Young people living with chronic illness frequently encounter stigma and uninformed attitudes in school and the community—they reported finding support and acceptance in the support group, among peers living with diverse chronic illnesses.

One participant discussed learning about her HIV condition at age 11, after she inquired about why she was taking pills, only to learn that her father had different partners and infected her mom. She described her personal journey of adjusting to a future with a chronic illness, in this case, HIV.

> I live with this thing that cannot be cured. … But I learned to accept it because I thought to myself, you know what? I can look at this from a different point of view. I thought about so many people who are out there successful, who are HIV positive. Because it does not mean a death sentence when you are HIV positive. (PID 00015; Female Age 22, living with HIV)

This participant also spoke about finding it easier to accept her status by seeing how others navigate their chronic illnesses:

> If we were to look at all sicknesses, I would rather have HIV. For example, with diabetes, some people have to get rid of some of their body parts. There's a lot of sicknesses that are unbearable. There are even diseases that affect your lungs, so I'd rather be HIV positive because being HIV positive, you can look at me, you won't see it. You will see a beautiful round girl… (PID 00015; Female Age 22, living with HIV)

A common theme among participants living with chronic illnesses was that participation in groups allowed them to consider the future, and the unique challenges of navigating futures—life goals, marriage and children—and to see the future as a possibility. For example, the following adolescent who required a kidney transplant described how the group supported a view of the future being a real possibility:

> I won't lie … it does affect me because I am human, there are some days where I would feel like if I did not have this, things would have been much better. But now I am very much in acceptance. My life has gotten easier with the transplant. I don't feel as weak as I used to. Things are getting better and the part of people telling me that my having this and still pursuing my dreams is inspiring them. And I bring birth to new dreamers, and people who want to achieve goals. (PID 00001, Male Age 20, living with kidney failure/renal disease)

Another participant spoke about the challenges of living with cancer while also raising a young child:

> I am grateful for the things that I have achieved. I feel like there have been so many blessings that came my way, so much mercy has been shown up on me and even my daughter is a miracle. OK, but circumstances of how it happened were not what I wanted, of course, because I was in my matric year, but because of the radiation that I went for my spinal operation it was said that I wouldn't be able to have children. And then somehow, I have my daughter, so she is my miracle. (PID 00002; Female Age 21, living with cancer)

Across illness types and experiences, youth in the peer support groups found a safe place to express themselves freely, and to be understood. Additionally, many youth faced challenges at home in addition to the already heavy burden of living with a chronic illness as a young person. Some participants mentioned additional and unexpected benefits they derived from the need to take care of themselves, such as being removed from the culture of drugs and alcohol use that is prevalent among youth in many communities. Further, they learned specific skills to manage their own illness and tools to address the mental health consequences of being a young person living with a serious illness.

Theme 3 Young people with a variety of chronic illnesses described the benefits of participation in the peer support group.

Young people reflected on the vital importance of social support provided by the peer mentor and peer support program. Below, an interviewer (I) and a peer group participant (P) discussed this:

> I: Now you have highlighted that it feels like a family away from your family. You have different chronic illnesses, but you see similarities and you take yourself as just one….
>
> P: I know I would get more and more support. I know that I would probably know things that I did not know before. There are so many different people, so I get to experience different personalities. …. And how it has helped me is as I said, everyone has a different illness. And as you have mentioned that sometimes chronic illnesses are stigmatised in societies, so we don't always exactly know what it means or what it's about, how it works, or how to interact with this person. You need to interact in a certain way. So, it teaches me a lot about other illnesses and how to approach or interact with others. (PID 00013; Female Age 22, living with HIV)

The interviewers also asked peer group participants to reflect on anything that was not positive about the groups:

> At first, I thought what if they're going to tell someone else? To disclose my status to someone else, and I wasn't ready about it. And I faced that. And then we had this say that says what happens in Vegas stays in Vegas. And then we spoke about it. And then we shared all of our problems, personal problems, and when you leave that door, we said nothing that we say here is going to leave the place. So it was safe for people to actually open up. (PID00009; Male age 24, living with HIV)

Further, dealing with other young people's illnesses is not always straightforward or emotionally easy. Although interacting with other young people with chronic illness was perceived as widely beneficial, there is an emotional toll from such participation, including sharing one's story and working to understand and provide support to others. One participant described coming to terms with their own illness:

> I have accepted it. No one is motivating me more than the chronic illness itself; I've learned that time management is important. Secondly, determination is also important. Everything I do must be positive. I am proud about the fact that I am HIV positive. So, I have to be positive in life and see light at the end of the tunnel every time. (PID 00008, Male Age 22, living with HIV)

Finally, one of the peer mentors explained their role:

> For me it is an honor because I get to understand other patients from other clinics, I get to actually understand their illness, the things they go through. For me it is an honor in a way that I also get to meet new people because I actually meet new people. I did not know people I can have conversation with. I get to experience some new people or get some new information from them. (PID 00003, Age 20, living with HIV)

4 | DISCUSSION

This mixed methods analysis of pilot data from a clinic-based peer support group intervention in Cape Town, South Africa found encouraging psychosocial and mental health benefits of providing peer support groups to adolescents living with diverse chronic conditions. Quantitative analysis shows several benefits associated with the *Better Together* programme, with participants of five or more sessions exhibiting better outcomes across a number of psychosocial measures. The qualitative data are highly complementary, with detailed illness narratives giving insights into young people's need for enhanced social support in relation to living with chronic illness, and their reflections on how the peer support programme helped them to meet those needs. Patients who attended five or more *Better Together* peer support group sessions exhibited enhanced individual resilience, greater acceptance of their chronic illness, lower internalised stigma, a stronger self-concept and lower depressive symptoms. In multivariable logistic regression models, attending at least five group sessions was statistically significantly associated with a reduced odds of screening positive for anxiety ($p < 0.05$) or moderate to severe depression ($p < 0.10$), compared to non-peer group patients. This corresponded to a 23%–45% reduction in the probability of a positive depression or anxiety screening given peer group participation.

The interview data underscore some of the potential reasons for these positive outcomes, and provide insight into young people's quality of life related to living with chronic illnesses, including HIV. Irrespective of diagnosis, young people described facing stigma and unwanted attention related to their condition and frequent social isolation due to living a life that is distinctly different from their non-chronically ill peers. Participants voiced that a key benefit of the peer support group was the space it gave them to interact with and learn from peers who are living with other conditions but still facing similar disease management challenges. The qualitative data also provide insight into the specific benefits of a mixed chronic illness group for youth living with HIV. The experience of engaging with other adolescents who have different chronic illnesses seemed to normalise HIV as a chronic illness "just like any other illness." Many adolescents with HIV were able to reflect on the burden of managing HIV as being something that seems more manageable than diabetes or cancer. Learning about other chronic illnesses seemed to mitigate some of the internalised stigma of living with HIV which is a persistent barrier to treatment adherence and care engagement.

This mixed methods analysis builds on our prior work [70, 71] and adds to the body of evidence around peer support programs for adolescents with chronic illnesses. Peer support models are recommended as part of best practices to improve youth medication adherence [39, 72], reduce disease-related stigma [73, 74] and improve other mental health outcomes [38]. Yet, to the best of our knowledge, the current effectiveness evidence of these models is overwhelmingly derived from approaches that provide peer support to youth living with the same chronic condition [73–77]. Focusing solely on one chronic condition may limit the full potential of peer support groups by preventing youth from capitalizing on the increased knowledge that stems from sharing experiences and disease management habits across conditions. The present analysis advances the evidence [78, 79] by demonstrating that routine peer support groups for youth with diverse chronic conditions can expand an individual's disease management toolkit, and increase their ability to empathise with others living with unique disease-related challenges.

4.1 | Limitations

A main limitation of this preliminary efficacy assessment is the small sample size; qualitative data were ascertained from 20 interviews, while quantitative survey data were ascertained from 58 adolescent patients of the hospital. Thus, our findings of positive associations between peer group participation and better psychosocial health should be interpreted with caution, in light of the modest sample size and potential for sampling and selection biases. Further research is needed to assess the impact in a larger sample over time. Also, the study site comprises one location, in one particular setting, and it is possible that different youth populations might require a different approach.

5 | CONCLUSIONS

This pilot evidence supports the acceptability, feasibility and potential positive mental health impact(s) of a peer support group that includes young people living with diverse chronic diseases. The acceptability of this approach is high, with young people expanding on multiple benefits that they receive from interacting with other youth living with varied chronic illnesses. Feasibility has been well demonstrated with the continuation of the *Better Together* programme since 2017, including during disruptions of the COVID-19 pandemic in 2020 and 2021. To fully understand the effectiveness and causal mechanisms of mixed condition peer groups on mental and social health outcomes, a fully powered randomised trial is needed.

AUTHORS' AFFILIATIONS

[1]International Health Institute, Brown University School of Public Health, Providence, Rhode Island, USA; [2]School of Public Health and Family Medicine, University of Cape Town, Cape Town, South Africa; [3]Division of Psychiatry & Groote Schuur Hospital, University of Cape Town, Cape Town, South Africa; [4]Department of Health Studies, American University, Washington, DC, USA

COMPETING INTERESTS

All authors assert no competing interests.

AUTHORS' CONTRIBUTIONS

AH, OG and JH led the conception and design of the work. BM, BD and RS were responsible for the acquisition and interpretation of the data. AH, MW-B, CK and OG led data analysis. AH and MW-B wrote the first draft of the manuscript. All authors revised the work critically for important intellectual content, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

ACKNOWLEDGEMENTS

We thank the adolescents of Groote Schuur Hospital for their time and willingness to participate in this study. We gratefully acknowledge the peer leaders and care providers for facilitating the Better Together programme, and for their ongoing commitment to improving the health of the hospital's young adult patients.

FUNDING

Research reported in this publication was supported by private funds obtained by South African investigators (JH, BD and RS). We acknowledge the Population Studies and Training Center (PSTC) at Brown University, which receives funding from the NIH (P2C HD041020), for general support.

DATA AVAILABILITY STATEMENT

Following publication, the de-identified data and analytic code that support the quantitative findings in this manuscript are openly available in the Brown University Digital Repository at https://doi.org/10.7910/DVN/NSCUS4.

REFERENCES

1. Patton GC, Coffey C, Cappa C, Currie D, Riley L, Gore F, et al. Health of the world's adolescents: a synthesis of internationally comparable data. Lancet. 2012;379(9826):1665–75. https://doi.org/10.1016/S0140-6736(12)60203-7
2. Idele P, Gillespie A, Porth T, Suzuki C, Mahy M, Kasedde S, et al. Epidemiology of HIV and AIDS among adolescents. J Acquir Immune Defic Syndr. 2014;66(Suplement 2):S144–53. https://doi.org/10.1097/QAI.0000000000000176.
3. The Lancet Child & Adolescent Health. Children and youth are crucial in the global AIDS response. Lancet Child Adolesc Health. 2018;2(9):621. https://doi.org/10.1016/S2352-4642(18)30246-3
4. Laughton B, Cornell M, Boivin M, Van Rie A. Neurodevelopment in perinatally HIV-infected children: a concern for adolescence. J Int AIDS Soc. 2013;16(1):18603. https://doi.org/10.7448/IAS.16.1.18603
5. Davidson B, Okpechi I, McCulloch M, Wearne N. Adolescent nephrology: an emerging frontier for kidney care in sub-Saharan Africa. Nephrology. 2017;22(12):933–9. https://doi.org/10.1111/nep.13135
6. Kayange NM, Smart LR, Tallman JE, Chu EY, Fitzgerald DW, Pain KJ, et al. Kidney disease among children in sub-Saharan Africa: systematic review. Pediatr Res. 2015;77(2):272–81. https://doi.org/10.1038/pr.2014.189
7. Naicker S. End-stage renal disease in sub-Saharan Africa. Ethn Dis. 2009;19(1 Suppl 1):S1–13–5.
8. Pinquart M, Shen Y. Depressive symptoms in children and adolescents with chronic physical illness: an updated meta-analysis. J Pediatr Psychol. 2011;36(4):375–84. https://doi.org/10.1093/jpepsy/jsq104.
9. Boyes ME, Cluver LD, Meinck F, Casale M, Newnham E. Mental health in South African adolescents living with HIV: correlates of internalising and externalising symptoms. AIDS Care. 2019;31(1):95–104. https://doi.org/10.1080/09540121.2018.1524121.
10. World Health Organization. Global Accelerated Action for the Health of Adolescents (AA-HA!): guidance to support country implementation [Internet]. World Health Organisation; 2017 [cited 2023 Feb 1] https://apps.who.int/iris/bitstream/handle/10665/255415/9789241512343-eng.pdf;jsessionid=DBC51C51FCF765B297ED29726EFA5019?sequence=1
11. Dick B, Ferguson BJ. Health for the world's adolescents: a second chance in the second decade. J Adolesc Health. 2015;56(1):3–6. https://doi.org/10.1016/j.jadohealth.2014.10.260.
12. Enane LA, Mokete K, Joel D, Daimari R, Tshume O, Anabwani G, et al. "We did not know what was wrong"—barriers along the care cascade among hospitalized adolescents with HIV in Gaborone, Botswana. PLoS One. 2018;13(4):e0195372. https://doi.org/10.1371/journal.pone.0195372
13. Zanoni BC, Sibaya T, Cairns C, Haberer JE. Barriers to retention in care are overcome by adolescent-friendly services for adolescents living with HIV in South Africa: a qualitative analysis. AIDS Behav. 2019;23(4):957–65. https://doi.org/10.1007/s10461-018-2352-6.

14. MacCarthy S, Saya U, Samba C, Birungi J, Okoboi S, Linnemayr S. "How am I going to live?": exploring barriers to ART adherence among adolescents and young adults living with HIV in Uganda. BMC Public Health. 2018;18(1):1158. https://doi.org/10.1186/s12889-018-6048-7
15. Zelikovsky N, Schast AP, Palmer J, Meyers KE. Perceived barriers to adherence among adolescent renal transplant candidates. Pediatr Transplant. 2008;12(3):300–8. https://doi.org/10.1111/j.1399-3046.2007.00886.x.
16. Kratzer J. Structural barriers to coping with type 1 diabetes mellitus in Ghana: experiences of diabetic youth and their families. Ghana Med J. 2012;46(2 Suppl):39–45.
17. Dobbels F, Van Damme-Lombaert R, Vanhaecke J, De Geest S. Growing pains: non-adherence with the immunosuppressive regimen in adolescent transplant recipients. Pediatr Transplant. 2005;9(3):381–90. https://doi.org/10.1111/j.1399-3046.2005.00356.x.
18. Corrigan PW, Sokol KA, Rüsch N. The impact of self-stigma and mutual help programs on the quality of life of people with serious mental illnesses. Community Ment Health J. 2013;49(1):1–6. https://doi.org/10.1007/s10597-011-9445-2.
19. Corrigan PW, Fong MWM. Competing perspectives on erasing the stigma of illness: what says the dodo bird? Soc Sci Med. 2014;103:110–7. https://doi.org/10.1016/j.socscimed.2013.05.027
20. Kim SH, Gerver SM, Fidler S, Ward H. Adherence to antiretroviral therapy in adolescents living with HIV. AIDS. 2014;28(13):1945–56. https://doi.org/10.1097/QAD.0000000000000316
21. Djonou C, Tankeu AT, Dehayem MY, Tcheutchoua DN, Mbanya JC, Sobngwi E. Glycemic control and correlates in a group of sub Saharan type 1 diabetes adolescents. BMC Res Notes. 2019;12(1):50. https://doi.org/10.1186/s13104-019-4054-1.
22. Mbanya JCN, Motala AA, Sobngwi E, Assah FK, Enoru ST. Diabetes in sub-Saharan Africa. Lancet. 2010;375(9733):2254–66. https://doi.org/10.1016/S0140-6736(10)60550-8.
23. Otovwe A, Akpojubaro EH. Diabetes mellitus in primary and secondary schools in Africa: an exploratory review. Alexandria J Med. 2020;56(1):166–72. https://doi.org/10.1080/20905068.2020.1833278
24. International Diabetes Federation. IDF Diabetes Atlas Ninth Edition. [Internet]. International Diabetes Federation; 2019 [cited 2023 Feb 1] https://www.diabetesatlas.org/upload/resources/material/20200302_133351_IDFATLAS9e-final-web.pdf
25. Borus JS, Laffel L. Adherence challenges in the management of type 1 diabetes in adolescents: prevention and intervention. Curr Opin Pediatr. 2010;22(4):405–11. https://doi.org/10.1097/MOP.0b013e32833a46a7.
26. Babatunde GB, van Rensburg AJ, Bhana A, Petersen I. Barriers and facilitators to child and adolescent mental health services in low- and-middle-income countries: a scoping review. Glob Soc Welf. 2021;8(1):29–46. https://doi.org/10.1007/s40609-019-00158-z
27. Enimil A, Nugent N, Amoah C, Norman B, Antwi S, Ocran J, et al. Quality of life among Ghanaian adolescents living with perinatally acquired HIV: a mixed methods study. AIDS Care. 2016;28(4):460–4. https://doi.org/10.1080/09540121.2015.1114997
28. Ankrah D, Koster E, Mantel-Teeuwisse A, Arhinful D, Agyepong I, Lartey M. Facilitators and barriers to antiretroviral therapy adherence among adolescents in Ghana. Patient Prefer Adherence. 2016;10:329. https://doi.org/10.2147/PPA.S96691
29. Arnett JJ. Emerging adulthood: a theory of development from the late teens through the twenties. Am Psychol. 2000;55(5):469–80.
30. Foster BJ. Heightened graft failure risk during emerging adulthood and transition to adult care. Pediatr Nephrol. 2015;30(4):567–76. https://doi.org/10.1007/s00467-014-2859-7.
31. Campagna BR, Weatherley K, Shemesh E, Annunziato RA. Adherence to medication during transition to adult services. Pediatr Drugs. 2020;22(5):501–9. https://doi.org/10.1007/s40272-020-00414-2
32. MacDonell KK, Naar S. Self-management frameworks for youth living with human immunodeficiency virus. Pediatr Clin N Am. 2022;69(4):759–77. https://doi.org/10.1016/j.pcl.2022.04.007
33. Butow P, Palmer S, Pai A, Goodenough B, Luckett T, King M. Review of adherence-related issues in adolescents and young adults with cancer. J Clin Oncol. 2010;28(32):4800–9. https://doi.org/10.1200/JCO.2009.22.2802
34. Wurm F, McKeaveney C, Corr M, Wilson A, Noble H. The psychosocial needs of adolescent and young adult kidney transplant recipients, and associated interventions: a scoping review. BMC Psychol. 2022;10(1):186. https://doi.org/10.1186/s40359-022-00893-7
35. Earnshaw VA, Quinn DM. The impact of stigma in healthcare on people living with chronic illnesses. J Health Psychol. 2012;17(2):157–68. https://doi.org/10.1177/1359105311414952.
36. Rhee H, Wicks MN, Dolgoff JS, Love TM, Harrington D. Cognitive factors predict medication adherence and asthma control in urban adolescents with asthma. Patient Prefer Adherence. 2018;12:929–37. https://doi.org/10.2147/PPA.S162925.
37. Lindsay S, Kingsnorth S, Hamdani Y. Barriers and facilitators of chronic illness self-management among adolescents: a review and future directions. J Nurs Healthc Chronic Illn. 2011;3(3):186–208. https://doi.org/10.1111/j.1752-9824.2011.01090.x
38. Bhana A, Abas MA, Kelly J, van Pinxteren M, Mudekunye LA, Pantelic M. Mental health interventions for adolescents living with HIV or affected by HIV in low- and middle-income countries: systematic review. BJPsych Open. 2020;6(5):e104. https://doi.org/10.1192/bjo.2020.67.
39. Denison JA, Burke VM, Miti S, Nonyane BAS, Frimpong C, Merrill KG, et al. Project YES! Youth engaging for success: a randomized controlled trial assessing the impact of a clinic-based peer mentoring program on viral suppression, adherence and internalized stigma among HIV-positive youth (15–24 years) in Ndola, Zambia. PLoS One. 2020;15(4):e0230703. https://doi.org/10.1371/journal.pone.0230703
40. Swartz S, Deutsch C, Makoae M, Michel B, Harding JH, Garzouzie G, et al. Measuring change in vulnerable adolescents: findings from a peer education evaluation in South Africa. SAHARA J. 2012;9(4):242–54. https://doi.org/10.1080/17290376.2012.745696.
41. Boyes ME, Cluver LD, Meinck F, Casale M, Newnham E. Mental health in South African adolescents living with HIV: correlates of internalising and externalising symptoms. AIDS Care. 2019;31(1):95–104.
42. Melesse TG, Chau JPC, Nan MA. Effectiveness of psychosocial interventions on health outcomes of children with cancer: a systematic review of randomised controlled trials. Eur J Cancer Care. 2022;31(6):e13695. https://doi.org/10.1111/ecc.13695.
43. Laurenzi CA, Melendez-Torres GJ, Page DT, Vogel LS, Kara T, Sam-Agudu NA, et al. How do psychosocial interventions for adolescents and young people living with HIV improve adherence and viral load? A realist review. J Adolesc Health. 2022;71(3):254–69. https://doi.org/10.1016/j.jadohealth.2022.03.020
44. Osborn TL, Wasil AR, Venturo-Conerly KE, Schleider JL, Weisz JR. Group intervention for adolescent anxiety and depression: outcomes of a randomized trial with adolescents in Kenya. Behav Ther. 2020;51(4):601–15. https://doi.org/10.1016/j.beth.2019.09.005
45. Scheel A, Beaton A, Okello E, Longenecker CT, Otim IO, Lwabi P, et al. The impact of a peer support group for children with rheumatic heart disease in Uganda. Patient Educ Couns. 2018;101(1):119–23. https://doi.org/10.1016/j.pec.2017.07.006.
46. Robb L. Support group to reduce diabetes distress in adolescents with type 1 diabetes. J Pediatr Nurs. 2020;52:110–1. https://doi.org/10.1016/j.pedn.2020.02.024
47. Kumakech E, Cantor-Graae E, Maling S, Bajunirwe F. Peer-group support intervention improves the psychosocial well-being of AIDS orphans: cluster randomized trial. Soc Sci Med. 2009;68(6):1038–43. https://doi.org/10.1016/j.socscimed.2008.10.033
48. One to One Africa. Better Together: a toolkit for clinicians to improve support for adolescents with chronic health conditions. [Internet]. 2020 [cited 2023 Feb 1] https://www.onetooneafrica.org/adolescents/
49. Campbell-Sills L, Stein MB. Psychometric analysis and refinement of the Connor-Davidson Resilience Scale (CD-RISC): validation of a 10-item measure of resilience. J Trauma Stress. 2007;20(6):1019–28. https://doi.org/10.1002/jts.20271.
50. Jorgensen IE, Seedat S. Factor structure of the Connor-Davidson Resilience Scale in South African adolescents. Int J Adolesc Med Health. 2008;20(1):23–32.
51. Ramsey RR, Ryan JL, Fedele DA, Mullins LL, Chaney JM, Wagner JL. Child Attitude Toward Illness Scale (CATIS): a systematic review of the literature. Epilepsy Behav. 2016;59:64–72. https://doi.org/10.1016/j.yebeh.2016.03.026
52. Heimlich TE. Brief report: adolescents' attitudes toward epilepsy: further validation of the Child Attitude Toward Illness Scale (CATIS). J Pediatr Psychol. 2000;25(5):339–45. https://doi.org/10.1093/jpepsy/25.5.339
53. Austin JK, Huberty TJ. Development of the Child Attitude Toward Illness Scale. J Pediatr Psychol. 1993;18(4):467–80. https://doi.org/10.1093/jpepsy/18.4.467
54. Berger BE, Ferrans CE, Lashley FR. Measuring stigma in people with HIV: psychometric assessment of the HIV Stigma Scale. Res Nurs Health. 2001;24(6):518–29. https://doi.org/10.1002/nur.10011
55. Reinius M, Wettergren L, Wiklander M, Svedhem V, Ekström AM, Eriksson LE. Development of a 12-item short version of the HIV Stigma Scale. Health

Qual Life Outcomes. 2017;15(1):115. https://doi.org/10.1186/s12955-017-0691-z
56. Pantelic M, Boyes M, Cluver L, Thabeng M. 'They say HIV is a punishment from god or from ancestors': cross-cultural adaptation and psychometric assessment of an HIV Stigma Scale for South African Adolescents Living with HIV (ALHIV-SS). Child Indic Res. 2018;11(1):207–23. https://doi.org/10.1007/s12187-016-9428-5.
57. Beck A, Beck J, Jolly J, Steer R. Beck Youth Inventories™—Second Edition for Children and Adolescents (BYI-II). Pearson Education Limited; 2005.
58. Hoare J, Phillips N, Brittain K, Myer L, Zar HJ, Stein DJ. Mental health and functional competence in the Cape town adolescent antiretroviral cohort. J Acquir Immune Defic Syndr. 2019;81(4):e109–16. https://doi.org/10.1097/QAI.0000000000002068.
59. Hoare J, Phillips N, Joska JA, Paul R, Donald KA, Stein DJ, et al. Applying the HIV-associated neurocognitive disorder diagnostic criteria to HIV-infected youth. Neurology. 2016;87(1):86–93. https://doi.org/10.1212/WNL.0000000000002669
60. Louw KA, Ipser J, Phillips N, Hoare J. Correlates of emotional and behavioural problems in children with perinatally acquired HIV in Cape Town, South Africa. AIDS Care. 2016;28(7):842–50. https://doi.org/10.1080/09540121.2016.1140892
61. Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. Int J Qual Health Care. 2007;19(6):349–57. https://doi.org/10.1093/intqhc/mzm042
62. Coast J, Al-Janabi H, Sutton EJ, Horrocks SA, Vosper AJ, Swancutt DR, et al. Using qualitative methods for attribute development for discrete choice experiments: issues and recommendations. Health Econ. 2012;21(6):730–41. https://doi.org/10.1002/hec.1739.
63. Bray JH, Maxwell S. Multivariate analysis of variance. SAGE Publications, Inc.; 1985.
64. Butcher JN, Taylor J, Cynthia Fekken G. 4.14 Objective personality assessment with adults. In: Bellack AS, Hersen M, editors. Comprehensive clinical psychology. 1998. p. 403–29.
65. Stein MB, Roy-Byrne PP, McQuaid JR, Laffaye C, Russo J, McCahill ME, et al. Development of a brief diagnostic screen for panic disorder in primary care. Psychosom Med. 1999;61(3):359–64. https://doi.org/10.1097/00006842-199905000-00016
66. Wasserstein RL, Schirm AL, Lazar NA. Moving to a world beyond "$p < 0.05$." Am Stat. 2019;73:1–19. https://doi.org/10.1080/00031305.2019.1583913
67. Amrhein V, Greenland S, McShane B. Scientists rise up against statistical significance. Nature. 2019;567:305–7. https://doi.org/10.1038/d41586-019-00857-9.
68. Thiese MS, Ronna B, Ott U. *P* value interpretations and considerations. J Thorac Dis. 2016;8(9):E928–31. https://doi.org/10.21037/jtd.2016.08.16.
69. Dahiru T. *P*-value, a true test of statistical significance? A cautionary note. Ann Ib Postgrad Med. 2008;6(1):21–6. https://doi.org/10.4314/aipm.v6i1.64038.
70. Barker D, Enimil A, Galárraga O, Bosomtwe D, Mensah N, Thamotharan S, et al. In-clinic adolescent peer group support for engagement in sub-Saharan Africa: a feasibility and acceptability trial. J Int Assoc Provid AIDS Care. 2019;18:2325958219835786. https://doi.org/10.1177/2325958219835786
71. Rencken CA, Harrison AD, Mtukushe B, Bergam S, Pather A, Sher R, et al. "Those people motivate and inspire me to take my treatment." Peer support for adolescents living with HIV in Cape town, South Africa. J Int Assoc Provid AIDS Care. 2021;20:23259582211000525. https://doi.org/10.1177/23259582211000525
72. World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach–2nd ed. [Internet]. 2016 [cited 2023 Feb 1] https://www.who.int/publications/i/item/9789241549684.
73. Elafros MA, Mulenga J, Mbewe E, Haworth A, Chomba E, Atadzhanov M, et al. Peer support groups as an intervention to decrease epilepsy-associated stigma. Epilepsy Behav. 2013;27(1):188–92. https://doi.org/10.1016/j.yebeh.2013.01.005
74. Ammon N, Mason S, Corkery JM. Factors impacting antiretroviral therapy adherence among human immunodeficiency virus-positive adolescents in sub-Saharan Africa: a systematic review. Public Health. 2018;157:20–31. https://doi.org/10.1016/j.puhe.2017.12.010.
75. Bateganya MH, Amanyeiwe U, Roxo U, Dong M. Impact of support groups for people living with HIV on clinical outcomes: a systematic review of the literature. J Acquir Immune Defic Syndr. 2015;68(Suppl 3):S368–74. https://doi.org/10.1097/QAI.0000000000000519.
76. Núñez-Baila MLÁ, Gómez-Aragón Anjhara, González-López JR. Social support and peer group integration of adolescents with diabetes. Int J Environ Res Public Health. 2021;18(4):2064. https://doi.org/10.3390/ijerph18042064.
77. Thornton CP, Ruble K, Kozachik S. Psychosocial interventions for adolescents and young adults with cancer: an integrative review. J Pediatr Oncol Nurs. 2020;37(6):408–22.
78. Olsson CA, Boyce MF, Toumbourou JW, Sawyer SM. The role of peer support in facilitating psychosocial adjustment to chronic illness in adolescence. Clin Child Psychol Psychiatry. 2005;10(1):78–87.
79. Clark HB, Ichinose CK, Meseck-Bushey S, Perez KR, Hall MS, Gibertini M, et al. Peer support group for adolescents with chronic illness. Child Health Care. 1992;21(4):233–8. https://doi.org/10.1207/s15326888chc2104_6.

SUPPORTING INFORMATION

Additional information may be found under the Supporting Information tab for this article:

Appendix 1: Summary of psycho-social measures administered to N = 58 study participants.

de Beer ST et al. *Journal of the International AIDS Society* 2023, **26**(S4):e26151
http://onlinelibrary.wiley.com/doi/10.1002/jia2.26151/full | https://doi.org/10.1002/jia2.26151

JIAS JOURNAL OF THE INTERNATIONAL AIDS SOCIETY

RESEARCH ARTICLE

Change in HIV-related characteristics of children hospitalised with infectious diseases in Western Cape, South Africa, 2008–2021: a time trend analysis

Shani T. de Beer[1,2,3,§], Amy L. Slogrove[4], Brian Eley[5], Suzanne M. Ingle[3], Hayley E. Jones[3], Florence Phelanyane[1,2], Kim Anderson[1], Emma Kalk[1], Andrew Boulle[1,2,6] and Mary-Ann Davies[1,2,6]

[§]**Corresponding author**: Shani Tamlyn de Beer, University of Cape Town Medical Campus, Falmouth Building, Anzio Road, Observatory, Cape Town 7925, South Africa. (shanidebeer@gmail.com)

Abstract

Introduction: With the scaling up of vertical HIV transmission prevention programmes, the HIV-related population profile of children in South Africa has shifted. We described temporal changes in HIV-related characteristics of children, aged ≤3 years (up to the third birthday), with infectious disease hospitalisations across the Western Cape province.

Methods: We used routinely collected electronic data to identify children born in the Western Cape with infectious disease hospital records for lower respiratory tract infections, diarrhoea, meningitis and tuberculous meningitis, from 2008 to 2021. Linked maternal and child unique identifiers were used to extract pregnancy, HIV-related, laboratory, pharmacy and hospitalisation data. We described temporal changes in child HIV exposure and acquisition status, timing of maternal HIV diagnosis and antiretroviral therapy (ART) start, infant exposure to maternal ART and timing thereof, and maternal CD4 and HIV viral load closest to delivery. We used logistic and multinomial regression to assess changes in characteristics between the Pre-Option B+ (2008–2013), Option B+ (2013–2016) and Universal ART periods (2016–2021).

Results: Among 52,811 children aged ≤3 years with hospitalisations, the proportion living with HIV dreased from 7.0% (2008) to 1.1% (2021), while those exposed to HIV and uninfected increased from 14.0% (2008) to 16.1% (2021) with a peak of 18.3% in 2017. Among mothers with HIV ($n = 9873$), the proportion diagnosed with HIV and starting ART before pregnancy increased from 20.2% to 69.2% and 5.8% to 59.0%, respectively, between 2008 and 2021. Children hospitalised during the Universal ART period had eight times higher odds (Odds Ratio: 8.41; 95% CI: 7.36–9.61) of exposure to maternal ART versus children admitted Pre-Option B+. Among mothers of children exposed to HIV and uninfected with CD4 records ($n = 7523$), the proportion with CD4 <350 cells/μl decreased from 90.6% (2008) to 27.8% (2021).

Conclusions: In recent years, among children hospitalised with infectious diseases, there were fewer children with perinatally acquired HIV, while an increased proportion of those without HIV acquisition are exposed to maternal HIV and ART. There is a need to look beyond paediatric HIV prevalence and consider child exposure to HIV and ART among children without HIV, when assessing the HIV epidemic's impact on child health services.

Keywords: HIV exposure; HEU; hospitalisation; infectious disease; vertical HIV transmission prevention; South Africa

Additional information may be found under the Supporting Information tab of this article.

Received 27 January 2023; **Accepted** 15 August 2023

1 | INTRODUCTION

Infectious diseases are a leading cause of paediatric morbidity and mortality and place a burden on public healthcare services, particularly those that are already stretched [1–4]. Evidence suggests that both HIV acquisition and exposure without HIV acquisition are associated with infectious diseases. Between 1992 and 1997, HIV prevalence among paediatric admissions at an urban hospital in South Africa (SA) increased from 2.9% to 20.0%[5, 6], with a related increase in infectious diseases admissions. Furthermore, children exposed to HIV and uninfected (HEU) have been reported to have a higher risk of infection-related morbidity than children unexposed to HIV and uninfected (HUU) [7, 8].

The last two decades have seen substantial scale-up and success of vertical HIV transmission prevention (VTP) in SA

[9]. This success was largely attributable to increased access to antiretroviral therapy (ART) for pregnant people living with HIV, with improved and simplified guideline recommendations. In 2004, ART was only recommended in pregnancy for those with CD4 count <200 cells/μl; in 2008, ART was expanded to those with CD4 <350 cells/μl [9, 10]. Only in 2015 (2013 in the Western Cape province of SA) did ART become available to all pregnant and breastfeeding persons living with HIV, regardless of CD4 count ("Option B+") [11]. In 2016, ART became universally available to all persons living with HIV, meaning more of them would have access to ART before their first pregnancy [12]. Consequently, SA has seen a shift in the HIV-related profile of children under the age 15 years; between 2000 and 2018 HIV prevalence in children decreased by 74.0%, while the proportion who are HEU increased over seven-fold, accounting for 21.6% of all children (age 0–14 years) in SA in 2018 [13, 14]. Furthermore, ART coverage in pregnancy in SA was 96.0% in 2019 [15, 16], meaning that most children HEU are exposed to ART during gestation. Studies have previously used HIV prevalence among hospitalised children as an indicator of the HIV epidemic's impact on child health services [6, 17]. However, with the growing population of children HEU, and evidence that in utero HIV and ART exposure are also associated with child health outcomes in the absence of child HIV acquisition [13], it is also important to measure these characteristics, to more comprehensively understand the effect of the HIV epidemic on child health services.

We aimed to describe, at a provincial-level, the temporal changes in HIV-related characteristics of children hospitalised with infectious diseases from 2008 to 2021, using longitudinal individual-level routine care data from the Western Cape Provincial Health Data Centre.

2 | METHODS

2.1 | Study design and data source

This retrospective, population-based analysis used digitised routine maternal and child healthcare data from the Western Cape Provincial Health Data Centre. The data centre is an electronic health information platform that uses a unique health identifier to consolidate multiple sources of individual-level data from provincial public sector health services in the Western Cape [18]. Data including hospital admissions, outpatient visits, laboratory test results and pharmacy records are linked into a single individual-level data repository. Data on mothers and children are also electronically linked.

2.2 | Study setting

The Western Cape, one of SA's nine provinces, has an estimated population of seven million [18]. The province's antenatal HIV prevalence increased from 16.1% (2008) to 17.9% (2019) [15]. About three-quarters of the population, including most persons living with HIV, utilise public-sector health services [18, 19]. The public sector includes 51 hospitals consisting of District, Regional, Tertiary and Central hospitals [20]. District hospitals are the usual entry point into the hospital system, with complicated cases being referred to Regional, Tertiary or Central hospitals for specialist care [21]. In the late 1990s and early 2000s, ill children, particularly children with HIV (CWH) or children HEU, were admitted to Tertiary/Central hospitals. However, over time, there have been changes to paediatric healthcare organisation in SA, with increased district hospital capacity and less dependence on tertiary hospitals [22, 23].

2.3 | Study participants

We used routinely collected electronic data to identify children born in the Western Cape between 2008 and 2018, with a known live birth outcome, who had infectious disease hospitalisation records for lower respiratory tract infection (LRTI) (including influenza, viral, bacterial and congenital pneumonias, and bronchitis), diarrhoea, meningitis or tuberculous meningitis (TBM), from 2008 to 2021 (Supplementary Figure 1). We included first admissions in children hospitalised aged ≤3 years (by their third birthday). Within the Western Cape Provincial Health Data Centre, hospital admissions are classified using ICD-10 codes. Admissions with more than one of the above infectious diagnoses were counted in each relevant category.

To accurately classify child HIV acquisition and in utero HIV exposure, children were excluded if they could not be linked to their mothers, if child HIV-positive status was confirmed after hospital discharge but with unknown timing of acquisition, if their mothers were diagnosed with HIV more than 10 weeks after child's date of birth (10 weeks postnatal was used as a reasonable time-period to consider that maternal HIV acquisition might have occurred during pregnancy) or if they or their mothers had data inconsistencies (e.g. a negative HIV-PCR result after evidence of having HIV).

2.4 | Procedures and measurements

We extracted data on demographics, pregnancy, HIV testing, HIV evidence, ART start and dispensary dates, laboratory test results (HIV PCR and ELISA, CD4 count and viral load) and death from the Western Cape Provincial Health Data Centre. Using HIV-related data, including data on most recent negative HIV test results relative to the time of hospital admission, we categorised the in utero HIV exposure status and HIV acquisition status of each child at infectious disease hospitalisation discharge date as CWH, HEU or HUU, according to simplified DECIPHER (Data Evaluation and Collaborative Initiation for Paediatric HIV Education and Research) definitions (Table S1) [24]. Children who tested positive were considered HIV negative until their last negative HIV test and to have an unknown HIV status thereafter until the date of first HIV evidence. CWH whose mothers were not known to be living with HIV were included for assessing change in HIV acquisition status over time, but excluded for the analysis of other HIV-related characteristics.

For mothers with HIV, we categorised timing of maternal HIV diagnosis (before pregnancy, during pregnancy, at delivery/postnatally); timing of maternal ART start (before pregnancy, during pregnancy, delivery/postnatally, no ART evidence); infant exposure to maternal ART (yes/no) by using ART dispensing dates to determine if mothers were on ART at any point between conception and 3 months post-delivery; timing of earliest infant exposure to maternal ART (at conception, early/middle gestation [post-conception to 3 months predelivery], late gestation/postnatally [within 3 months pre or post-delivery]) based on the earliest point mothers were dispensed ART between conception and 3 months post-delivery; maternal CD4 count (<350 cells/μl, 350–499 cells/μl, ≥500 cells/μl) and viral load (<1000 copies/ml, ≥1000 copies/ml), using records closest to delivery, within a 365-day window of delivery. We described these characteristics over time by year of infectious disease hospital admission. We categorised the time of hospital admission into periods: January 2008–April 2013 (Pre-Option B+), May 2013–August 2016 (Option B+) and September 2016–December 2021 (Universal ART).

2.5 | Statistical analyses

We described and assessed differences in non-HIV-related child and maternal characteristics, by categorised year of admission, using proportions (categorical variables) and means or medians (continuous variables). We plotted trends in the proportions of different HIV-specific characteristics among hospitalised children. Statistical evidence for changes in proportions across the three time periods was assessed using univariable logistic and multinomial regression models, for binary and non-binary categorical variables, respectively, with the HIV-related characteristic as the dependent variable and time (in periods) as the independent variable. All statistical analyses were done using STATA 17.0 [25, 26].

2.6 | Ethics

This analysis was approved by the University of Cape Town Human Research Ethics Committee (REF 101/2021).

A waiver of informed consent was obtained for this research as all data had already been routinely collected by health services and no participant recruitment was required.

3 | RESULTS

Between 2008 and 2018, there were 54,181 children (born at Western Cape public health facilities) who had a hospital admission record for at least one of the four infectious diseases of interest by age 3 years, of whom 52,811 (97.5%) were included in our analysis (Figure S1). Of the 1370 children who were excluded from our analysis, 70% had mothers diagnosed with HIV postnatally. The main difference between them and children included in the analysis was the proportion of child deaths by age 3 (2.4% vs. 1.5%) and the proportion of maternal deaths by child age 3 (1.1% vs. 0.5%). Of the admissions, 64.9% included LRTI, 36.5% diarrhoea, 4.0% meningitis and 0.6% TBM. The number of annual admissions varied substantially during the study period, with 75.5% of all admissions occurring from 2015 onwards (Table S2).

3.1 | Non-HIV-related characteristics of infants and mothers

Among children included, 56.4% were male and 1.5% died before the age 3 years (Table 1). The proportion of admitted children with very low (1000–1499 g) and low birthweight (1500–2499 g) decreased between the Pre-Option B+, Option B+ and Universal ART periods from 8.3% to 4.8% to 3.2% and 23.3% to 19.0% to 17.0%, respectively. Mean maternal age at delivery remained constant at 27 years throughout, while the proportion of mothers who died by child age 3 years decreased from 1% Pre-Option B+ to 0.5% during Option B+ and 0.4% during the Universal ART period.

3.2 | HIV-related characteristics of infants and mothers

3.2.1 | Infant HIV exposure and HIV acquisition status

By hospital discharge, 17.0% of children were HEU, 81.2% HUU and 1.9% CWH (Table 1). The certainty of the combined HIV exposure and acquisition status of most (56.4%) children HEU was high, but low for most children HUU (92.8%) (Table S3). The proportion of CWH among infectious disease admissions decreased from 7.0% in 2008 to 1.1% in 2021. The proportion of children classified as HEU at hospital discharge increased from 14.1% in 2008 to 16.1% in 2021, with a peak of 18.3% in 2017 (Figure 1.1). Children hospitalised with infectious diseases were less likely to have HIV, compared to being HEU, during the Option B+ (Relative Risk Ratio [RRR]: 0.35; 95% CI: 0.29–0.42) and Universal ART (RRR: 0.26; 95% CI: 0.22–0.31) periods, relative to children admitted during the Pre-Option B+ period (Figure 1.2).

3.2.2 | Maternal HIV diagnosis and ART start time

Of CWH, 7.6% of mothers did not have evidence of HIV and were excluded from further analysis (Table S4). A descriptive summary of the proportion of mothers in respective maternal HIV diagnosis and ART start categories is shown in Table S5. Among mothers of hospitalised children HEU and CWH, who were living with HIV, the proportion diagnosed with HIV before pregnancy increased from 20.2% in 2008 to 69.2% in 2021, with a peak of 75.2% in 2020 (Figure 2.1). Mothers were more likely to have been diagnosed with HIV before pregnancy, versus during pregnancy, among children admitted during the Option B+ and Universal ART periods, compared to children admitted before the Option B+ period (Figure 2.2).

The proportion of mothers with HIV (N = 9873) starting ART before pregnancy increased from 5.8% in 2008 to 59.0% in 2021, peaking at 62% in 2020 (Figure 3.1), with mothers more likely to have started ART before pregnancy, versus at delivery/postnatally, among children admitted during the Option B+ and Universal ART periods, compared to children admitted before the Option B+ period (Figure 3.2).

3.3 | Infant exposure to maternal ART

The proportion of children exposed to HIV (HEU and CWH) who were exposed to maternal ART increased from 16.3% in 2008 to 87.2% in 2021 (Figure S2.1). The odds of having been exposed to maternal ART increased eight-fold (Odds Ratio: 8.41; 95% CI: 7.36–9.61) for children admitted to the hospital during the Universal ART period compared to children admitted before the Option B+ period (Figure S2.2).

Table 1. Characteristics of infants (and their mothers), born in Western Cape from 2008 to 2018, who had an infectious disease hospital admission (LRTI, diarrhoea, meningitis and TBM), by different ART policy periods (Pre-Option B+, Option B+ and Universal ART)

	Infectious disease hospitalisation			
Variable	**Total** **N = 52,811 (100%)**	**Pre-Option B+ (A)** ***n* = 7223 (13.7%)**	**Option B+ (B)** ***n* = 16,030 (30.4%)**	**Universal ART (C)** ***n* = 29,558 (56.0%)**
Infant Characteristics				
Sex: *n* (%)				
Male	29,761 (56.4)	4052 (56.1)	9101 (56.8)	16,608 (56.2)
Missing	15 (0.03)	0 (0)	4 (0.02)	11 (0.03)
Birthweight (g): *n* (%)				
Foetal macrosomia (≥4000 g)	1799 (3.4)	233 (3.2)	528 (3.3)	1038 (3.5)
Normal (2500–3999 g)	37,830 (71.6)	4448 (61.6)	11,316 (70.6)	22,066 (74.7)
Low (1500–2499 g)	9759 (18.5)	1681 (23.3)	3042 (19.0)	5036 (17.0)
Very low (1000–1499 g)	2318 (4.4)	600 (8.3)	774 (4.8)	944 (3.2)
Extremely low (<1000 g)	926 (1.8)	251 (3.5)	330 (2.1)	345 (1.2)
Missing	179 (0.3)	10 (0.1)	40 (0.3)	129 (0.4)
Mean (95% CI)	2868 (2862; 2874)	2684 (2665; 2704)	2844 (2832; 2856)	2926 (2918; 2934)
Twins: *n* (%)				
	2252 (4.3)	525 (7.3)	716 (4.5)	1011 (3.4)
Died before 3 years of age (all-cause): *n* (%)				
	808 (1.5)	276 (3.8)	242 (1.5)	290 (1.0)
Age (months) at first infectious-cause hospitalisation				
Median (IQR)	7.27 (11.97)	4.73 (8.35)	5.85 (9.86)	9.01 (13.58)
Exposure and HIV acquisition status at time of hospital discharge: *n* (%)				
Children HEU	8969 (17.0)	1025 (14.2)	2802 (17.5)	5142 (17.4)
Children HUU	42,864 (81.2)	5899 (81.7)	12,942 (80.7)	24,023 (81.3)
Children with HIV	978 (1.9)	299 (4.1)	286 (1.8)	393 (1.3)
Maternal Characteristics				
Age (years) at delivery:				
Mean (95% CI)	27.20 (27.11; 27.22)	27.23 (27.09; 27.38)	27.09 (26.99; 27.19)	27.19 (27.12; 27.26)
Missing: *n* (%)	243 (0.5)	48 (0.7)	77 (0.5)	118 (0.4)
Maternal death by child age 3 years: *n* (%)				
	253 (0.5)	74 (1.0)	73 (0.5)	106 (0.4)

Note: Pre-Option B+ (January 2008–April 2013); Option B+ (May 2013–August 2016); Universal ART (September 2016–December 2021).
Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HEU, exposed to HIV and uninfected; HUU, unexposed to HIV and uninfected; IQR, interquartile range; LRTI, lower respiratory tract infection; TBM, tuberculous meningitis.

Among children exposed to maternal ART, the proportion exposed for the first time during late gestation/postnatally decreased from 58.8% in 2008 to 17.6% in 2021 (Figure S3.1). Children admitted to hospital with an infectious disease during the Option B+ and Universal ART periods were more likely to have first been exposed to maternal ART at conception, relative to late gestation/postnatally, compared with children admitted before the Option B+ period) (Figure S3.2).

3.4 | Maternal viral load and CD4 count closest to pregnancy start

Among hospitalised children HEU with mothers who had viral load tests, >80% of mothers had viral loads <1000 copies/ml for all years except 2010 (72.7%) (Figure 4.1). Mothers of children HEU were more likely to have viral loads <1000 copies/ml (vs. ≥1000 copies/ml) for children admitted during the Universal ART period, compared to the period Pre-Option B+ (Figure 4.3). Among hospitalised CWH, the proportion of mothers with viral loads <1000 copies/ml peaked at 58.3% in 2009 and decreased to 25% in 2021 (Figure 4.2). Mothers of hospitalised CWH were less likely to have viral loads <1000 copies/ml (vs. ≥1000 copies/ml), for children admitted during the Option B+ period, compared to children admitted before the Option B+ period (Figure 4.4).

Among hospitalised children HEU with mothers who had a CD4 count recorded, the proportion of mothers with CD4 count <350 cells/μl decreased from 90.6% in 2008 to 27.8% in 2021 (Figure 5.1). Among hospitalised CWH, the proportion of mothers with a CD4 count <350 cells/μl was 70.8% in 2008 and 75.0% in 2021, with a minimum of 41.2% in 2020 (Figure 5.2). Mothers of hospitalised children HEU were more

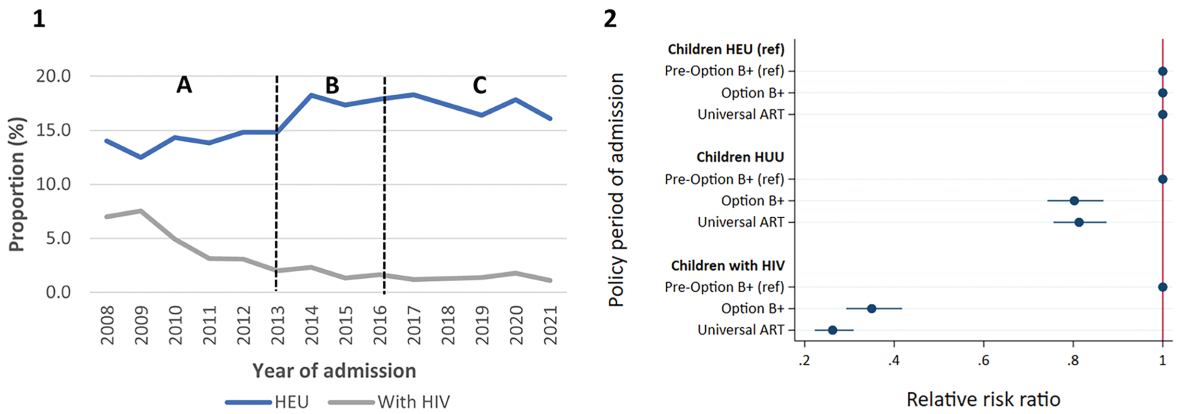

Figure 1. HIV exposure and aquisition status. [1]—Trends in HIV exposure and aquisition status among children HEU and CWH who were hospitalised with at least one of four infectious diseases (lower respiratory tract infection, diarrhoea, meningitis and tuberculous meningitis), by year. The vertical dotted lines demarcate different policy periods: A—Pre-Option B+, B—Option B+, C—Universal ART; [2]—Plot of the relative risk ratios (with 95% confidence intervals) from multinomial logistic regressions assessing the association between child HIV exposure and aquisition status with policy period of hospital admission. *N* = 52,811. ART, antiretroviral therapy; CWH, children with HIV; HEU, exposed to HIV and uninfected; HUU, unexposed to HIV and uninfected; ref, reference group.

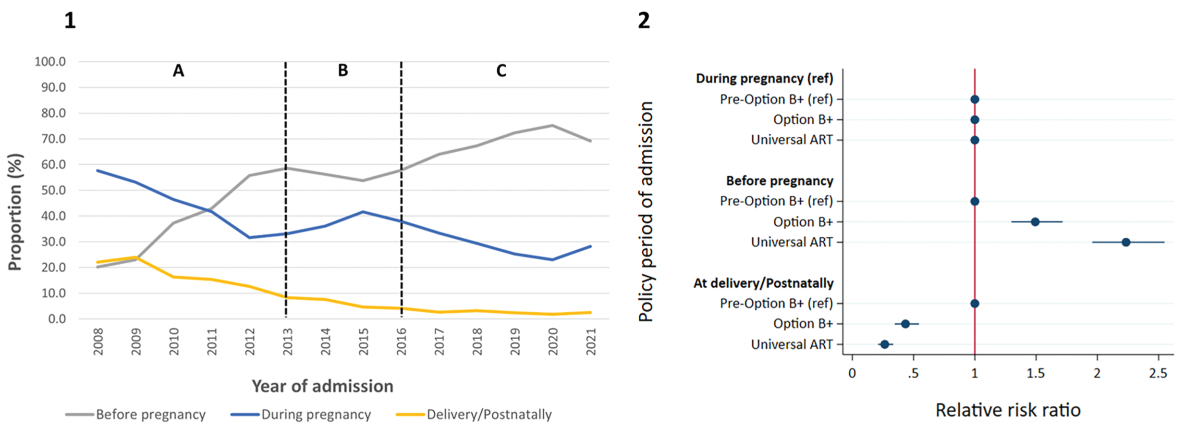

Figure 2. Timing of HIV diagnosis. [1]—Trends in timing of HIV diagnoses among mothers of children HEU and CWH, who were hospitalised with at least one of four infectious diseases (lower respiratory tract infection, diarrhoea, meningitis and tuberculous meningitis), by year. The vertical dotted lines demarcate different policy periods: A—Pre-Option B+, B—Option B+, C—Universal ART; [2]—Plot of the relative risk ratios (with 95% confidence intervals) from multinomial logistic regression assessing the association of timing of mother HIV diagnosis (relative to pregnancy and delivery) with policy period of hospital admission. *N* = 9,873. ART, antiretroviral therapy; CWH, children with HIV; HEU, exposed to HIV and uninfected; ref, reference group.

likely to have a CD4 count ≥500 cells/μl (vs. <350 cells/μl), for children admitted during the Option B+ (RRR: 3.54; 95 CI%: 2.90-4.31) and Universal ART periods (RRR: 4.74; 95 CI%: 3.92–5.73), compared to children admitted before the Option B+ period (Figure 5.3). Mothers of hospitalised CWH were less likely to have a CD4 count ≥500 cells/μl (vs. <350 cells/μl), for children admitted during the Universal ART period (RRR: 0.61; 95 CI%: 0.40–0.93), compared to children admitted before the Option B+ period (Figure 5.4).

4 | DISCUSSION

Since the scale-up of VTP in SA from 2002, tremendous gains have been made in preventing and treating paediatric HIV acquisition [9, 27]. Our findings demonstrate how the HIV-related profile of children hospitalised for infectious diseases has changed from 2008 to 2021 in the Western Cape, in the context of guideline amendments.

During the scale-up of VTP, the stabilisation of antenatal HIV prevalence and reduction in vertical HIV transmission resulted in a progressive decline in the CWH population and consequent increase in the prevalence of children HEU, since 2004 [27]. Thembisa model estimates show a decrease in HIV prevalence, among children under the age 3 years in the Western Cape, from 1.0% in 2008 to 0.4% in 2021 [28]. While we do not have estimates for the prevalence of children HEU in the Western Cape, UNAIDS estimates of the national prevalence of children HEU (0–14 years) in SA increased from 11.8% in 2008 to 21.6% in 2018 [13]. Antenatal HIV prevalence in SA is higher than in the Western Cape (30.0% vs. 18.9% in 2019), therefore, we expect the prevalence of

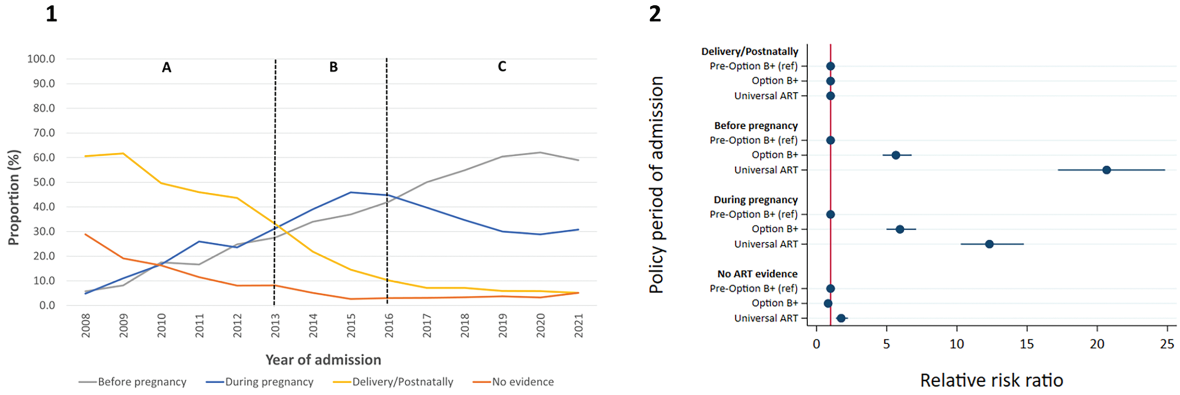

Figure 3. Timing of ART start. [1]—Trends in timing of ART start among mothers of children HEU and CWH who were hospitalised with at least one of four infectious diseases (lower respiratory tract infection, diarrhoea, meningitis and tuberculous meningitis), by year. The vertical dotted lines demarcate different policy periods: A—Pre-Option B+, B—Option B+, C—Universal ART; [2]—Plot of the relative risk ratios (with 95% confidence intervals) from multinomial logistic regression assessing the association of timing of mother's ART start (relative to pregnancy and delivery) with policy period of hospital admission. *N* = 9873. ART, antiretroviral therapy; CWH, children with HIV; HEU, exposed to HIV and uninfected; ref, reference group.

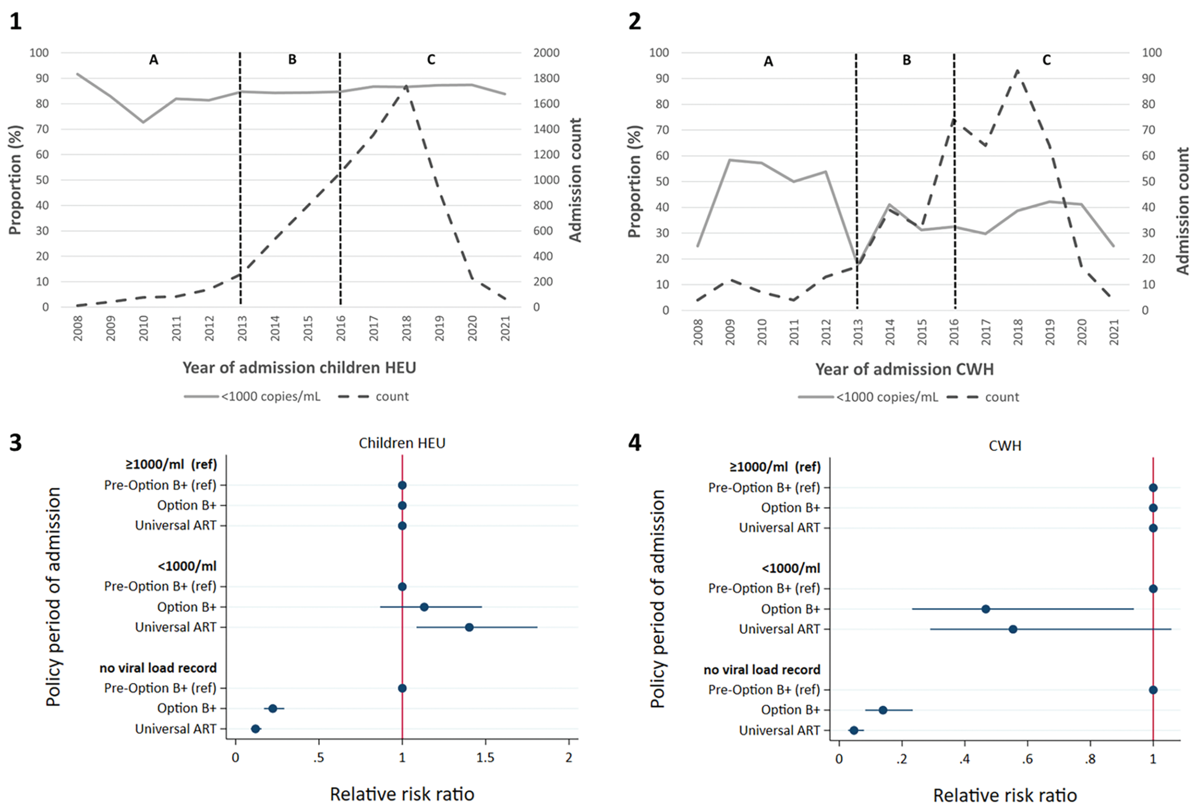

Figure 4. Maternal viral load. [1] and [2]—Total numbers of and trends in the proportion of infectious disease (lower respiratory tract infection, diarrhoea, meningitis and tuberculous meningitis) hospital admittees HEU [1] (*n* = 7306) or with HIV [2] (*n* = 444) whose mothers had a viral load of <1000 copies/ml during pregnancy (including only mothers with a viral load record). The vertical dotted lines demarcate different policy periods: A—Pre-Option B+, B—Option B+, C—Universal ART; [3] and [4]—Plot of the relative risk ratios (with 95% confidence intervals) from multinomial logistic regression assessing the association of maternal viral load during pregnancy with policy period of hospital admission, for children HEU [3] (*N* = 8969) and CWH [4] (904), respectively. *We had no viral load record for 1663 (18.5%) of mothers to children HEU and 460 (51.0%) of CWH. ART, antiretroviral therapy; CWH, children with HIV; HEU, exposed to HIV and uninfected; ref, reference group.

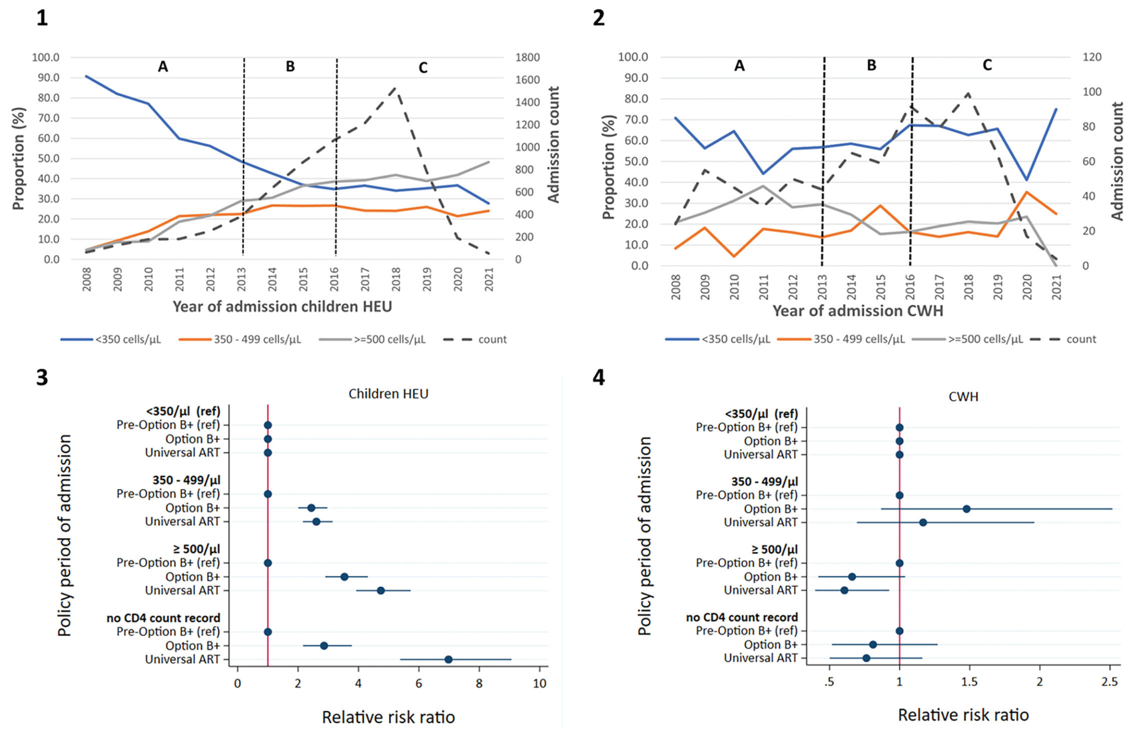

Figure 5. Maternal CD4 count. [1] and [2]—Total numbers of and trends in the proportion of infectious disease (lower respiratory tract infection, diarrhoea, meningitis and tuberculous meningitis) hospital admittees HEU [1] (*n* = 7523) or with HIV [2] (*n* = 731) whose mothers had CD4 count <350 cells/µl, 350–499 cells/µl or ≥500 cells/µl during pregnancy (including only mothers with a CD4 count record). The vertical dotted lines demarcate different policy periods: A—Pre-Option B+, B—Option B+, C—Universal ART; [3] and [4]—Plot of the relative risk ratios (with 95% confidence intervals) from multinomial logistic regression assessing the association of mother CD4 count during pregnancy with policy period of hospital admission, for children HEU [3] (*n* = 8969) and CWH [4] (*n* = 904), respectively. *We had no CD4 count record for 1456 (16.2%) of mothers to children HEU and 173 (19.1%) of CWH. ART, antiretroviral therapy; CWH, children with HIV; HEU, exposed to HIV and uninfected; ref, reference group.

children HEU to be correspondingly lower in the Western Cape and that the average prevalence of children HEU between 2008 and 2018 (the birth cohorts of this analysis) would be lower than 17% [15]. These patterns are reflected in our analysis. During the 14-year period under analysis, the proportion of CWH among infectious disease hospital admittees age ≤3 years dropped from 7.0% in 2008 to 1.3% in 2018. This corresponded with an increase in the proportion of children HEU from 14.1% in 2008 to 17.3% in 2018. With an average prevalence of children HEU over the study period of 17%, this suggests an over-representation of hospitalised children HEU than in the general population. A study by Meyers et al. also showed a decreasing trend in the HIV prevalence among hospital admittees (0–14 years), although the HIV prevalence among hospital admittees that they reported for 2007 and 2010/11 (29.5% and 19.3%) was substantially higher than what we observed in 2008 and 2010, respectively [17]. The Meyers et al. study was conducted at a single large urban academic hospital in Gauteng province, which has a higher HIV prevalence among children than Western Cape, and results may not be generalizable to our province-wide setting in the Western Cape.

The introduction of Option B+ has improved access to ART for all pregnant people living with HIV and dramatically reduced vertical HIV transmission [9]. In the Western Cape, between 2010 and 2013, Myer et al. observed a substantial increase in the proportion of pregnant people living with HIV entering antenatal care on ART, and initiating ART before delivery [29]. They also reported a substantial reduction in delays to antenatal ART initiation after CD4 eligibility criteria were removed during the Option B+ period. In our analysis, mothers of children admitted to hospital in the Option B+ and universal ART periods, compared to Pre-Option B+, were significantly more likely to have been diagnosed with HIV before pregnancy versus during pregnancy and to have initiated ART before or during pregnancy versus at delivery/postnatally. As a result, the proportion of children exposed to maternal ART increased over time, with children admitted during universal ART versus Pre-Option B+, having eight times higher odds of maternal ART exposure. Furthermore, with mothers initiating ART earlier, children admitted in the later periods, compared to Pre-Option B+, were more likely to have been exposed to maternal ART for the first time at conception versus late gestation/postnatally. The apparent slight increase from 2016 onwards in the proportion who had no ART evidence among mothers with HIV may be due to better ascertainment of maternal HIV status in this period.

Throughout the study period, mothers of CWH at the time of infectious disease hospital admission predominantly had viral loads ≥1000 copies/ml near delivery, while the proportion of mothers of children HEU with viral loads <1000 copies/ml near delivery was >80% for all years except 2010. This is expected, given that the risk of vertical HIV transmission is increased with a higher maternal viral load, particularly ≥1000 copies/ml [30, 31].

As access to maternal ART improved over the years, and CD4 count was no longer recommended for monitoring persons living with HIV who are virally suppressed on ART, the proportion of mothers of children HEU who had CD4 count recorded reduced, as did the proportion with CD4 <350 cells/μl near delivery, suggesting that maternal ART has not only reduced vertical HIV transmission, but also improved maternal health, as expected. The reduction in maternal deaths by the time of child age 3 years supports this. We found that among CWH admittees, mothers predominantly had CD4 counts <350 cells/μl near delivery, corresponding with high viral loads observed in these mothers, suggesting that mothers not optimally sustaining ART in the context of a high coverage effective VTP programme remain especially vulnerable.

4.1 | Strengths and limitations

The Western Cape Provincial Health Data Centre provided a novel opportunity to assess, province-wide, the real-world trends in HIV-related characteristics of hospitalised children, using individual-level longitudinal health service data. We were also able to classify HIV exposure and acquisition status of children at the time of hospitalisation, according to standardised certainty definitions [32], enabling better comparability with other studies that use the same definitions.

A limitation is that not all children were classified by HIV exposure and acquisition status with high certainty, particularly children HUU, of whom >90% were classified with low certainty (largely because Rapid point-of-care HIV results are not routinely digitised). It is possible that CWH may have been misclassified as HEU and children HEU as HUU. However, due to high rates of antenatal HIV testing within SA (>95%) [9], we are confident that most mothers living with HIV would have been identified during pregnancy, thereby limiting the misclassification of children exposed to HIV as unexposed. Additionally, of the children excluded from our analysis (*n* = 1370), 70% had mothers diagnosed with HIV postnatally. We may, therefore, have a slight underestimation of children HEU or with HIV in our sample.

Another limitation of our findings is the accuracy and completeness of ICD-10 codes, particularly in the earlier years of the analysis. Our classification of hospital admissions due to infectious causes relied on ICD-10 codes, which were previously shown to have poor reliability [33]. However, in more recent years, the implementation of a standardised discharge summary has improved ICD-10 code completeness and accuracy [34], likely resulting in improved identification of infectious cause hospitalisations. As a result, a large proportion of admissions included in our analyses were from 2015 onwards. Furthermore, it is probable that in the earlier years, admission codes were captured more accurately in tertiary hospitals and among more severely sick children. In the Pre-Option B+ period, >70% of admissions in our analyses were to tertiary hospitals (not shown), whereas >70% were to non-tertiary hospitals during the universal ART period. It is possible that the Pre-Option B+ cohort is more representative of severely ill children than the cohorts of children admitted in the later periods, potentially overestimating the prevalence of CWH, and other risk factors for severe disease, particularly low birth weight.

We did not include children born out of the province who relocated to and were hospitalised in the Western Cape. We also only considered four infectious diseases that cause substantial morbidity and mortality in children. Other childhood infections, including pulmonary tuberculosis, were not included in this analysis. Our results may, therefore, not be generalizable to all child infectious diseases burdening the healthcare system.

5 | CONCLUSIONS

Temporal trends among children hospitalised with infectious diseases highlight the positive impact of VTP and increased ART access within SA. Whereas children of mothers with HIV were previously exposed to no or short-duration maternal ART, in recent years, the majority were exposed to maternal ART, frequently from early gestation. There were fewer CWH and a higher proportion of children HEU in recent years.

However, the finding that at least one in six children hospitalised in recent years were HEU, of which up to 87% were exposed to maternal ART, highlights the need to consider HIV and ART exposure status, and not just child HIV prevalence, when assessing the impact of the HIV epidemic on child health services. Further research is needed to quantify the burden of infectious diseases on the health system that is due to higher risk among children HEU relative to children HUU and whether there is a need for HEU-specific interventions in addition to interventions that improve the health and wellbeing of all children in resource-limited settings.

AUTHORS' AFFILIATIONS

[1]Centre for Infectious Disease Epidemiology and Research, School of Public Health, University of Cape Town, Cape Town, South Africa; [2]Health Intelligence Directorate, Western Cape Government Health, Cape Town, South Africa; [3]Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK; [4]Department of Paediatrics & Child Health, Faculty of Medicine & Health Sciences, Stellenbosch University, Worcester, South Africa; [5]Paediatric Infectious Diseases Unit, Red Cross War Memorial Children's Hospital and the Department of Paediatrics and Child Health, University of Cape Town, Cape Town, South Africa; [6]Division of Public Health Medicine, School of Public Health, University of Cape Town, Cape Town, South Africa

COMPETING INTERESTS

KA, EK, AB and M-AD receive funding from ViiV Healthcare for an unrelated project.

AUTHORS' CONTRIBUTIONS

STdB, M-AD, ALS, BE, SMI and HEJ conceptualised the research study. STdB managed the data with assistance from FP and insight from M-AD, ALS, KA and EK. AB provided data engineering oversight within the Western Cape Provincial Health Data Centre. STdB conducted the data analyses and drafted the manuscript with subject matter expertise and/or scientific oversight from M-AD, ALS, BE, SMI, HEJ and KA. All authors reviewed and approved the final manuscript.

ACKNOWLEDGEMENTS

Kathleen Kehoe and Erna Modern contributed to the curation and management of the data.

FUNDING

This work was supported by the University of Bristol's (i) Pro Vice-Chancellor Research and Enterprise Strategic Research Fund and (ii) Global Challenge Research Fund Strategy funded by Research England; by the NIH Fogarty International Centre under grant K43TW010683 to ALS; by the Eunice Kennedy Shriver National Institute of Child Health and Human Development of the National Institutes of Health under grant R61HD103093 to ALS and M-AD; by the Western Cape Department of Health to the Western Cape Provincial Health Data Centre; by the US National Institutes for Health under grants R01 HD080465 and U01 AI069924 to the Western Cape Provincial Health Data Centre; and the Bill and Melinda Gates Foundation under grants 1164272 and 1191327 to the Western Cape Provincial Health Data Centre.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the Western Cape Provincial Health Data Centre, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are available, however, from the corresponding author upon reasonable request and with permission of the Western Cape Provincial Health Data Centre.

REFERENCES

1. Kassebaum N, Kyu HH, Zoeckler L, Olsen HE, Thomas K, Pinho C, et al. Child and adolescent health from 1990 to 2015: findings from the Global Burden of Diseases, Injuries, and Risk Factors 2015 Study. JAMA Pediatr. 2017;171(6):573–92.
2. Rodríguez L, Cervantes E, Ortiz R. Malnutrition and gastrointestinal and respiratory infections in children: a public health problem. Int J Environ Res Public Health. 2011;8(4):1174–205.
3. Ramokolo V, Goga AE, Slogrove AL, Powis KM. Unmasking the vulnerabilities of uninfected children exposed to HIV. BMJ. 2019;366(14479):1–4.
4. Slogrove AL. The pattern and pathways of infectious morbidity in South African HIV exposed uninfected infants. University of British Columbia; 2015.
5. Statistics South Africa. Millennium Development Goals 4: reduce child mortality. 2015.
6. Zwi KJ, Pettifor JM, Soderlund N. Paediatric hospital admissions at a South African urban regional hospital: the impact of HIV, 1992–1997. Ann Trop Paediatr. 1999;19(2):135–42.
7. Anderson K, Kalk E, Madlala HP, Nyemba DC, Kassanjee R, Jacob N, et al. Increased infectious-cause hospitalization among infants who are HIV-exposed uninfected compared to HIV-unexposed. AIDS. 2021;35:1–13.
8. le Roux SM, Abrams EJ, Donald KA, Brittain K, Phillips TK, Zerbe A, 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;4(3):220–31.
9. Goga A, Sherman G, Chirinda W, Ng 'oma K, Bhardwaj S, Doherty T, et al. Eliminating mother-to-child transmission of HIV in South Africa, 2002–2016: progress, challenges and the Last Mile Plan. In: Padarath A, Barron P, editors. South African Health Review 2017. Health Systems Trust; 2017. p. 137–46.
10. South African National Department of Health. Clinical guidelines: PMTCT (prevention of mother-to-child transmission). 2010.
11. South African National Department of Health. South African National Consolidated Guidelines for the Prevention of Mother-To-Child Transmission of HIV (PMTCT) and the Management of HIV in Children, Adolescents and Adults. 2015.
12. South African National Department of Health. Circular: Implementation of the Universal Test and Treat Strategy for HIV Positive Patients and Differentiated Care for Stable Patients. 2016.
13. Slogrove AL, Powis KM, Johnson LF, Stover J, Mahy M. Estimates of the global population of children who are HIV-exposed and uninfected, 2000–18: a modelling study. Lancet Glob Health. 2020;8(1):e67–75.
14. Joint United Nations Programme on HIV/AIDS (UNAIDS). 2023 UNAIDS estimates [Internet]. 2023 [cited 2023 Jan 3]. http://aidsinfo.unaids.org
15. Woldesenbet SA, Lombard C, Manda S, Kufa T, Ayalew K, Cheyip M, et al. The 2019 National Antenatal Sentinel HIV Survey, South Africa. National Department of Health; 2021.
16. Western Cape Government. PMTCT Clinical Guidelines. 2013.
17. Meyers T, Dramowski A, Schneider H, Gardiner N, Kuhn L, Moore D. Changes in pediatric HIV-related hospital admissions and mortality in Soweto, South Africa, 1996–2011: light at the end of the tunnel. J Acquir Immune Defic Syndr. 2012;60(5):503–10.
18. Boulle A, Heekes A, Tiffin N, Smith M, Mutemaringa T, Zinyakatira N, et al. Data Centre Profile: the Provincial Health Data Centre of the Western Cape Province, South Africa. Int J Popul Data Sci. 2019;4(2):06.
19. Woldesenbet SA, Kufa T, Lombard C, Manda S, Aylew K, Cheyip M, et al. The 2017 National Antenatal Sentinel HIV Survey Key Findings, South Africa. National Department of Health; 2019.
20. Western Cape Government. Western Cape Government Annual Report 2020/2021. 2021.
21. Cullinan K. Health services in South Africa: a basic introduction. The South African Health News Service; 2006.
22. South African Government. Update on new Mitchells Plain Hospital and temporary closure of GF Jooste Hospital [Internet]. 2013 [cited 2022 Dec 19]. https://www.gov.za/update-new-mitchells-plain-hospital-and-temporary-closure-gf-jooste-hospital
23. Western Cape Government. New Khayelitsha Hospital officially opened [Internet]. 2012 [cited 2022 Dec 19]. https://www.westerncape.gov.za/news/new-khayelitsha-hospital-officially-opened#:~:text=Premier%20Helen%20Zille%20and%20the,Hospital%20on%2017%20April%202012
24. Slogrove AL, Burmen B, Davies M-A, Edmonds A, Abrams EJ, Chadwick EG, et al. Standardized definitions of in utero human immunodeficiency virus and antiretroviral drug exposure among children. Clin Infect Dis. 2022;75(2):347–55.
25. StataCorp. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC; 2021.
26. Jann B. Plotting regression coefficients and other estimates. Stata J. 2014;14(4):708–37.
27. Goga A, Slogrove A, Wedderburn CJ, Feucht U, Wessels J, Ramokolo V, et al. The impact of health programmes to prevent vertical transmission of HIV. Advances, emerging health challenges and research priorities for children exposed to or living with HIV: perspectives from South Africa. South Afr Med J. 2019;109(11):77–82.
28. Johnson L, Dorrington R. Thembisa version 4.6: national and provincial model outputs. 2023.
29. Myer L, Phillips T, Manuelli V, McIntyre J, Bekker L-G, Abrams EJ. Evolution of antiretroviral therapy services for HIV-infected pregnant women in Cape Town, South Africa. J Acquir Imune Defic Syndr. 2015;69(2):e57–65.
30. Johnson LF, Stinson K, Newell M-L, Bland RM, Moultrie H, Davies M, et al. The contribution of maternal HIV seroconversion during late pregnancy and breastfeeding to mother-to-child transmission of HIV. J Acquir Immune Defic Syndr. 2012;59(4):417–25.
31. Osório D, Munyangaju I, Nacarapa E, Muhiwa A, Nhangave AV, Ramos JM. Mother-to-child transmission of HIV infection and its associated factors in the district of Bilene, Gaza Province—Mozambique. PLoS One. 2021;16(12):e0260941.
32. de Beer S, Phelanyane F, Davies M, Heekes A, Kalk E, Mendelsohn A, et al. Implementation of standardized in utero HIV exposure definitions using routinely collected public sector data across the Western Cape Province, South Africa. International Workshop on HIV & Pediatrics. 2022.
33. Daniels A, Muloiwa R, Myer L, Buys H. Examining the reliability of ICD-10 discharge coding in Red Cross War Memorial Children's Hospital administrative database. South Afr Med J. 2021;111(2):137–42.
34. Dyers R, Ward G, du Plooy S, Fourie S, Evans J, Mahomed H. Training and support to improve ICD coding quality: a controlled before-and-after impact evaluation. South Afr Med J. 2017;107(6):501–6.

SUPPORTING INFORMATION

Additional information may be found under the Supporting Information tab for this article:

Figure S1: Flow diagram of mother-infant pairs included in the cohort of children, born in the Western Cape (2008 – 2018), who had an infectious disease hospital admission (lower respiratory tract infection, diarrhoea, meningitis, tuberculous meningitis) by age three years.

Figure S2: Infant exposure to maternal ART. (1) - Trend in the proportion of hospital admittees HEU or with HIV who were exposed to maternal ART and hospitalised with at least one of four infectious diseases (lower respiratory tract infection, diarrhoea, meningitis, tuberculous meningitis), by year. The vertical dotted lines demarcate different policy periods: A Pre-Option B+, B - Option B+, C - Universal ART; **(2)** - Plot of the odds ratios (with 95% confidence intervals) from logistic regression assessing the association of infant exposure to maternal ART with policy period of hospital admission. N = 9,873.

Figure S3: Timing of earliest infant exposure to maternal ART. (1) - Trends in the proportion of hospital admittees' earliest exposure to maternal ART at different time points, among those who were exposed to maternal ART and hospitalised with at least one of four infectious diseases (lower respiratory tract infection, diarrhoea, meningitis, tuberculous meningitis), by year. The vertical dotted lines demarcate different policy periods: A Pre-Option B+, B - Option B+, C - Universal ART; **(2)** - Plot of the relative risk ratios (with 95% confidence intervals) from multinomial logistic regression assessing the association of timing of initial infant exposure to mother's ART start (relative to pregnancy and delivery) with policy period of hospital admission. N = 7,612.

Table S1: Simplified DECIPHER definitions for classification of children as HEU and HUU from routinely-collected data.

Table S2: Count and proportion of hospital admissions per year

Table S3: Certainty of HIV exposure status in children born to women with and without HIV, in Western Cape, South Africa (2008-2021), at hospitalisation.

Table S4: Number of mothers and children with evidence for maternal HIV, maternal ART, Infant exposure to maternal ART, maternal viral loads and maternal CD4 counts, among children HEU and with HIV.

Table S5: Descriptive statistics for Maternal HIV diagnosis and Maternal ART start across the three policy periods, for mothers who had evidence of an HIV diagnosis (N=9,873).

Bulterys MA et al. *Journal of the International AIDS Society* 2023, **26**(S4):e26149
http://onlinelibrary.wiley.com/doi/10.1002/jia2.26149/full | https://doi.org/10.1002/jia2.26149

JIAS JOURNAL OF THE INTERNATIONAL AIDS SOCIETY

RESEARCH ARTICLE

Neurodevelopment of children who are HIV-exposed and uninfected in Kenya

Michelle A. Bulterys[1,2,§], Irene Njuguna[1,3], Maureen King'e[4], Daisy Chebet[4], Hellen Moraa[3], Laurén Gomez[1], Alvin Onyango[3], Kenneth Malavi[3], Gladys Nzia[3], Martin Chege[3], Jillian Neary[2], Anjuli D. Wagner[1], Kendall A. Lawley[1,2], Dalton Wamalwa[4], Sarah Benki-Nugent[1,†] and Grace John-Stewart[1,2,5,6,†]

[§]**Corresponding author**: Michelle A. Bulterys, 3980 15th Ave NE, Seattle, WA 98195, USA. Tel: +1 (626) 375-8610. (mbult@uw.edu)
[†]Co-senior authors.

Introduction: Predictors of neurodevelopment among children who are HIV-exposed uninfected (CHEU) are poorly understood.

Methods: Mothers with and without HIV and their children were enrolled during 6-week postnatal care visits across seven sites in Kenya between March 2021 and June 2022. Infant neurodevelopment was assessed using the Malawi Developmental Assessment Tool, including social, language, fine motor and gross motor domains. We used multivariate linear mixed effects models to identify associations between 1-year neurodevelopment scores, HIV and antiretroviral therapy (ART) exposures, and household factors, adjusted for potential confounders and clustered by the site.

Results: At 1-year evaluation, CHEU ($n = 709$) and children who are HIV-unexposed uninfected (CHUU) ($n = 715$) had comparable median age (52 weeks) and sex distribution (49% vs. 52% female). Mothers living with HIV were older (31 vs. 27 years), had lower education (50% vs. 26% primary) and were more likely to be report moderate-to-severe food insecurity (26% vs. 9%) ($p < 0.01$ for all). Compared to CHUU, CHEU had higher language scores (adjusted coeff: 0.23, 95% CI: 0.06, 0.39) and comparable social, fine and gross motor scores. Among all children, preterm birth was associated with lower gross motor scores (adjusted coeff: −1.38, 95% CI: −2.05, −0.71), food insecurity was associated with lower social scores (adjusted coeff: −0.37, 95% CI: −0.73, −0.01) and maternal report of intimate partner violence (IPV) was associated with lower fine motor (adjusted coeff: −0.76, 95% CI: −1.40, −0.13) and gross motor scores (adjusted coeff: −1.07, 95% CI: −1.81, −0.33). Among CHEU, *in utero* efavirenz (EFV) exposure during pregnancy was associated with lower gross motor scores compared to dolutegravir (DTG) exposure (adjusted coeff: −0.51, 95% CI: −1.01, −0.03). Lower fine and gross motor scores were also associated with having a single or widowed mother (adjusted coeff: −0.45, 95% CI: −0.87, −0.03) or a deceased or absent father (adjusted coeff: −0.81, 95% CI: −1.58, −0.05), respectively.

Conclusions: Biologic and social factors were associated with child neurodevelopment. Despite socio-demographic differences between CHEU and CHUU, 1-year neurodevelopment was similar. Addressing IPV and food insecurity may provide benefits regardless of maternal HIV status. DTG use was associated with higher neurodevelopmental scores in CHEU, compared to EFV regimens, potentially contributing to a lack of neurodevelopmental difference between CHEU and CHUU.

Keywords: neurodevelopment; HIV exposure; children who are HIV-exposed uninfected; CHEU; maternal mental health; intimate partner violence

Additional information may be found under the Supporting Information tab of this article.

Received 25 January 2023; **Accepted** 14 August 2023

1 | INTRODUCTION

Successful prevention of vertical transmission programmes over the last decade has contributed to a rapidly growing population of almost 16 million children who are HIV-exposed uninfected (CHEU) around the world, with an additional one million born every year in sub-Saharan Africa (SSA) [1, 2]. Compared to children who are HIV-unexposed uninfected (CHUU), CHEU are at increased risk of morbidity, adverse birth outcomes, growth faltering, environmental and pathogenic exposures, poor mental health and social inequities as a member of a family affected by HIV [2–10]. In multiple high HIV burden countries in SSA, the population of CHEU accounts for over 20% of all children under 15 years of age, and the SSA region is estimated to have the largest proportion of children under 5 years of age at risk of not meeting their developmental potential [11, 12]. Early neurodevelopmental delays are associated with poorer physical and mental health and learning potential [11]. A child's neurodevelopment is remarkably sensitive to parental caregiving and home environment factors, especially during the first 1000 days of life. It is possible to reverse early delays in children, and the earlier the intervention, the greater the impact [13, 14].

Most, but not all, studies have found an increased risk of neurodevelopmental delays in CHEU compared to their CHUU peers. Previous studies have been limited by small sample sizes. Preterm birth, *in utero* ART exposure, maternal viremia and early child inflammatory markers have been associated with significantly poorer neurodevelopment among CHEU [15–17]. Studies have noted differences in language, social and motor skills, brain composition and structure, and altered cell-mediated immunity between CHEU and CHUU [9, 18, 19]. While biologic aetiologies of neurodevelopmental outcomes among CHEU have been assessed, there are fewer data on modifiable, social and behavioural factors that may synergistically influence neurodevelopmental outcomes. Women living with HIV are especially vulnerable to poverty, parental relationship instability, low paternal involvement, intimate partner violence (IPV) and poor maternal mental health; such factors may influence their ability to care responsively for their children and promote healthy neurodevelopment [12, 20–29].

Kenya alone is home to nearly one million CHEU for whom research is urgently needed to identify caregiver and home factors to reduce the risk of suboptimal child neurodevelopment [1]. In 2016, the World Health Organisation (WHO) recommended dolutegravir (DTG), an integrase strand transfer inhibitor, as first-line treatment for all adolescents and adults living with HIV, and in 2019, for women of reproductive age [30]. Prior to DTG scale-up, non-nucleoside reverse transcriptase inhibitor regimens containing efavirenz (EFV) were commonly used during pregnancy. *In utero* exposure to EFV-based regimens has been associated with neurodevelopmental deficits among 2-year-old CHEU in Botswana, compared to non-EFV-based regimens [31]. DTG-based regimens and EFV-based regimens have comparable safety in pregnancy [32]; however, there are few data on the impact of *in utero* DTG exposure on neurodevelopmental outcomes of CHEU. This study aimed to assess the associations between caregiver and household factors, HIV and ART exposure, and child neurodevelopment in Kenya.

2 | METHODS

2.1 | Study overview

The HOPE Study is an ongoing prospective longitudinal cohort in Kenya aimed to understand the impacts of HIV and ART exposure on infant health and development. Mothers living with and without HIV were recruited with their infants (1000 CHEU and 1000 CHUU) at 4–10 weeks of age during routine postnatal care at seven maternal and child health clinics across the Nairobi and Western Kenya regions between March 2021 and June 2022. Mother-infant pairs are being followed every 6 months until children reach 3 years. This exploratory analysis identified cofactors associated with child neurodevelopment among the subset of children who have reached age 1 year and had complete neurodevelopmental assessments by June 2023 (Figure S1).

2.2 | Data collection

2.2.1 | *Outcome ascertainment*

To measure child neurodevelopment, we administered the Malawi Developmental Assessment Tool (MDAT) [33], a validated test designed specifically for the SSA cultural context. The MDAT assessment generates scores for four domains, social, language, fine motor and gross motor, with 36–42 pass/fail items in each. Scripts for each item were translated and back-translated to Kiswahili and Dholou. Tests were administered by a trained assessor in the preferred language of the mother/caregiver and combined direct child observation and caregiver reporting. Once a child reached six consecutively failed items in a domain, the assessors moved on to the subsequent domains until all were complete. Assessments that were either incomplete (e.g. due to noisy environment, fussy child, assessor still completing training) or invalid (e.g. the assessment did not note six consecutive fails) were excluded from this analysis (Figure S1). Assessors underwent a rigorous training curriculum and each conducted ≥10 supervised practice assessments prior to certification and study start. We utilised a train-the-trainer approach involving six half-day didactic and practical sessions over the course of several weeks. Certified trainers then employed a similar training to all study nurses and routinely reviewed in-person and over video recordings to ensure consistency. MDAT scores were assessed as raw continuous scores per domain.

2.2.2 | *Exposures ascertainment*

A primary exposure of interest was maternal HIV status (CHEU vs. CHUU). Per national Kenyan guidelines, all pregnant women presenting with unknown HIV status are tested for HIV. Maternal HIV status was confirmed by self-report and review of medical records. Women living with and without HIV were enrolled into this study when their infants reached approximately 6 weeks of age. At health facilities, infants of children born to women living with HIV are tested for HIV DNA on dried blood spots at 6 weeks, 6 and 12 months and then tested using an HIV antibody test at 18 months. For this study, infant HIV status was abstracted from medical records at each time point to ensure CHEU remained HIV negative. A small subset of the 709 CHEU (n = 34) included in this analysis still had pending HIV test results by the time of this analysis. Other exposure variables collected at baseline (6 weeks postpartum) included maternal socio-demographic information, family characteristics, medical history and household factors. The gestational age of children was ascertained by maternal report and antenatal care medical records, and preterm birth was defined as less than 37 weeks of gestation.

The following mental health assessments were conducted: the 9-item Patient Health Questionnaire (PHQ-9, ≥10 cut-off) [34] for clinically significant, moderate-to-severe depression, 10-item Kessler Psychological Distress Scale

Table 1. Socio-demographic characteristics comparing CHEU and CHUU

Characteristic: *n* (%) or median (interquartile range)	Overall N = 1424	CHEU n = 709	CHUU n = 715	Unadjusted p-value
Region				
Nairobi	588 (41%)	272 (38%)	316 (44%)	ref
W Kenya	835 (59%)	437 (62%)	398 (56%)	**0.03**
Child sex is female	723 (51%)	348 (49%)	375 (52%)	0.2
Child age (weeks)	52 (52, 52)	52 (52, 53)	52 (52, 52)	0.6
Preterm birth (gestational age <37 weeks)	39 (2.7%)	21 (3.0%)	18 (2.5%)	0.6
Child is orphaned (maternally, paternally or both)	109 (7.7%)	71 (10%)	38 (5.3%)	**<0.001**
Exclusively breastfed at 6 weeks	1381 (97%)	695 (98%)	686 (96%)	**0.005**
Number of times breastfed in last 24 hours	14.0 (11.0, 16.0)	14.0 (12.0, 18.0)	14.0 (10.0, 16.0)	**<0.001**
Child has siblings	1126 (79%)	622 (88%)	504 (71%)	**<0.001**
Mother age (years)	29.0 (25.0, 33.0)	31.0 (27.0, 35.0)	27.0 (24.0, 31.0)	**<0.001**
Mother education, primary or less	540 (38%)	352 (50%)	188 (26%)	**<0.001**
Mother is employed (professionally or casually)	279 (20%)	142 (20%)	137 (19%)	0.7
Mother marital status				
Married (monogamous)	1112 (78%)	517 (73%)	595 (83%)	ref
Married (polygamous)	109 (7.7%)	79 (11%)	30 (4.2%)	**<0.001**
Steady partner	57 (4.0%)	22 (3.1%)	35 (4.9%)	0.2
Single, separated or widowed	144 (10%)	91 (13%)	53 (7.4%)	**<0.001**
Mother height (cm)	162 (158, 167)	162 (157, 167)	162 (158, 167)	0.2
Mother body mass index <18.5	41 (2.9%)	27 (3.8%)	14 (2.0%)	**0.04**
Moderate-to-severe household food insecurity	246 (17%)	181 (26%)	65 (9.1%)	**<0.001**
Moderate-to-severe maternal depression	47 (3.4%)	21 (3.1%)	26 (3.6%)	0.4
Moderate-to-severe maternal anxiety	113 (8.1%)	68 (9.9%)	45 (6.3%)	0.5
Moderate-to-severe maternal distress	135 (9.6%)	76 (11%)	59 (8.3%)	**0.01**
Maternal report of intimate partner violence	33 (2.4%)	14 (2.0%)	19 (2.7%)	0.1
Perceived level of social support				
High	972 (69%)	446 (63%)	526 (74%)	Ref
Medium	401 (28%)	227 (32%)	174 (24%)	**<0.001**
Low	45 (3.2%)	32 (4.5%)	13 (1.8%)	**<0.001**

Note: Table 1 presents basic child and maternal socio-demographic characteristics among the overall cohort of children ($n = 1424$), as well as comparing children who are HIV-exposed uninfected (CHEU, $n = 709$) and children who are HIV-unexposed uninfected (CHUU, $n = 715$). The unadjusted *p*-value indicates whether there was a statistically significant difference in each characteristic between the two comparison groups using a chi-squared test.
Unadjusted *p*-values that indicate statistical significance at the $p < 0.05$ level are bolded.
Abbreviations: CHEU, children who are HIV-exposed uninfected; CHUU, children who are HIV-unexposed uninfected.

(K10, ≥20 cut-off) [35, 36] for anxiety, the Multidimensional Scale of Perceived Social Support (MSPSS, ≤35 = low, 36–60 = medium, ≥61 = high) and the Hurt-Insult-Threaten-Scream (HITS, ≥10 cut-off) [37] for IPV. The degree of household food insecurity was assessed using the Household Hunger Scale [38]. Existing referral pathways in each of the participating clinics were identified for study nurses to refer caregivers and/or infants for psychiatric, IPV, child neurodevelopmental or nutritional support. Neurodevelopmental referrals were informed by failed "red flag" items on MDAT assessments. Additionally, mothers living with HIV were asked questions regarding HIV, experience with status disclosure to their partner, and ART initiation, duration and regimen. Data on maternal ART regimens were abstracted from medical records, including information on any regimen switches during or after pregnancy. The final models assessed the most recently prescribed regimen during pregnancy and compared mothers who most recently received DTG-based regimens compared to EFV-based regimens. We additionally compared the subset women who received DTG-only to those who received EFV-only.

2.3 | Data analysis

Descriptive statistics and univariable log-binomial models described differences between CHEU and CHUU (Table 1). Univariable and multivariable linear mixed effects models determined associations between neurodevelopment scores, HIV-exposure status and caregiver factors, adjusting for confounders selected *a priori*. We expected some degree of site-specific differences, as sites spanned across Nairobi and Western Kenya, and therefore, we included facility as a random intercept in all models. Mean MDAT scores at 1 year of age were compared between CHEU and CHUU, and scores were compared among all children to test for associations with caregiver cofactors. Potential confounders adjusted in multivariable analyses included preterm birth, maternal age (years), education level, marital status, and infant sex and age (weeks). Based on the literature, we expected these factors to be associated with exposures, such as maternal HIV status, and child neurodevelopment scores. Collinearity was examined using a threshold of 10% change in standard error and multivariable models included non-collinear variables univariately associated with neurodevelopment ($p < 0.05$). Exposures evaluated in the models included maternal depression, anxiety, distress (depression and/or anxiety), marital status, IPV, household food insecurity and absence of a biologic father (defined as either deceased or uninvolved in any way in the child's life, including physically, financially and emotionally). Among CHEU, MDAT scores were compared by maternal ART start timing (pre/post-pregnancy), HIV disclosure to partner (ever/never) and ART regimen (DTG, EFV or protease inhibitor [PI]-based).

2.4 | Ethical board approvals

The study was approved by the University of Washington's Institutional Review Board and the Kenyatta National Hospital's Ethical Review Committee. All participants provided written informed consent.

3 | RESULTS

3.1 | Study population

3.1.1 | All children (N = 1424)

This analysis used data collected from 709 CHEU and 715 CHUU mother-child pairs who had complete MDAT data. Compared to CHUU, CHEU had a comparable median age at 1-year neurodevelopmental assessment (52 weeks), proportion born preterm (3% each) and sex distribution (49% vs. 52% female) (Table 1). A greater proportion of CHEU had a father who was either deceased or absent from the child's life (10% vs. 5%). At baseline, mothers living with HIV were more likely to be older (31 vs. 27 years), with only primary school education (50% vs. 26%), have other children (88% vs. 71%), either single or widowed (13% vs. 7%) or in a polygamous marriage (11% vs. 4%), and report moderate-to-severe food insecurity (26% vs. 9%, $p < 0.01$ for all). Prevalence of depression, anxiety and IPV were similar between mothers with and without HIV.

3.1.2 | CHEU only (n = 709)

Among mothers living with HIV, all were on ART; 88% started ART pre-pregnancy, and 12% post-pregnancy (Table 2). At baseline, 88% of mothers had already disclosed their HIV status to their primary partner and had been taking ART for a median of 54 months (Interquartile Range [IQR]: 22–89). Of 608 mothers with data on ART regimen during pregnancy, the most recently used regimen during pregnancy was DTG-based (74%), followed by EFV-based (20%) and PI-based regimens (6%). Overall, 30% of mothers switched their ART regimen during pregnancy, and 66% of them had switched from EFV to DTG-based regimens. Table S1 summarises ART changes during pregnancy and the median duration of ART use.

Table 2. HIV and ART-related characteristics of CHEU population

Characteristic: *n* (%) or median (interquartile range)	*n* = 709
Child received ART prophylaxis by 6 weeks	693 (98%)
Child ART regimen	
AZT based	329 (47%)
NVP alone	364 (53%)
Unknown	*16*
Maternal ART start timing	
Pre-pregnancy	590 (88%)
Post-pregnancy	83 (12%)
Unknown	*36*
Most recent maternal ART regimen during pregnancy	
DTG based	448 (74%)
EFV based	122 (20%)
PI based or other	38 (6.3%)
Unknown	*101*
Mother switched ART regimen during pregnancy	191 (30%)
Unknown	*67*
Mother ART regimen changes during pregnancy	
DTG only	316 (52%)
DTG from EFV	129 (21%)
EFV only	110 (18%)
EFV from DTG	12 (2.0%)
Other regimens	38 (6.3%)
Unknown	*104*
Maternal duration on ART (months)	54.1 (22.2, 88.7)
Unknown	*131*
Disclosed HIV status to partner	622 (88%)

Note: Table 2 presents data on child and maternal HIV and ART-related characteristics among the subset of children who are HIV-exposed uninfected (CHEU) in this cohort (*n* = 709).
Abbreviations: ART, antiretroviral therapy; AZT, azithromycin; DTG, dolutegravir; EFV, efavirenz; NVP, nevirapine; PI, protease inhibitor.

3.2 | Cofactors of child neurodevelopment

3.2.1 | MDAT score comparison for CHEU versus CHUU

Overall, the CHEU and CHUU groups had comparable 1-year neurodevelopment scores across all domains, in both univariable and multivariable mixed linear effects models with site clustering and adjustment for infant age, sex, preterm birth, and maternal age, education and marital status (Table 3). CHEU exhibited statistically higher language scores than CHUU (adjusted coeff: 0.23, 95% CI: 0.06, 0.39, $p < 0.01$).

Table 3. Cofactors of MDAT scores at 1 year among overall cohort (CHEU and CHUU)

	Social, adjusted coeff (95% CI)	*p*	Language, adjusted coeff (95% CI)	*p*	Fine motor, adjusted coeff (95% CI)	*p*	Gross motor, adjusted coeff (95% CI)	*p*
ENTIRE COHORT—CHEU versus CHUU								
CHEU (ref: CHUU)—Unadjusted	−0.02 (−0.29, 0.25)	0.88	**0.21 (0.06, 0.37)**	**<0.01**	−0.01 (−0.20, 0.19)	0.96	0.15 (−0.08, 0.37)	0.20
CHEU (ref: CHUU)—Adjusted[a]	0.07 (−0.22, 0.36)	0.64	**0.23 (0.06, 0.39)**	**<0.01**	0.02 (−0.19, 0.23)	0.86	0.12 (−0.12, 0.36)	0.33
ENTIRE COHORT−adjusting for CHEU status[b]								
Child sex is male (ref: female)	**−0.46 (−0.72, −0.19)**	**<0.01**	**−0.18 (−0.33, −0.02)**	**0.02**	0.06 (−0.13, 0.25)	0.52	0.10 (−0.12, 0.32)	0.37
Child was born preterm	−0.29 (−1.10, 0.51)	0.47	−0.09 (−0.55, 0.38)	0.71	−0.23 (−0.80, 0.35)	0.44	**−1.38 (−2.05, −0.71)**	**<0.001**
Maternal mental health at 6 weeks postpartum								
Moderate/severe depression (PHQ-9 score ≥10)	−0.42 (−1.17, 0.32)	0.26	−0.02 (−0.45, 0.41)	0.92	−0.09 (−0.63, 0.44)	0.74	0.08 (−0.54, 0.70)	0.80
Moderate/severe anxiety (K10 score ≥20)	0.27 (−0.22, 0.77)	0.28	0.04 (−0.25, 0.32)	0.79	0.00 (−0.35, 0.35)	0.99	−0.33 (−0.74, 0.08)	0.11
Level of perceived social support (ref: High)	Ref		Ref		Ref		Ref	
Medium	−0.21 (−0.52, 0.09)	0.17	0.04 (−0.13, 0.22)	0.65	−0.09 (−0.30, 0.13)	0.44	**−0.31 (−0.56, −0.06)**	**0.02**
Low	−0.12 (−0.88, 0.64)	0.76	0.07 (−0.37, 0.50)	0.77	0.43 (−0.12, 0.97)	0.12	−0.09 (−0.72, 0.54)	0.78
Family factors at 6 weeks postpartum								
Deceased or absent biologic father	0.15 (−0.35, 0.65)	0.56	−0.16 (−0.45, 0.12)	0.26	−0.27 (−0.63, 0.08)	0.13	−0.02 (−0.44, 0.39)	0.91
Intimate partner violence (HITS score ≥10)	−0.08 (−0.96, 0.80)	0.86	0.28 (−0.23, 0.79)	0.28	**−0.76 (−1.40, −0.13)**	**0.02**	**−1.07 (−1.81, −0.33)**	**<0.01**
Moderate to severe household food insecurity	**−0.37 (−0.73, −0.01)**	**0.047**	−0.06 (−0.27, 0.15)	0.58	0.01 (−0.25, 0.27)	0.96	−0.21 (−0.51, 0.09)	0.17
Marital status (ref: Married—monogamous)	Ref		Ref		Ref		Ref	
Married—polygamous	−0.26 (−0.76, 0.25)	0.32	0.01 (−0.28, 0.30)	0.92	−0.12 (−0.48, 0.24)	0.52	0.25 (−0.17, 0.67)	0.25
Steady partner, not married	−0.40 (−1.08, 0.27)	0.25	−0.07 (−0.46, 0.32)	0.72	−0.32 (−0.80, 0.16)	0.20	−0.06 (−0.62, 0.50)	0.84
Single or widowed	−0.19 (−0.63, 0.25)	0.40	−0.10 (−0.35, 0.16)	0.46	−0.21 (−0.53, 0.11)	0.20	−0.02 (−0.39, 0.35)	0.90

Note: Table 3 presents results from multivariate mixed effects linear models testing for associations between multiple factors and child neurodevelopmental scores at 1 year of age across four domains (social, language, fine motor and gross motor), among the overall cohort. The first models compared domain scores between CHEU and CHUU, unadjusted and then adjusted for infant sex, age, preterm birth, and maternal age, education and marital status; subsequent models adjusted for CHEU status, infant sex, age and preterm birth. Bolded results highlighted in green represent statistically significant findings.

Abbrevitaions: CHEU, children who are HIV-exposed uninfected; CI, confidence interval; CHUU, children who are HIV-unexposed uninfected; HITS, Hurt, Insult, Threaten, Scream Assessment Tool; K10, Kessler Psychological Distress Scale; MDAT, Malawi Developmental Assessment Tool; PHQ-9, Patient Health Questionnaire.

[a]Multivariable mixed effects linear models adjusted for infant age and sex, preterm birth, and maternal age and marital status.

[b]Multivariable mixed effects linear models adjusted for infant age and sex, preterm birth and maternal HIV status (child is CHEU vs. CHUU).

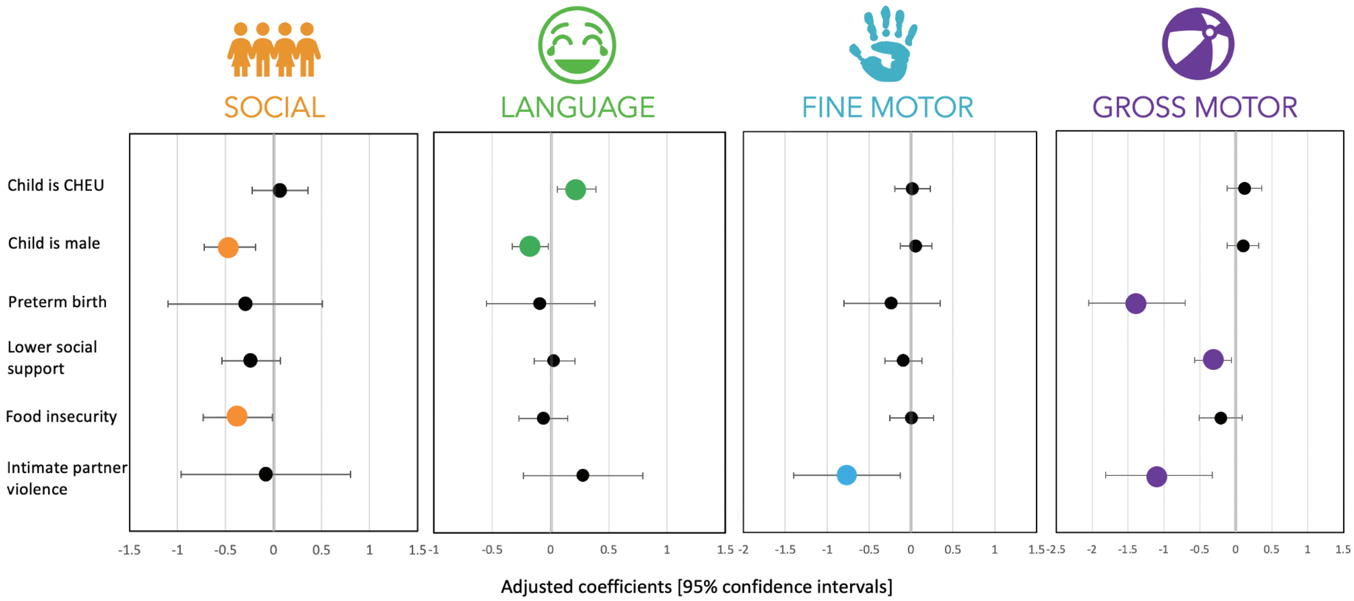

Figure 1. Forest plot of statistically significant cofactors of neurodevelopment among all children. These forest plots present important cofactors of neurodevelopmental scores within the four tested neurodevelopmental domains (social, language, fine motor and gross motor), among all children in this cohort. The small black dots in the forest plots represent the adjusted coefficients with 95% confidence intervals, within each neurodevelopmental domain, and the coloured dots represent the statistically significant findings. Abbreviation: CHEU, children who are HIV-exposed uninfected.

3.2.2 | Entire cohort, adjusting for CHEU status

Compared to female children, male children scored significantly lower in the social (adjusted coeff: −0.46, 95% CI: −0.72, −0.19, $p < 0.01$) and language domains (adjusted coeff: −0.18, 95% CI: −0.33, −0.02, $p = 0.02$) (Table 3 and Figure 1). Children born preterm scored lower in gross motor than children born full-term (adjusted coeff: −1.38, 95% CI: −2.05, −0.71, $p < 0.001$). IPV was significantly associated with lower fine motor (adjusted coeff: −0.76, 95% CI: −1.40, −0.13, $p = 0.02$) and gross motor scores (adjusted coeff: −1.07, 95% CI: −1.81, −0.33, $p < 0.01$). Moderate-to-severe food insecurity was associated with lower social scores (adjusted coeff: −0.37, 95% CI: −0.73, −0.01, $p = 0.047$). Lower gross motor scores were associated with lower levels of maternal perceived social support (adjusted coeff: −0.31, 95% CI: −0.56, −0.06, $p = 0.02$), but not with other mental health measures.

3.2.3 | CHEU only

Consistent with analyses among all children, male CHEU scored significantly lower than female CHEU in the social domain (adjusted coeff: −0.58, 95% CI: −0.97, −0.20, $p < 0.01$) and CHEU born preterm scored significantly lower in the gross motor domains compared to CHEU born full-term (adjusted coeff: −1.00, 95% CI: −1.95, −0.05, $p = 0.04$) (Table 4 and Figure 2). Lower gross motor scores were observed among CHEU with deceased or absent fathers (adjusted coeff: −0.81, 95% CI: −1.58, −0.05, $p = 0.04$) and lower fine motor scores were observed among CHEU with single or widowed mothers (adjusted coeff: −0.45, 95% CI: −0.87, −0.03, $p = 0.04$), compared to CHEU with monogamously married mothers.

Neurodevelopment was significantly associated with the maternal ART regimen used during pregnancy. Gross motor scores were significantly lower with most-recent *in utero* exposure to EFV-based regimens than DTG-based regimens (adjusted coeff: −0.47, 95% CI: −0.92, −0.02, $p = 0.04$). This finding remained the same in sensitivity analyses comparing CHEU exposed exclusively to EFV to those exposed exclusively to DTG (Table 4), as well as in analyses restricted to full-term infants only (data not shown).

4 | DISCUSSION

In this cohort of 1-year-old children, we found that CHEU and CHUU had comparable neurodevelopment scores and, unexpectedly, CHEU had higher scores in the language domain. Among all children, lower child neurodevelopment scores were associated with male sex, preterm birth, lower perceived level of social support, and maternal report of IPV and food insecurity. Among CHEU only, lower child neurodevelopment scores were also associated with having a deceased or absent father, single or widowed mother and *in utero* exposure to EFV-based ART regimens.

Reassuringly, CHEU in this study had similar neurodevelopmental scores to their HIV-unexposed peers which could be explained by more recent universal test and treat guidelines for people living with HIV and newer, improved ART regimens using DTG-based combinations. We observed that CHEU had higher language scores, a surprising finding, given that other studies have found a higher risk of language and motor skill

Table 4. Cofactors of MDAT scores among CHEU alone

	Social, adjusted coeff (95% CI)	*p*	Language, adjusted coeff (95% CI)	*p*	Fine motor, adjusted coeff (95% CI)	*p*	Gross motor, adjusted coeff (95% CI)	*p*
Child sex is male (ref: female)[a]	**−0.58 (−0.97, −0.20)**	**<0.01**	−0.17 (−0.38, 0.05)	0.14	−0.05 (−0.33, 0.22)	0.71	−0.03 (−0.35, 0.30)	0.88
Child was born preterm[a]	−0.32 (−1.45, 0.80)	0.57	−0.05 (−0.69, 0.59)	0.88	−0.12 (−0.93, 0.70)	0.78	**−1.00 (−1.95, −0.05)**	**0.04**
Maternal mental health at 6 weeks postpartum[a]								
Moderate/severe depression (PHQ-9 score ≥10)	0.05 (−1.11, 1.20)	0.94	0.02 (−0.63, 0.68)	0.94	−0.08 (−0.92, 0.77)	0.86	−0.50 (−1.48, 0.48)	0.32
Moderate/severe anxiety (K10 score ≥20)	0.33 (−0.32, 0.97)	0.32	−0.13 (−0.49, 0.24)	0.50	−0.07 (−0.53, 0.40)	0.79	−0.19 (−0.74, 0.36)	0.49
Level of perceived social support (ref: High)	Ref		Ref		Ref		Ref	
Medium	−0.24 (−0.66, 0.18)	0.26	0.07 (−0.17, 0.31)	0.57	−0.17 (−0.47, 0.14)	0.29	−0.26 (−0.61, 0.10)	0.16
Low	−0.16 (−1.09, 0.76)	0.73	−0.07 (−0.60, 0.45)	0.69	0.10 (−0.57, 0.78)	0.76	−0.43 (−1.21, 0.36)	0.29
Family factors at 6 weeks postpartum[a]								
Deceased or absent father	0.27 (−0.64, 1.18)	0.56	−0.44 (−0.96, 0.07)	0.09	−0.38 (−1.04, 0.27)	0.26	**−0.81 (−1.58, −0.05)**	**0.04**
Intimate partner violence (HITS score ≥10)	−0.05 (−1.43, 1.34)	0.95	0.44 (−0.35, 1.23)	0.28	−0.08 (−1.09, 0.93)	0.87	−0.96 (−2.13, 0.23)	0.11
Marital status (ref: Married—monogamous)	Ref		Ref		Ref		Ref	
Married—polygamous	0.03 (−0.58, 0.64)	0.92	0.16 (−0.19, 0.51)	0.37	−0.26 (−0.71, 0.18)	0.25	0.00 (−0.52, 0.51)	0.99
Steady partner, not married	−0.67 (−1.80, 0.45)	0.24	−0.22 (−0.86, 0.41)	0.50	−0.46 (−1.28, 0.36)	0.27	−0.72 (−1.67, 0.23)	0.14
Single or widowed	0.23 (−0.35, 0.82)	0.43	−0.08 (−0.41 0.23)	0.63	**−0.45 (−0.87, −0.03)**	**0.04**	−0.04 (−0.52, 0.46)	0.89
Moderate to severe household food insecurity	−0.37 (−0.82, 0.08)	0.11	0.03 (−0.22, 0.28)	0.83	0.02 (−0.31, 0.35)	0.91	−0.11 (−0.49, 0.27)	0.56

(Continued)

Table 4. (Continued)

	Social, adjusted coeff (95% CI)	*p*	Language, adjusted coeff (95% CI)	*p*	Fine motor, adjusted coeff (95% CI)	*p*	Gross motor, adjusted coeff (95% CI)	*p*
Maternal ART characteristics[a]								
Disclosed HIV status by 6 weeks postpartum	0.13 (−0.52, 0.78)	0.69	0.03 (−0.34, 0.40)	0.88	−0.02 (−0.49, 0.45)	0.94	0.23 (−0.32, 0.77)	0.42
Mother started ART post-pregnancy (ref: pre-pregnancy)	0.05 (−0.56, 0.67)	0.88	0.21 (−0.13, 0.56)	0.23	0.26 (−0.18, 0.71)	0.25	0.38 (−0.13, 0.91)	0.15
Duration on ART (months)	0.00 (−0.00, 0.01)	0.78	−0.00 (−0.00, 0.00)	0.59	−0.00 (−0.00, 0.00)	0.61	−0.00 (−0.01, 0.00)	0.20
Most recently prescribed ART regimen during pregnancy (ref: DTG based)	Ref		Ref		Ref		Ref	
EFV based	−0.19 (−0.74, 0.35)	0.50	0.09 (−0.21, 0.39)	0.56	0.11 (−0.28, 0.49)	0.59	**−0.47 (−0.92, −0.02)**	**0.045**
PI based	0.45 (−0.39, 1.29)	0.29	0.11 (−0.34, 0.56)	0.64	0.16 (−0.43, 0.75)	0.60	0.02 (−0.68, 0.72)	0.96
ART changes during pregnancy (ref: DTG only)	Ref		Ref		Ref		Ref	
DTG, switched from EFV	0.04 (−0.49, 0.58)	0.87	0.26 (−0.03, 0.55)	0.08	−0.20 (−0.58, 0.17)	0.29	−0.26 (−0.71, 0.18)	0.25
EFV only	−0.05 (−0.65, 0.54)	0.86	0.18 (−0.14 0.50)	0.29	0.12 (−0.30, 0.54)	0.57	**−0.52 (−1.01, −0.03)**	**0.04**
EFV, switched from DTG	−0.99 (−2.44, 0.45)	0.18	0.06 (−0.72, 0.85)	0.87	−0.44 (−1.46, 0.59)	0.41	−0.76 (−1.97, 0.45)	0.22
Other regimens	0.48 (−0.37, 1.33)	0.27	0.18 (−0.28, 0.64)	0.44	0.12 (−0.48, 0.72)	0.71	−0.06 (−0.78, 0.65)	0.87

Note: Table 4 presents results from multivariate mixed effects linear models testing for associations between multiple factors and child neurodevelopmental scores at 1 year of age across four domains (social, language, fine motor and gross motor), among subset of CHEU only. Models adjusted for infant sex, age, preterm birth, and maternal age, education and marital status. Bolded text in the model results represents statistically significant findings.

Abbreviations: ART, antiretroviral therapy; CHUU, children who are HIV-unexposed uninfected; CI, confidence interval; DTG, dolutegravir; EFV, efavirenz; HITS, Hurt, Insult, Threaten, Scream Assessment Tool; K10, Kessler Psychological Distress Scale; MDAT, Malawi Developmental Assessment Tool; PHQ-9, Patient Health Questionnaire; PI, protease inhibitor.

[a]Multivariable mixed effects linear models adjusted for infant age and sex, preterm birth, and maternal age, education and marital status.

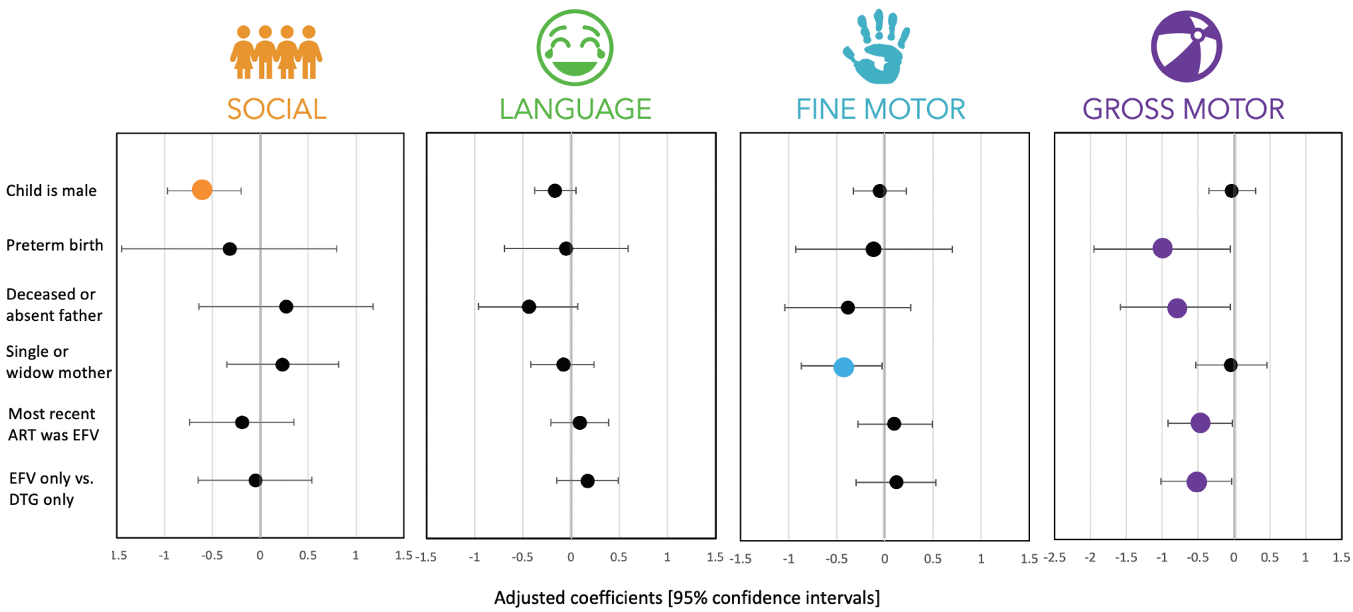

Figure 2. Forest plot of statistically significant cofactors of neurodevelopment, among CHEU only. ART, antiretroviral therapy; CHEU, child who is HIV-exposed uninfected; DTG, dolutegravir; EFV, efavirenz. These forest plots present important cofactors of neurodevelopmental scores within the four tested neurodevelopmental domains (social, language, fine motor and gross motor), among the subset of CHEU only. The small black dots in the forest plots represent the adjusted coefficients with 95% confidence intervals, within each neurodevelopmental domain, and the coloured dots represent the statistically significant findings. Abbreviation: CHEU, children who are HIV-exposed uninfected.

delays in CHEU. It is possible that having more siblings (as seen in CHEU) could impact language development, but this finding warrants further investigation. Neurodevelopmental differences between CHEU and CHUU in other studies have been linked to altered brain composition and structure, immune function, adverse birth outcomes and growth faltering [9, 16, 18, 19, 39–42]. In an extensive meta-analysis of 21 studies comparing neurodevelopment between CHEU and CHUU under 5 years, 57% of studies found subtle delays among CHEU in at least one domain, and primarily in the language and gross motor domains [40]. Included studies had relatively small sample sizes, and relied on studies published prior to May 2020 prior to newer HIV treatment guidelines.

The effects of ART regimens on CHEU neurodevelopment have been studied with mixed results [40]. To the best of our knowledge, our study is the first to assess CHEU neurodevelopment in a largely DTG-exposed cohort. DTG has superior efficacy, less frequent drug resistance and comparable safety during pregnancy compared to EFV-based regimens [32]. EFV-based regimens have been associated with a higher risk of microcephaly and other neurologic disorders among CHEU [43]. We found that *in utero* EFV-exposed CHEU scored significantly lower in gross motor than DTG-exposed CHEU, even when accounting for regimen switches during pregnancy. A study in Botswana among 2-year-old CHEU found that *in utero* EFV exposure was associated with significantly poorer language and motor skills, compared to exposure to non-EFV-regimens (abacavir/ZDV/lamivudine or PI-based regimens) [31]. Moreover, EFV-exposed children had longer ART exposure than children exposed to other regimens, and longer EFV exposure was associated with more pronounced deficits [31]. In our study, women on EFZ had longer ART duration than those on DTG and a higher likelihood of pre-pregnancy ART use (Table S1). To disentangle the potential collinearity of duration and EFZ exposure, we compared EFZ and DTG in a subset of women with pre-pregnancy use of ART (Table S2). In this analysis, the association of EFZ with lower gross motor scores persisted, albeit not significantly, likely due to the much smaller sample. In addition, in the overall CHEU cohort, the duration of ART was not associated with lower gross motor scores. Together, these findings suggest that the effect may be related to EFZ exposure rather than ART duration. Despite WHO recommendation, DTG uptake has remained suboptimal in SSA among reproductive-aged women, partly due to initial concerns around neural tube defects [44]. Over time, the vast majority of mothers living with HIV will be on DTG-based regimens, making it impossible to discern the impact of DTG-based regimens. Our study was conducted in the opportune period of changing regimen implementation, providing a unique opportunity to examine the impact of different regimens.

Maternal marital status, absence of a biologic father, IPV and food insecurity were significantly associated with lower child neurodevelopment scores. Parental relationship conflict and household violence can threaten a child's neurodevelopment [22, 45–51]. Over a quarter of women of reproductive age in eastern Africa were estimated to have experienced IPV in the past year [26, 52, 53]; the prevalence of IPV among Kenyan pregnant women is estimated to be approximately 10%, with almost all perpetrators being a current or former husband or partner [54]. Among Kenyan women, previous experiences with IPV were strongly predictive of incident IPV during pregnancy and postpartum, and could serve as an important screening tool for women at increased risk of IPV [54, 55]. A large meta-analysis of psychological therapies for women experiencing IPV concluded that individualised counselling and therapy was beneficial. The standard of care for Kenyan women living with HIV includes referrals to IPV counsellors; however, barriers to successful referral include disclosure of IPV and low rates of referral uptake [56]. A randomised controlled trial tested an intervention package, which included IPV-centred training for HIV care providers, an onsite IPV counsellor for immediate support, and pictorial take-home materials for clients, all tailored for women attending HIV services in Nairobi, Kenya. Compared to the standard of care, this intervention was associated with a significantly higher likelihood of IPV disclosure, as well as improved mental health, desire to adhere to ART treatment to prevent vertical transmission and eagerness to take actions to improve their home situations [57]. Implementing similar programmes to better identify and support women living with HIV who are experiencing IPV during pregnancy and postpartum could provide benefits for CHEU, but have yet to be tested.

Abuse and separation can often lead to disproportionate burdens on women, leading to financial hardship, childcare responsibility and social stigma [58, 59]. However, separation in abusive relationships may benefit parents and children. Studies from Western nations show that children with separated parents who co-parent have better neurodevelopmental outcomes than children whose parents stay together with persistent conflict, but this has yet to be studied in the SSA context [60, 61]. Couples affected by HIV separate frequently during pregnancy/postpartum when HIV testing is common. HIV-serodifferent couples in which the female is living with HIV separate significantly more often than couples in which the male is living with HIV [62]. Paternal involvement can improve birth outcomes, parental satisfaction, maternal engagement with care, and child growth and development [63–68]. Rwanda's *Sugira Muryango ("Strengthen the Family")*, a nationally scaled home-delivered IPV-reduction intervention, has successfully reduced acts of abuse, and improved paternal engagement, paternal and maternal mental health, relationship satisfaction and child neurodevelopment [69–72]. This or similar interventions could be adopted within maternal child health or prevention of vertical transmission programmes in Kenya. Food insecurity has been significantly associated with a greater risk of IPV among Kenyan women living with HIV, as well as a greater risk of preterm birth, which we found to be strongly associated with neurodevelopmental delay among CHEU [73]. Multifactorial interventions to address food insecurity and IPV among pregnant women living with HIV are urgently needed. Ensuring the safety and nutritional health of women and infants during pregnancy and breastfeeding will be paramount to protect CHEU from neurodevelopmental delay and growth faltering [74–78].

Among all children, regardless of *in utero* HIV exposure, the male sex was associated with lower MDAT scores, a finding not previously observed [41, 42]. Historically, child sex bias has skewed clinical diagnoses for neurodevelopmental disorders and intellectual delays towards boys, most notably in autism spectrum disorder [79]. Research into the mechanistic pathways of such neurodevelopmental sex differences has found complex interactions between different behavioural expression, biologic and environmental factors [80]. Further assessment into possible interactions between male child sex and paternal absence is necessary.

Our study has several strengths, including its large sample size and longitudinal design. This large cohort assessed ART regimen heterogeneity during pregnancy, including the contemporaneous DTG-based regimens, and is currently undergoing 6-monthly neurodevelopment assessments until children reach 3 years which will allow for future longitudinal analyses. We conducted the MDAT assessment, which was developed specifically for use in SSA, and relies on both direct child observation and caregiver report. Limitations of the study include the enrolment of infants at 6 weeks of age, which may result in selection bias, as we excluded infants potentially at greatest risk of neurodevelopmental delay (e.g. preterm and/or hospitalised infants, or infants who did not return for their standard 6-week visit). Additionally, 11% of our study population were lost-to-follow-up by their 12-month visit; as a result, mother-infant pairs who were disengaged in routine postnatal care and who could be at elevated risk of poorer outcomes were excluded. Loss-to-follow-up among CHEU in Kenya remains high and is associated with poor child growth and being orphaned, both risk factors for poor neurodevelopment [81]. A small proportion (5%) of our 1-year-old CHEU population had pending HIV test results at the time of analysis, posing a risk for misclassification of child HIV status. We anticipate that <1% of these children would be misclassified based on available data for the other 1-year-olds in the cohort. Another limitation of our study is that we did not confirm the HIV-negative status of mothers of CHUU at 1 year postpartum; however, we anticipate few women (~1%) would have seroconverted between 6 weeks and 12 months postpartum. Our analysis assessed factors collected at baseline to assess associations with 1-year neurodevelopment; longitudinal analyses using repeated measures on caregiver exposures, such as relationship factors or mental health, are needed to improve the estimation of these associations. The cofactors discussed in this paper were identified through exploratory analyses and may have some degree of false discovery; confirmatory analyses are needed. Some mothers were missing ART data, and analyses assessing ART exposures were only conducted among those with ART data. Our study does not capture mothers <18 years old, mothers not engaged in postnatal care or prevention of vertical transmission programmes and children whose mothers died prior to the child reaching 6 weeks of age. Differential misclassification and recall bias could have influenced findings if mothers with psychological distress and/or mothers living with HIV were more likely to recall factors that influenced their wellbeing and child neurodevelopment. Nurses conducting MDAT assessments were unblinded to maternal HIV status, which could have introduced bias, irrespective of the lack of difference between CHEU and CHUU. The COVID-19 pandemic led to viral load testing shortages in Kenya, limiting our ability to assess the role of maternal viral load on CHEU neurodevelopment.

5 | CONCLUSIONS

In this cohort of Kenyan CHEU and CHUU, biologic and social factors were associated with 1-year neurodevelopment.

CHEU and CHUU had similar neurodevelopmental scores across all domains and may be due to the high frequency of DTG use during pregnancy but warrants further investigation. Among CHEU, *in utero* exposure to DTG-based regimens was associated with higher gross motor scores, compared to EFV-based regimens. Maternal marital status, father absence, IPV and food insecurity were associated with poorer neurodevelopmental scores. Rigorous longitudinal and mixed methods research are needed to identify modifiable factors among families impacted by HIV and caregiver relationship conflict. It is critical to develop strategies to incorporate neurodevelopmental screening programmes into health systems in SSA with clear referral pathways that equip healthcare workers and caregivers to identify early signs of delays, and to design multi-factorial interventions that best support children at the highest risk of suboptimal outcomes.

AUTHORS' AFFILIATIONS

[1]Department of Global Health, University of Washington, Seattle, Washington, USA; [2]Department of Epidemiology, University of Washington, Seattle, Washington, USA; [3]Kenyatta National Hospital, Nairobi, Kenya; [4]Department of Pediatrics and Child Health, University of Nairobi, Nairobi, Kenya; [5]Departments of Pediatrics, Medicine, University of Washington, Seattle, Washington, USA; [6]Department of Medicine, University of Washington, Seattle, Washington, USA

COMPETING INTERESTS

The authors have no competing interests to disclose.

AUTHORS' CONTRIBUTIONS

The initial research question was developed by MAB, GJ-S, IN and SB-N. SB-N, MK, DC, HM, LG, DW, AO, KM, MC and GN conducted and oversaw data collection. MAB and KAL led data management and cleaning. MAB led data analysis and interpretation, with close input from GJ-S, IN, SB-N, ADW, JN and DW. The manuscript was first developed by MAB and GJ-S, and all authors reviewed, contributed to and approved the manuscript for publication.

ACKNOWLEDGEMENTS

We thank the mothers and children who participated in this study, and the anonymous reviewers whose comments greatly improved our analysis and manuscript.

FUNDING

The HOPE Study is funded by the National Institutes of Health's National Institute of Child Health and Human Development (4R33HD103079, PI: John-Stewart), the National Institutes of Health Fogarty International Center (K43TW011422-01A1, PI: Njuguna) and the National Institute of Mental Health (K01MH121124, PI: Wagner).

DISCLAIMER

The sponsors did not play any role in the study design, execution of data collection or analysis, manuscript preparation or decision to submit for publication.

DATA AVAILABILITY STATEMENT

Data may be made available by authors GJ-S and SB-N, upon reasonable request.

REFERENCES

1. UNAIDS. UNAIDS Spectrum Estimates. AIDSinfo: people living with HIV receiving ART. https://aidsinfo.unaids.org. 2023. Last accessed July 2, 2023.
2. Slogrove AL, Becquet R, Chadwick EG, Côté HCF, Essajee S, Hazra R, et al. Surviving and thriving-shifting the public health response to HIV-exposed uninfected children: report of the 3rd HIV-Exposed Uninfected Child Workshop. Front Pediatr. 2018;6:157.
3. Slogrove A, Powis KM, Johnson LF, Stadler JAM, Nhapi RT, Barnett W, et al. Estimates of the global population of children who are HIV-exposed and uninfected, 2000–18: a modeling study. Lancet Glob Health. 2020;8(1):67–75.
4. Wedderburn CJ, Yeung S, Rehman AM, Stadler JAM, Nhapi RT, Barnett W, et al. Neurodevelopment of HIV-exposed uninfected children in South Africa: outcomes from an observational birth cohort. Lancet Child Adolesc Health. 2019;3(11):P803–13.
5. Mcgrath CJ, Nduati R, Richardson BA, Kristal AR, Mbori-Ngacha D, Farquhar C, et al. The prevalence of stunting is high in HIV-1-exposed uninfected infants in Kenya. J Nutr. 2012;142(4):757–63.
6. Kuhn L, Sinkala M, Semrau K, Kankasa C, Kasonde P, Mwiya M, et al. Elevations in mortality associated with weaning persist into the second year of life among uninfected children born to HIV-infected mothers. Clin Infect Dis. 2010;50(3):437–44.
7. Slogrove AL. It is a question of equity: time to talk about children who are HIV-exposed and "HIV-free". J Int AIDS Soc. 2021;24(11):e25850.
8. Anderson K, Kalk E, Madlala HP, Nyemba DC, Kassanjee R, et al. Increased infectious-cause hospitalization among infants who are HIV-exposed uninfected compared with HIV-unexposed. AIDS. 2021;35(14):2327–39.
9. Mchenry MS, Mcateer CI, Oyungu E, Mcdonald BC, Bosma CB, Mpofu PB, et al. Neurodevelopment in young children born to HIV-infected mothers: a meta-analysis. Pediatrics. 2018;141(2):e20172888.
10. Makasa M, Kasonka L, Chisenga M, Sinkala M, Chintu C, Tomkins A, et al. Early growth of infants of HIV-infected and uninfected Zambian women. Trop Med Int Health. 2007;12(5):594–602.
11. Grantham-McGregor S, Cheung YB, Cueto S, Glewwe P, Richter L, Strupp BJ. Developmental potential in the first 5 years for children in developing countries. Lancet. 2007;369(9555):60–70.
12. Engle PL, Black MM, Behrman JR, Cabral De Mello M, Gertler PJ, Kapiriri L, et al. Strategies to avoid the loss of developmental potential in more than 200 million children in the developing world. Lancet. 2007;369(9557):229–42.
13. Blair C, Raver CC. New directions for prevention and intervention. Acad Pediatr. 2016;16(3 Suppl):S30–6.
14. Jeong J, Franchett EE, Ramos De Oliveira CV, Rehmani K, Yousafzai AK. Parenting interventions to promote early child development in the first three years of life: a global systematic review and meta-analysis. PLoS Med 2021;18(5):e1003602.
15. Caniglia EC, Patel K, Huo Y, Williams PL, Kapetanovic S, Rich KC, et al. Atazanavir exposure in utero and neurodevelopment in infants: a comparative safety study. AIDS. 2016;30(8):1267–78.
16. Le Roux SM, Donald KA, Kroon M, Phillips TK, Lesosky M, Esterhuyse L, et al. HIV viremia during pregnancy and neurodevelopment of HIV-exposed uninfected children in the context of universal antiretroviral therapy and breastfeeding: a prospective study. Pediatr Infect Dis J. 2019;38(1):70–5.
17. Sevenoaks T, Wedderburn CJ, Donald KA, Barnett W, Zar HJ, Stein DJ, et al. Association of maternal and infant inflammation with neurodevelopment in HIV-exposed uninfected children in a South African birth cohort. Brain Behav Immun. 2021;91:65–73.
18. Abu-Raya B, Kollmann TR, Marchant A, Macgillivray DM. The immune system of HIV-exposed uninfected infants. Front Immunol. 2016;7:383.
19. Wedderburn CJ, Groenewold NA, Roos A, Yeung S, Fouche J-P, Rehman AM, et al. Early structural brain development in infants exposed to HIV and antiretroviral therapy in utero in a South African birth cohort. J Int AIDS Soc. 2022;25(1):e25863.
20. O'donnell KJ, Glover V, Barker ED, O'connor TG. The persisting effect of maternal mood in pregnancy on childhood psychopathology. Dev Psychopathol. 2014;26(2):393–403.
21. Huizink AC, Robles De Medina PG, Mulder EJH, Visser GHA, Buitelaar JK. Stress during pregnancy is associated with developmental outcome in infancy. J Child Psychol Psychiatry. 2003;44(6):810–8.
22. World Health Organization (WHO). WHO Report: INSPIRE: Seven strategies for Ending Violence Against Children. https://www.who.int/publications/i/item/inspire-seven-strategies-for-ending-violence-against-children. 2016. Last accessed July 2, 2023.
23. WHO, UNICEF. NURTURING CARE for Early Childhood Development: a framework for helping children survive and thrive to transform health and human potential. 2018.
24. Madlala HP, Myer L, Malaba TR, Newell M-L. Neurodevelopment of HIV-exposed uninfected children in Cape Town, South Africa. PLoS One. 2020;15(11):e0242244.

25. Porter L, Hao L, Bishai D, Serwadda D, Wawer MJ, Lutalo T, et al. HIV status and union dissolution in sub-Saharan Africa: the case of Rakai, Uganda. Demography. 2004;41(3):465–82.
26. Wagman JA, Charvat B, Thoma ME, Ndyanabo A, Nalugoda F, Ssekasanvu J, et al. Intimate partner violence as a predictor of marital disruption in rural Rakai, Uganda: a longitudinal study. Int J Public Health. 2016;61(8):961–70.
27. Bhatia DS, Harrison AD, Kubeka M, Cecilia M, Angela K, Francis B, et al. The role of relationship dynamics and gender inequalities as barriers to HIV-serostatus disclosure: qualitative study among women and men living with HIV in Durban, South Africa. Front Public Health. 2017;5:188.
28. Choko AT, Kumwenda MK, Johnson CC, Sakala DW, Chikalipo MC, Fielding K, et al. Acceptability of woman-delivered HIV self-testing to the male partner, and additional interventions: a qualitative study of antenatal care participants in Malawi. J Int AIDS Soc. 2017;20(1):21610.
29. Bulterys MA, Mujugira A, Nakyanzi A, Wyatt MA, Kamusiime B, Kasiita V, et al. “Him leaving me—that is my fear now”: a mixed methods analysis of relationship dissolution between Ugandan pregnant and postpartum women living with HIV and their male partners. AIDS Behav. 2022;27:1776–92. https://doi.org/10.1007/s10461-022-03910-3.
30. World Health Organization (WHO). Update on the transition to dolutegravir-based antiretroviral therapy: report of a WHO meeting, 29–30 March 2022. 2022.
31. Cassidy AR, Williams PL, Leidner J, Mayondi G, Ajibola G, Makhema J, et al. In utero efavirenz exposure and neurodevelopmental outcomes in HIV-exposed uninfected children in Botswana. Pediatr Infect Dis J. 2019;38(8):828–34.
32. Zash R, Jacobson DL, Diseko M, Mayondi G, Mmalane M, Essex M, et al. Comparative safety of dolutegravir-based or efavirenz-based antiretroviral treatment started during pregnancy in Botswana: an observational study. Lancet Glob Health. 2018;6(7):e804–10.
33. Gladstone M, Lancaster GA, Umar E, Nyirenda M, Kayira E, Van Den Broek NR, et al. The Malawi Developmental Assessment Tool (MDAT): the creation, validation, and reliability of a tool to assess child development in rural African settings. PLoS Med. 2010;7(5):e1000273.
34. Kroenke K, Spitzer RL, Williams JBW. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med. 2001;16(9):606–13.
35. Andersen LS, Grimsrud A, Myer L, Williams DR, Stein DJ, Seedat S. The psychometric properties of the K10 and K6 scales in screening for mood and anxiety disorders in the South African Stress and Health study. Int J Methods Psychiatr Res. 2011;20(4):215–23.
36. Kessler RC, Barker PR, Colpe LJ, Epstein JF, Gfroerer JC, Hiripi E, et al. Screening for serious mental illness in the general population. Arch Gen Psychiatry. 2003;60(2):184–9.
37. Sherin KM, Sinacore JM, Li XQ, Zitter RE, Shakil A. HITS: a short domestic violence screening tool for use in a family practice setting. Fam Med. 1998;30(7):508–52.
38. Food and Nutrition Technical Assistance (FANTA). Household Hunger Scale (HHS): indicator definition and measurement guide. https://www.fantaproject.org/monitoring-and-evaluation/household-hunger-scale-hhs. Last accessed on July 2, 2023.
39. Le Doaré K, Bland R, Newell M-L. Neurodevelopment in children born to HIV-infected mothers by infection and treatment status. Pediatrics. 2012;130(5):e1326–44.
40. Wedderburn CJ, Weldon E, Bertran-Cobo C, Rehman AM, Stein DJ, Gibb DM, et al. Early neurodevelopment of HIV-exposed uninfected children in the era of antiretroviral therapy: a systematic review and meta-analysis. Lancet Child Adolesc Health. 2022;6(6):393–408.
41. Sirajee R, Conroy AL, Namasopo S, Opoka RO, Lavoie S, Forgie S, et al. Growth faltering and developmental delay in HIV-exposed uninfected Ugandan infants: a prospective cohort study. J Acquir Immune Defic Syndr. 2021;87(1):730–40.
42. Ntozini R, Chandna J, Evans C, Chasekwa B, Majo FD, Kandawasvika G, et al. Early child development in children who are HIV-exposed uninfected compared to children who are HIV-unexposed: observational sub-study of a cluster-randomized trial in rural Zimbabwe. J Int AIDS Soc. 2020;23(5):e25456.
43. Williams PL, Yildirim C, Chadwick EG, Van Dyke RB, Smith R, Correia KF, et al. Surveillance Monitoring for ART Toxicities (SMARTT) study of the Pediatric HIV/AIDS Cohort Study. Association of maternal antiretroviral use with microcephaly in children who are HIV-exposed but uninfected (SMARTT): a prospective cohort study. Lancet HIV. 2020;7(1):e49–58.
44. Romo ML, Patel RC, Edwards JK, Humphrey JM, Musick BS, Bernard C, et al. Disparities in dolutegravir uptake affecting females of reproductive age with HIV in low- and middle-income countries after initial concerns about teratogenicity: an observational study. Ann Intern Med. 2022;175(1):84–94.
45. Overbeek M, de Schipper JC, Willemen A, Lamers-Winkelman F, Schuengel C. Mediators and treatment factors in intervention for children exposed to interparental violence. J Clin Child Adolesc Psychol. 2017;46:411–27.
46. Garriga A, Pennoni F. The causal effects of parental divorce and parental temporary separation on children’s cognitive abilities and psychological well-being according to parental relationship quality. Soc Indic Res. 2020;161:963–87.
47. Xerxa Y, Rescorla LA, Serdarevic F, Van Ijzendorn MH, Jaddoe VW, Verhulst FC, et al. The complex role of parental separation in the association between family conflict and child problem behavior. J Clin Child Adolesc Psychol. 2020;49(1):79–93.
48. Walker SP, Wachs TD, Meeks Gardner J, Lozoff B, Wasserman GA, Pollitt E, et al. Child development: risk factors for adverse outcomes in developing countries. Lancet. 2007;369(9556):145–57.
49. Walker SP, Wachs TD, Grantham-Mcgregor S, Black MM, Nelson CA, Huffman SL, et al. Inequality in early childhood: risk and protective factors for early child development. Lancet. 2011;378(9799):1325–38.
50. Ramos De Oliveira CV, Sudfeld CR, Muhihi A, Mccoy DC, Fawzi WW, Masanja H, et al. Association of exposure to intimate partner violence with maternal depressive symptoms and early childhood socioemotional development among mothers and children in rural Tanzania. JAMA Netw Open. 2022;5(12):e2248836.
51. Chawla A, Chan A. Intimate partner violence associated with poor socioemotional development in children. 2023.
52. UN Women. What is intimate partner violence? An interactive guide. https://interactive.unwomen.org/multimedia/infographic/violenceagainstwomen/en/index.html#intimate-2. 2021. Last accessed on July 2, 2023.
53. Dagnew GW, Asresie MB, Fekadu GA, Gelaw YM. Factors associated with divorce from first union among women in Ethiopia: further analysis of the 2016 Ethiopia demographic and health survey data. PLoS One. 2020;15(12):e0244014.
54. Stiller M, Bärnighausen T, Wilson ML. Intimate partner violence among pregnant women in Kenya: forms, perpetrators and associations. BMC Womens Health. 2022;22(1):210.
55. Oseso LN, Krakowiak D, Nduati R, Farquhar C, Kinuthia J, Osoti AO, et al. Past intimate partner violence (IPV) predicts incident IPV during pregnancy and postpartum in pregnant women in Kisumu, Kenya. Int J Gynaecol Obstet. 2022;159(1):290–6.
56. Undie C-C, Maternowska MC, Mak’anyengo M, Askew I. Is routine screening for intimate partner violence feasible in public health care settings in Kenya? J Interpers Violence. 2016;31(2):282–301.
57. Haberland N, Ndwiga C, Mccarthy K, Pulerwitz J, Kosgei R, Mak’anyengo M, et al. Addressing intimate partner violence and power in intimate relationships in HIV testing services in Nairobi, Kenya. AIDS Behav. 2020;24(8):2409–20.
58. Holden KC, Smock PJ. The Economic Costs of Marital Dissolution: why do women bear a disproportionate cost? Annu Rev Sociol. 1991;17:51–78.
59. Ntoimo LF, Odimegwu CO. Health effects of single motherhood on children in sub-Saharan Africa: a cross-sectional study. BMC Public Health. 2014;14(1):1145.
60. Hardesty JL, Ogolsky BG, Raffaelli M, Whittaker A, Crossman KA, Haselschwerdt ML, et al. Coparenting relationship trajectories: marital violence linked to change and variability after separation. J Fam Psychol. 2017;31(7):844–54.
61. Clark AE. Breaking up for the kids’ sake: evidence from a British Birth Cohort. Psychology. 2015.
62. Mackelprang RD, Bosire R, Guthrie BL, Choi RY, Liu A, Gatuguta A, et al. High rates of relationship dissolution among heterosexual HIV-serodiscordant couples in Kenya. AIDS Behav. 2014;18(1):189–93.
63. Van Den Berg W, Brittain K, Mercer G, Peacock D, Stinson K, Janson H, et al. Improving men’s participation in preventing mother-to-child transmission of HIV as a maternal, neonatal, and child health priority in South Africa. PLOS Med. 2015;12(4):e1001811.
64. Wolf S, Mccoy DC. Household socioeconomic status and parental investments: direct and indirect relations with school readiness in Ghana. Child Dev. 2019;90(1):260–78.
65. Wilson S, Durbin CE. Effects of paternal depression on fathers’ parenting behaviors: a meta-analytic review. Clin Psychol Rev. 2010;30(2):167–80.
66. Eddy MM, Thomson-de Boor H, Mphaka K. “So we are ATM fathers”: a study of absent fathers in Johannesburg. South Africa: University of Johannesburg; 2013.
67. Sherr L, Croome N. Involving fathers in prevention of mother to child transmission initiatives–what the evidence suggests. J Int AIDS Soc. 2012;15(Suppl 2):17378.
68. Drysdale RE, Slemming W, Makusha T, Richter LM. Father involvement, maternal depression and child nutritional outcomes in Soweto, South Africa. Matern Child Nutr. 2021;17(Suppl 1):e13177.

69. Betancourt TS, Jensen SKG, Barnhart DA, Brennan RT, Murray SM, Yousafzai AK, et al. Promoting parent–child relationships and preventing violence via home-visiting: a pre-post cluster randomised trial among Rwandan families linked to social protection programmes. BMC Public Health. 2020;20(621). https://doi.org/10.1186/s12889-020-08693-7
70. Jensen SK, Placencio-Castro M, Murray SM, Brennan RT, Goshev S, Farrar J, et al. Effect of a home-visiting parenting program to promote early childhood development and prevent violence: a cluster-randomized trial in Rwanda. BMJ Glob Health. 2021;6:e003508.
71. Barnhart DA, Farrar J, Murray SM, Brennan RT, Antonaccio CM, Sezibera V, et al. Lay-worker delivered home visiting promotes early childhood development and reduces violence in Rwanda: a randomized pilot. J Child Fam Stud. 2020;29:1804–17.
72. The Evaluation Fund. Active coaching for early childhood development: a father-engaged home-visiting program. The Evaluation Fund: Reducing Violence Against Children. https://theevaluationfund.org/wp-content/uploads/2019/06/Rwanda-Active-Coaching-for-Early-Childhood-Development.pdf. 2020. Last accessed on July 2, 2023.
73. Hatcher AM, Weiser SD, Cohen CR, Hagey J, Weke E, Burger R, et al. Food insecurity and intimate partner violence among HIV-positive individuals in rural Kenya. Am J Prev Med. 2021;60(4):563–8.
74. Ndiaye A, Suneson K, Njuguna I, Ambler G, Hanke T, John-Stewart G, et al. Growth patterns and their contributing factors among HIV-exposed uninfected infants. Matern Child Nutr. 2021;17(2):e13110.
75. Le Roux SM, Abrams EJ, Donald KA, Brittain K, Phillips TK, Nguyen KK, 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;3(4):234–44.
76. Deichsel EL, Pavlinac PB, Mbori-Ngacha D, Walson JL, Maleche-Obimbo E, Farquhar C, et al. Maternal diarrhea and antibiotic use are associated with increased risk of diarrhea among HIV-exposed, uninfected infants in Kenya. Am J Trop Med Hyg. 2020;102(5):1001–8.
77. Lane CE, Bobrow EA, Ndatimana D, Ndayisaba GF, Adair LS. Determinants of growth in HIV-exposed and HIV-uninfected infants in the Kabeho Study. Matern Child Nutr. 2019;15(3):e12776.
78. Nyemba DC, Kalk E, Madlala HP, Malaba TR, Slogrove AL, Davies M-A, et al. Lower birth weight-for-age and length-for-age z-scores in infants with in-utero HIV and ART exposure: a prospective study in Cape Town, South Africa. BMC Pregnancy Childbirth. 2021;21(1):354.
79. Polyak A, Rosenfeld JA, Girirajan S. An assessment of sex bias in neurodevelopmental disorders. Genome Med. 2015;7(1):94.
80. May T, Adesina I, Mcgillivray J, Rinehart NJ. Sex differences in neurodevelopmental disorders. Curr Opin Neurol. 2019;32(4):622–26.
81. Braitstein P, Katshcke A, Shen C, Sang E, Nyandiko W, Ochieng VO, et al. Retention of HIV-infected and HIV-exposed children in a comprehensive HIV clinical care programme in Western Kenya. Trop Med Int Health. 2010;15(7):833–41.

SUPPORTING INFORMATION

Additional information may be found under the Supporting Information tab for this article:

Table S1: Maternal ART changes during pregnancy, and median duration of ART use.

Table S2: Associations between maternal ART regimen and child neurodevelopment scores, among mothers who started ART pre-pregnancy.

Figure S1: Consort diagram of study participants.

Ruff A et al. *Journal of the International AIDS Society* 2023, **26**(S4):e26158
http://onlinelibrary.wiley.com/doi/10.1002/jia2.26158/full | https://doi.org/10.1002/jia2.26158

JIAS
JOURNAL OF THE INTERNATIONAL AIDS SOCIETY

RESEARCH ARTICLE

A trial of nurturing care among children who are HIV-exposed and uninfected in eSwatini

Andrea Ruff[1,§], Xolisile Dlamini[2,#], Bareng AS Nonyane[1], Nicole Simmons[1], Duncan Kochelani[3,#], Fiona Burtt[4,#], Fakazi Mlotshwa[3,#], Ncamsile Gama[3,#], Esca Scheepers[4], Kathrin Schmitz[4], Lethokuhle Simelane[3,#], Lynn M. Van Lith[3] and Maureen M. Black[5,6]

[§]**Corresponding author**: Andrea Ruff, Johns Hopkins Bloomberg School of Public Health, Johns Hopkins University, 615 N. Wolfe Street, Baltimore, MD 21205, USA. Tel: +410 955 1633. (aruff1@jhu.edu)
[#]Affiliation at the time the study was conducted.
Clinical Trial Number: NCT04114305 (Evaluation of an Early Childhood Development Intervention Among Children Born to HIV-Infected Women in eSwatini)

Abstract

Introduction: Children who are HIV-exposed and uninfected (CHEU) are a growing population at potential risk of poor neurocognitive development. We tested a nurturing care intervention on children's neurocognitive development and maternal depressive symptoms (primary) with mediation through caregiving activities (secondary).

Methods: This study was conducted among six intervention and nine comparison antenatal-care/prevention of vertical transmission (ANC/PVT) HIV clinics in eSwatini. We enrolled pregnant women and measured infant development at 9 and 18 months. mothers2mothers (m2m) designed and implemented the clinic-home-community-based intervention. We measured infants' neurodevelopment, maternal depressive symptoms and caregiving activities with the Mullen Scales of Early Learning (MSEL), Edinburgh Postnatal Depression Scale, HOME Inventory and Family Care Indicators. We fitted linear mixed effects regression models with clinic random effects to compare intervention versus comparison arms, and generalised structural equation models to evaluate mediation, adjusting for confounders.

Results: Mother-infant pairs (n = 429) participated between January 2016 through May 2018. Socio-demographic characteristics were balanced between arms except for higher rates of peri-urban versus rural residence and single versus married mothers in the comparison group. The 18 month retention was 82% (180/220) intervention, 79% (166/209) comparison arm, with 25 infant deaths. Intervention MSEL scores were significantly, and modestly, higher in receptive language (55.7 [95% CI 54.6, 56.9] vs. 53.7 [95% CI 52.6, 54.8]), expressive language (42.5 [95% CI 41.6, 39.8] vs. 40.8 [95% CI 39.8, 41.7]) and composite MSEL (85.4 [95% CI 83.7, 84.5] vs. 82.7 [95% CI 81.0, 84.5]), with no difference in maternal depressive symptoms or in observations of mother-child interactions. Intervention book-sharing scores were higher (0.63 vs. 0.41) and mediated the effect on MSEL scores (indirect effect, p-values ≤ 0.024). The direct effects on visual reception and expressive language scores were significantly higher in the intervention compared to the comparison arm (coefficients 1.93 [95% CI 0.26, 3.60] and 1.66 [95% CI 0.51, 2.79, respectively]).

Conclusions: Nurturing care interventions can be integrated into ANC/PVT clinic-home-community programmes. The intervention, mediated through interactive caregiving activities, increased language development scores among CHEU. Partnering with a local team, m2m, to design and implement a culturally relevant intervention illustrates the ability to impact parent-child play and learning activities that are associated with children's neurodevelopment.

Keywords: CHEU; child development; HIV prevention; intervention; mothers to mothers; nurturing care

Additional information may be found under the Supporting Information tab of this article.

Received 20 January 2023; **Accepted** 21 August 2023

1 | INTRODUCTION

Paediatric HIV acquisitions have declined significantly, largely due to the expansion of antenatal-care/prevention of vertical transmission (ANC/PVT) programmes [1]. The population of children who are HIV-exposed and uninfected (CHEU) has increased substantially, with risks of morbidity and mortality, preterm birth, growth faltering and potential effects on neurodevelopment [2]. Several studies found no differences in neurodevelopmental scores between uninfected children living with and without HIV exposure [3–6], but others [7–9], including two meta-analyses [10, 11], found lower neurodevelopmental scores among CHEU, compared to children who are HIV unexposed. Variability in samples and environmental exposures associated with HIV, such as stress and depression, limited coping strategies and economic resources, stigma, violence, and drugs and alcohol, may explain the variable results [12].

Early neurodevelopment lays the foundation for academic and economic capabilities [13]. Nurturing care [14] supports children's development and promotes supportive caregiving along the life-course from conception through childhood and into adulthood [15]. During infancy, caregiving activities, including book-sharing and story-telling, have been positively associated with neurodevelopment [16–18]. Early child development (ECD) programmes have demonstrated significant improvements in children's neurodevelopment [19, 20], including for children with HIV [21, 22]. Nurturing care interventions have been recommended for all children [14] and may be effective among CHEU.

eSwatini's introduction of life-long antiretroviral therapy (ART) for pregnant women provided an opportunity to test the effectiveness of a nurturing care intervention among mothers with HIV and their exposed children within a national PVT programme. We tested two hypotheses: that a nurturing care-based intervention would improve children's neurodevelopment and mothers' mental health (primary) and that caregiving activities would mediate the effects on neurodevelopment (secondary).

2 | METHODS

We implemented a design using six mothers2mothers (m2m)-supported clinics (intervention) and nine clinics supported by PEPFAR partners (comparison), matched on providing PVT under the national AIDS programme, lifetime ART, comparable number of women HIV positive, DNA PCR testing for children and location within 2.5 hours of the capital, Mbabane. Exclusion criteria were high rates of client mobility and implementation of nurturing care interventions (Figure 1).

2.1 | Intervention

We collaborated with m2m, an African nonprofit organisation supporting women, children and their families which is integrated into eSwatini national programmes [23]. m2m designed and implemented the intervention by translating nurturing care principles into culturally appropriate activities (Table S1). They hired women living with HIV as Mentor Mothers [24] and trained them in maternal care and ECD, including sensitivity to women living with HIV, using a home-based intervention, and behaviour change strategies, a reference manual, a flipbook with key messages, and culturally and age-appropriate information for families.

The nurturing care intervention included home visits (biweekly through infant age 12 months, monthly through 24 months), community parenting groups and individual counselling during clinic visits. Mentor Mothers were trained to maintain friendly, mutually respectful and positive relationships with participating mothers and families. They discussed growth stages, provided picture books and coached caregivers on interactive play, story-telling, and book-sharing and recorded contacts in family folders and visit checklists. The intervention began prenatally and continued through the infant age 2 years. Comparison clinics received usual care.

2.2 | Sample size and study design

To estimate sample size, we used the age-normed standardisation sample of the Mullen Scales of Early Learning (MSEL) (mean 100, standard deviation 15), with a difference of 0.5 standard deviations (7.5 points). Participants were selected by site (cluster). We used the clustersampsi procedure in Stata version 12 [25], initially using six clusters per arm. Based on a similar ECD study [26], we set the intra-cluster correlation at 0.04 and allowed for a coefficient of variation among cluster participants of 0.31, resulting in an average of 27 participants per cluster to achieve 80% power and 7.5 points between-arm difference, with 0.05 Type 1 error. Repeating the estimate with nine clusters per arm, an average cluster size of 15, and a coefficient of variation of 0.29, yielded an intra-cluster correlation up to 0.06 with 80% power to detect 7.5 points between arms with 0.05 Type 1 error. We over-enrolled to allow for 30% loss-to-follow-up.

2.3 | Procedures

Participants were recruited from ANC clinics. Inclusion criteria were third trimester of pregnancy, confirmed HIV positive, intention to remain in the clinic catchment area for 18 months and ability to consent. Mentor Mothers and nurses informed clinic participants about the study; research staff verified eligibility and obtained informed consent. Ethical approval was granted by Institutional Review Board at the Johns Hopkins Bloomberg School of Public Health and the Scientific and Ethics Committee of the Ministry of Health in eSwatini; written consent was obtained from all participants. Between January and August 2016, we enrolled pregnant women and followed them through the child age 18 months. We collected data using tablets with Magpi software.

The evaluation team included site coordinators who conducted routine follow-up visits, and ECD assessors, who were unaware of intervention status. At enrolment, site coordinators collected demographic and contact information, abstracted data from patient-held HIV and maternal health cards and administered baseline assessments.

Two weeks after delivery and at child ages 3, 6, 9 and 18 months, site coordinators conducted clinic-based follow-up interviews with mothers. At 12–15 months, site coordinators

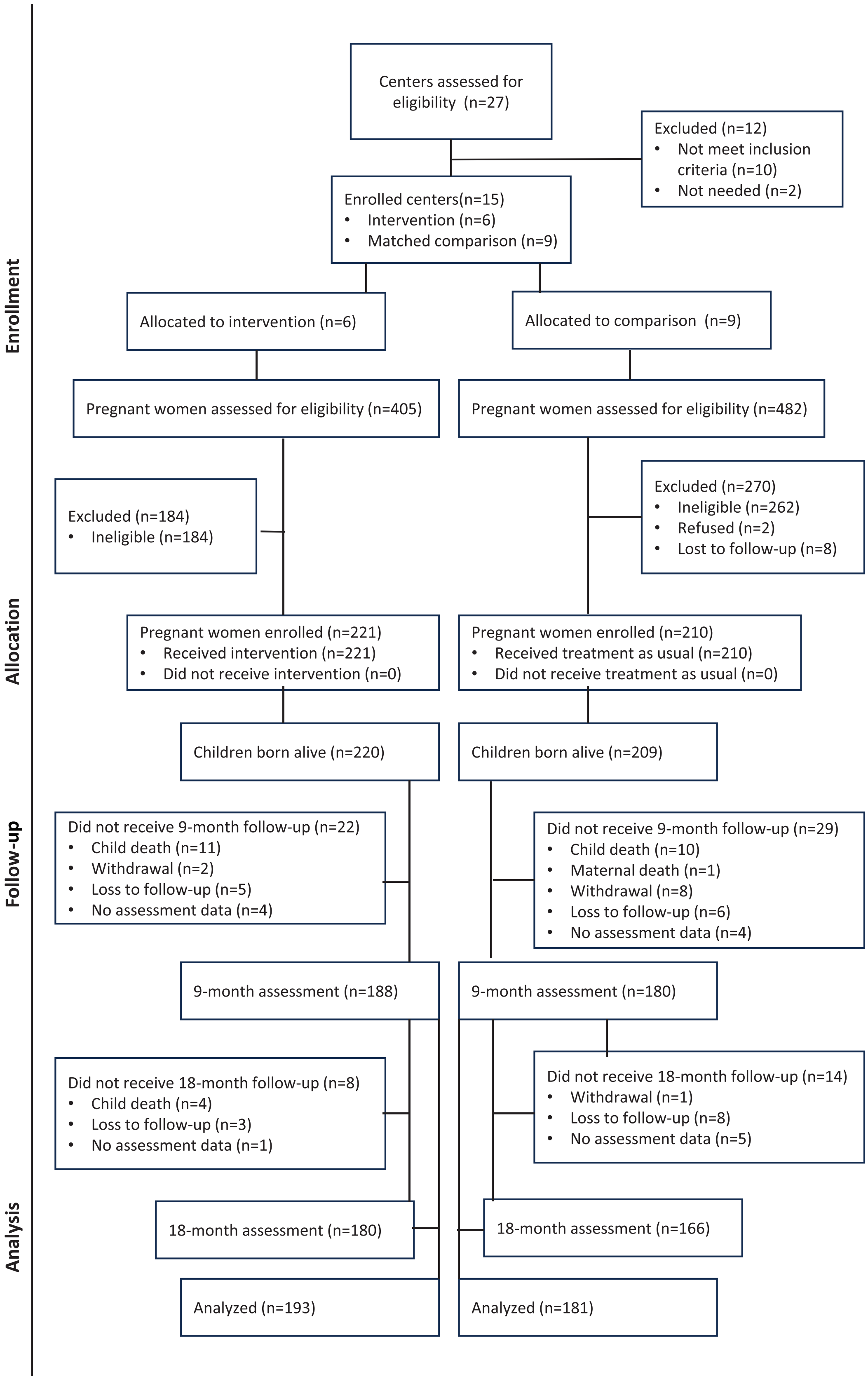

Figure 1. Consort diagram.

conducted home-visit observations. At 9 and 18 months, ECD assessors measured children's neurodevelopment and growth, and maternal depression and caregiving practices. To ensure that ECD assessors were unaware of the study arm, children and caregivers were transported to one of three centralised assessment stations that served both intervention and comparison arms; ECD assessors had no other contact with participants or children during the study.

2.4 | Measures

We selected measures that captured children's neurodevelopment and represented contextual variables from the nurturing care framework that support neurodevelopment, including maternal depression, caregiving behaviours and the home environment. We prioritised measures that had been standardised and validated with mothers and young children globally, preferably in Africa.

Items from all measures were culturally adapted for eSwatini, translated into siSwati and back-translated. We conducted pilot testing on non-study mothers and children from well-child visits, with modification to materials and procedures as necessary to ensure cultural appropriateness while retaining rigour.

2.4.1 | *Neurodevelopment*

We evaluated neurodevelopment using the MSEL [27], an individually administered assessment with excellent psychometric properties, used with CHEU in Uganda and Malawi [4]. It measures fine motor, gross motor, visual reception, receptive language and expressive language domains, and composite MSEL general cognitive ability. Raw scores were converted to age-adjusted standard scores, based on published norms (mean = 100, standard deviation [SD] = 15). Comparisons between arms were interpreted from a population perspective, based on SD differences in the distribution. ECD assessors were trained by a licensed child development professional, supplemented by MSEL observations conducted among CHEU in a companion project in Zimbabwe. Inter-rater reliability (Kappa) among 40 children scored by both ECD assessors at each time point ranged from 0.980 to 0.996.

2.4.2 | *Growth*

Site coordinators measured length (cm), weight (kg) and mid-upper arm circumference (cm) in triplicate using a digital scale and stadiometer. Measurements were converted into WHO growth standards z-scores: weight-for-age, length-for-age, weight-for-length and mid-upper-arm circumference-for-age [28]. Underweight, wasting and stunting were defined as < -2 weight-for-age, weight-for-length and length-for-age z-scores, respectively.

2.4.3 | *HIV testing*

Site coordinators assessed infant HIV testing abstracting data from participant-held maternal health/ANC and HIV cards and well childcare and child HIV cards, postnatal care and child welfare registers at the clinics, and caregiver-report. Over 90% of children had a DNA PCR test done within 60 days of age. Compliance at 9 months was: intervention 65% (131/201) and comparison 57% (110/192). At 18 months, overall compliance was 43% (167/386) with little difference between study arms.

2.4.4 | *Maternal mental health*

Maternal depressive symptoms were measured using the Edinburgh Postnatal Depression Scale (EPDS) [29], a 10-item measure of depressive symptoms, validated in South Africa [30]. The 4-point response choices (0–3) were summed, with scores of 0–30. High scores indicate increased symptom severity. We defined scores ≥13 as depression based on findings of 76.0% sensitivity, 81.8% specificity and 57.6% positive predictive value among South African women [31].

2.4.5 | *Household characteristics and caregiving practices*

Household information was obtained during the baseline interview. The Family Care Indicator scale (FCI) [32, 33] was used to measure maternal caregiving activities: in the last 3 days, an adult engaged in six caregiving activities (reading/looking/sharing picture books, telling stories, singing songs, taking child out from house, playing with toys and naming/counting/drawing). Scores were yes (1) or no (0).

The Infant-Toddler version of the Home Observation for the Measurement of the Environment (HOME) inventory was used to assess mother-child interactions [34]. After pilot testing, we retained 16 Yes/No items. During the 12- to 15-month home visit, site coordinators spent 40 minutes observing mother-child interactions. Scores were summed; high scores indicated more responsive mother-child interactions. Inter-rater reliability (Kappa) exceeded 0.90.

2.4.6 | *Contamination assessment*

Participants were asked about their contact with m2m and exposure to ECD information.

2.5 | Statistical analyses

We fitted linear mixed models for neurodevelopment scores at 9 and 18 months separately and across both time points, with random effects for clinic and child-within-clinic, and we evaluated time by arm interactions. We evaluated potential confounding of demographic variables on composite MSEL by fitting separate regressions, including study arm and potential confounders. We defined confounders as changing the mean study arm effects by >10% and changing the inference (confidence interval and *p*-value).

We conducted a contamination sensitivity analysis by excluding comparison arm mothers who reported m2m/ECD contact and re-running the linear mixed models for composite MSEL.

For maternal depression, we present the numbers and percentages of mothers with EPDS scores ≥13 at baseline (enrolment), 9 and 18 months. We used log-binomial generalised estimating equations to test whether changes in depression prevalence differed by study arm over time, and linear mixed models to evaluate whether baseline maternal depression was associated with composite MSEL.

To analyse the quality of mother-child interactions, we report the median (interquartile range) of HOME Inventory items observed. To analyse the FCIs, we report percentages (95% confidence intervals) of mother-endorsed caregiving activities (0–6).

We fitted a generalised structural equation model (GSEM) in STATA to evaluate mediation by caregiving activities on the relation between study arm and 18-month MSEL scores, adjusting for marital status and setting (rural vs. peri-urban). For parameter estimation, we used STATA's default mean-variance adaptive Gauss-Hermite quadrature estimation and 1001 iterations. The GSEM model included two paths, (1) an indirect path of a generalised linear model (glm) with a logit link for associating caregiving activity and study arm (binary outcome and mediator), and a Gaussian model within an identity link for MSEL score regressed on caregiving activity and (2) a direct path linking MSEL score regressed on study arm. Robust variance estimation accounted for site clustering. Total, direct and indirect coefficients were extracted using STATA's nlcom (non-linear combinations of estimators).

3 | RESULTS

We enrolled 431 pregnant women (221 intervention and 210 comparison) (Figure 1) with 429 children born alive (220 intervention and 209 comparison). Retention at the 18-month evaluation was 82% (180/220) intervention and 79% (166/209) comparison. Two participating mothers died, one per arm and 26 children died (16 intervention, 10 comparison). Two children (0.5%) had positive HIV tests, one per arm, and were retained. Most mothers accompanied their children to the assessments (9 months, 95.9% and 18 months, 87.5%). Attempts were made to contact non-attending mothers by telephone to complete the assessments. Retention in well childcare did not differ by arm: 161/220 (73.2%) intervention and 140/209 (67%) comparison.

Arms were balanced across number of children, maternal education, employment, timing of maternal ART treatment (54.5% prior to pregnancy), socio-economic status and utilities, including water, electricity and toilet facilities (Table 1). The comparison group was more likely to reside in peri-urban areas and less likely to own farmland and to be married. Most mothers had attended high school and were unemployed (~70%).

3.1 | Neurodevelopment

Mean intervention arm scores were higher than comparison arm scores at 9 months in receptive language (55.7 [54.6, 56.8] vs. 53.7 [52.6, 54.8], p-value 0.02); and at 18 months in expressive language (42.5 [41.6, 43.5] vs. 40.8 [39.8, 41.7], $p = 0.01$) and composite MSEL (85.4 [83.7, 87.2] vs. 82.7 [81.0, 84.4] $p = 0.03$) (Table 2).

For each domain, except gross motor, there was a significant decline in standard scores from 9 to 18 months (Table S2). Mean declines ranged from 9.4 points in fine motor to 25.1 points in expressive language (p-values < 0.001), and 31 points in composite MSEL. Across all domains, the time-by-arm interaction terms were statistically non-significant. No socio-demographic characteristics significantly confounded the association between study arm and MSEL outcomes (Table S4).

3.2 | Maternal depression

Comparison arm mothers had a higher prevalence of depression at baseline (83/181 [45.9%] vs. 66/193 [34.2%] $p < 0.021$) (see Table 1); reduced to 16.3% and 13.5% at 9 months, and 13.0% and 18.6% at 18 months, respectively. Random effects regression confirmed significant reduction in the comparison arm (prevalence ratio [PR] 0.35 [0.24, 0.49]) at 9 months, with no difference between study arms (time-by-arm interaction PR 1.14 [95% CI 0.68, 1.89]). At 18 months, the comparison arm reduction was significant (0.28 [0.18, 0.42]) and the intervention arm reduction attenuated, compared to the comparison arm (time-by-arm interaction PR 1.86 [1.06, 3.27]). Maternal baseline depression was not significantly associated with composite MSEL score across 9 and 18 months (mean effect 0.77 [−1.02, 2.55]).

3.3 | Growth

The prevalence of stunting (Table S3) increased significantly to over 35% from 9 to 18 months across arms. There were no intervention effects on growth.

3.4 | Caregiving activities

Median HOME Inventory scores were relatively high with no significant differences between the intervention and comparison arms (15 [13, 16], 16 [14, 16], respectively) and no associations with the composite MSEL score.

Among the six caregiving activities in the FCIs (Table 3), intervention-arm mothers were more likely to report book-sharing, story-telling and possessing children's books than comparison-arm mothers.

3.5 | Caregiving activities and mediation analysis

Mediation GSEM models were comprised of hypothesised direct effects: *study arm→MSEL scores* plus indirect effect: *study arm→book-sharing→MSEL scores*. The indirect paths (mediation) were associated with increased scores across all MSEL domains (Table 4), p-values ≤ 0.024. These indirect effects made up at least 45% of the total (direct + indirect) effects (Table S5).

3.6 | Intervention contamination sensitivity analysis

Twenty-four comparison arm mothers reported m2m/ECD contact. Excluding these mothers in a sensitivity analysis did not change the results (composite 18-month MSEL scores: 85.5 [83.9, 87.2 vs. 82.5 [80.7, 84.3], $p = 0.015$).

4 | DISCUSSION

This evaluation of a nurturing care intervention integrated into public antenatal clinics by Mentor Mothers and directed towards mothers of CHEU had three major findings. First, the intervention had significant effects on children's receptive

Table 1. Baseline characteristics of households, mothers and children with Mullen Scales of Early Learning (MSEL) assessments at 9 or 18 months

	Comparison *n* (%) *n* = 181	Intervention *n* (%) *n* = 193	*p*-value*
Sex			
Female	86 (47.5)	95 (49.2)	0.83
Male	95 (52.5)	98 (50.8)	
Number of other children			
0	33 (18.2)	29 (15.0)	0.86
1	57 (31.5)	60 (31.1)	
2	50 (27.6)	58 (30.1)	
3+	40 (22.1)	41 (21.2)	
Missing	1 (0.6)	5 (2.6)	
Mother's education			
Never attended	16 (8.80	21 (10.9)	0.14
Grades 1–2	4 (2.2)	1 (0.5)	
Standard 1–5	46 (25.4)	57 (29.5)	
Form 1–4	74 (40.9)	80 (40.5)	
Form 5	30 (16.6)	23 (11.9)	
University	8 (4.4)	2 (1.0)	
Missing	3 (1.7)	9 (4.7)	
Marital status			
Currently married	82 (45.3)	100 (51.8)	<0.001
Never married	49 (27.1)	64 (33.2)	
Other[a]	49 (27.1)	18 (9.3)	
Missing	1 (0.6)	11 (5.7)	
Employment status			
Unemployed	122 (67.4)	135 (70)	0.4
Employed	58 (32)	53 (27.5)	
Missing	1 (0.6)	5 (2.6)	
Timing of ART initiation			0.44
Before pregnancy	94 (51.9)	110 (57.3)	
During pregnancy	81 (44.8)	74 (38.5)	
After pregnancy	2 (1.1)	5 (2.6)	
Missing	4 (2.2)	4 (1.6)	
***SES quartile**			
Most poor	42 (23.2)	54 (28)	0.25
2	40 (22.1)	52 (26.9)	
3	65 (35.9)	53 (27.5)	
Least poor	31 (17.1)	29 (15)	
Missing	3 (1.7)	5 (2.6)	
Type of residence			
Rural	94 (51.9)	147 (71.2)	<0.001
Peri-urban	86 (47.5)	41 (21.2)	
Missing	1 (0.6)	5 (2.6)	
Electricity in household			
No	74 (40.9)	96 (49.7)	0.069
Yes	104 (57.5)	92 (47.7)	
Missing	3 (1.7)	5 (2.6)	
Clean/running water in household			
No	85 (47)	104 (53.9)	0.133
Yes	94 (51.9)	84 (43.5)	
Missing	2 (1.1)	5 (2.6)	
Toilet type			
Pit latrine/none	166 (91.7)	183 (94.8)	0.082
Flush/pour	12 (6.6)	5 (2.6)	
Missing	3 (1.7)	5 (2.6)	
Maternal depression status at baseline			
EPDS<13	98 (54.1)	127 (65.8)	0.021
EPDS≥13	83 (45.9)	66 (34.2)	

[a]Indicates divorced or cohabiting.
*SES scores: principal components analysis was used to develop a composite score of socio-economic status based on reported household assets. Abbreviations: ART, antiretroviral therapy; EPDS, Edinburgh Postnatal Depression Scale; SES, socio-economic status.

language at 9 months and expressive language and composite MSEL scores at 18 months. Second, maternal depressive symptoms in both arms declined over the 18-month study, with no significant intervention impact. Third, interactive caregiving activities, specifically book-sharing, mediated the effects of the intervention on children's neurodevelopment.

Effects on children's language scores were significant, albeit modest. The entire distribution shifted with fewer children displaying language skills at the lower end of the distribution and more children at the upper end. This pattern is consistent with a meta-analysis finding that parent-implemented language interventions significantly improve both expressive and receptive language [35]. During infancy and toddlerhood, language skills are developing rapidly and sensitive to intervention [36]. Disparities in language development at 18 months widen over time and can impact negatively on children's behaviour and academic performance [37]. Thus, strategies to promote early language development can have long-lasting benefits.

The language finding is encouraging evidence for future interventions based on nurturing care. The concept of nurturing care is based on evidence that children need nurturant and responsive relationships in a stable family environment, supported by communities and health and educational services [18]. Activities selected to promote nurturing care may vary to reflect cultural contexts and families' strengths and challenges. Improvements in the intervention arm may reflect the sensitivity and training of the Mentor Mothers and appropriate cultural adaptions [38].

The relative decline in standard neurodevelopmental scores indicates a slower gain in skills between 9 and 18 months than expected. However, this finding is not uncommon in low-resource settings [39]. Expectations for children's development increase with age and may reflect cultural variations. Slower gains in play and learning as children age are often

Table 2. Estimated mean difference in Mullen Scales of Early Learning (MSEL) T-scores (95% CIs and *p*-values) from the mixed model adjusting for site clustering at 9 and 18 months

		Mean differences	95% CI lower limit	95% CI upper limit	*p*-value
Visual reception	9 Months	−0.04	−2.07	1.99	0.97
	18 Months	1.85	−0.10	3.79	0.06
Fine motor	9 Months	−0.12	−2.07	1.84	0.91
	18 Months	1.32	−1.06	3.70	0.28
Receptive language	9 Months	1.99	0.39	3.58	0.02
	18 Months	0.99	−0.59	2.56	0.22
Expressive language	9 Months	1.48	−0.18	3.14	0.08
	18 Months	1.78	0.44	3.11	0.01
Gross motor	9 Months	0.19	−1.74	2.12	0.81
	18 Months	0.08	−1.79	1.95	0.78
Composite MSEL	9 Months	1.76	−1.26	4.78	0.25
	18 Months	2.71	0.29	5.14	0.03

Abbreviations: CI, confidence interval; MSEL, Mullen Scales of Early Learning.

Table 3. Family Care Indicators

	Comparison		Intervention		Chi-squared test
	n	Proportion	*n*	Proportion	*p*-value
Shared books	164	0.41	180	0.63	<0.001
Told stories	164	0.54	180	0.66	0.03
Sang songs	164	0.91	180	0.93	0.65
Took the child out	164	0.66	180	0.58	0.1
Played with child	164	0.96	180	0.99	0.02
Named, counted with child	164	0.57	180	0.59	0.68

Note: Proportion of caregivers reporting activities with child, in the past 3 days, at 18 months.

reflected in a relative decline in children's standardised, age-adjusted scores [40]. Interventions should be consistent with cultural variations while ensuring that children, regardless of HIV exposure, have access to opportunities that advance interactive play and learning.

Baseline maternal depressive symptoms were high among both arms, consistent with findings among other groups of pregnant women in Mentor Mother programmes in eSwatini [41]. Approximately half the sample (54.5%) initiated ART prior to pregnancy, suggesting that the remaining may have been newly diagnosed with HIV. In addition to concerns about their own HIV status, women may have been apprehensive about initiating ART and the health of their unborn infants [42]. Without data on the timing of the HIV diagnosis and possible co-morbidities, the elevated prevalence of baseline depressive symptoms in the intervention group may suggest other unmeasured confounders. There was no association between baseline maternal depressive symptoms and MSEL scores at 9 or 18 months. Depressive symptoms in both arms declined over the 18-month study, as expected [43], and may reflect women's adaptation to their infant's negative HIV status and their ability to parent their child. This finding is supported by relatively high scores in observed mother-child interactions across both arms at 12–15 months. Strategies to mitigate maternal depressive symptoms through community health workers in low-resource settings have been effective [44]; additional research is necessary to scale interventions to address HIV-associated maternal depression.

Children's growth did not differ across arms. At 18 months, the prevalence of stunting increased to approximately 35%. This finding matches a recent UNICEF report of 35% stunting prevalence among children aged 18–23 months in eSwatini, regardless of HIV exposure, potentially linked to a severe 2015/16 drought that increased food insecurity [37]. Our intervention provided nutrition guidance and did not address the factors leading to the increase in stunting across both groups.

The finding that interactive caregiving activities, specifically book-sharing, mediated the effects of the intervention on children's neurodevelopment provides suggestive evidence on the mechanisms underlying the intervention. Language skills are influenced by children's context, including verbal exchanges, [36] suggesting that caregiver-child interactions and children's language skills responded to the intervention.

Table 4. Mediating effect of book reading on relation between study arm and Mullen Scales of Early Learning (MSEL) scores, using generalised structural equation model

Visual reception		Coefficient	*p*-value	95% CI (lower limit)	95% CI (upper limit)
	Direct effect	1.928	0.024	0.257	3.599
	Indirect effect	2.499	0.001	1.044	3.955
	Total effect	4.427	0.001	1.804	7.050
Fine motor					
	Direct effect	0.128	0.903	−1.917	2.172
	Indirect effect	3.242	0.001	1.331	5.153
	Total effect	3.370	0.016	0.629	6.110
Receptive language					
	Direct effect	0.397	0.621	−1.176	1.970
	Indirect effect	2.758	0.002	1.009	4.506
	Total effect	3.155	0.008	0.830	5.480
Expressive language					
	Direct effect	1.655	0.004	0.513	2.796
	Indirect effect	1.408	0.024	0.187	2.629
	Total effect	3.063	<0.001	1.642	4.484
MSEL composite					
	Direct effect	1.919	0.092	−0.313	4.151
	Indirect effect	4.583	<0.001	2.286	6.881
	Total effect	6.502	<0.001	3.172	9.833

Abbreviations: CI, confidence interval; MSEL, Mullen Scales of Early Learning.

Global studies, including southern Africa, have shown that early caregiving interactions, including book-sharing, have beneficial effects on children's language and emerging literacy [16–18]. These findings suggest that conversational turn-taking in interactive play drives advances in expressive language and visual reception, working through neural pathways central to language and learning [45]. The m2m intervention incorporated verbal interactions into daily activities, including feeding and bathing. Our findings suggest that book-sharing and story-telling increased in the intervention group and may be adaptable strategies that increase interactive caregiving interactions.

The findings should be interpreted recognizing several limitations. The clinics were not randomised to study arms. Intervention and comparison clinics were matched on multiple characteristics, analyses adjusted for identified sociodemographic differences in location and marital status, and baseline maternal depressive symptoms were unlinked to children's neurodevelopmental scores. However, there may have been unmeasured confounding. Limited testing of children at older ages could have led to misclassification of their HIV status, though this should not have differed by arm and would be less likely with mothers receiving ART. Although the MSEL have been used among CHEU in other African countries, they were not standardised for eSwatini [4, 21]. In addition, we do not have an unexposed group of children for comparison. Finally, findings related to caregiving activities, including book-sharing, were based on caregiver-report and may have reflected respondent bias. Future studies should observe caregiving activities over time.

5 | CONCLUSIONS

While the implementation of effective PVT strategies has decreased the number of infants living with HIV, the number of CHEU will continue to increase. The need to optimise the health of CHEU is urgent in countries such as eSwatini with large numbers of women living with HIV. CHEU are potentially at risk for poor neurodevelopment due to both prenatal exposure to HIV, and conditions associated with HIV-exposed households [12]. CHEU may benefit from comprehensive interventions that address stable maternal functioning, promoting children's health and nutrition, and providing opportunities to learn and participate in responsive, emotionally supportive and developmentally enriching interactive caregiving activities [18, 46, 47]. The significant, albeit modest, differences in book-sharing and story-telling suggest that mothers incorporated book-sharing into parent-child play and learning activities associated with advances in children's neurodevelopment. Future randomised studies with focused interventions and longitudinal designs examining the impact of interventions on CHEU neurodevelopment are needed [48].

The m2m partnership is consistent with principles of implementation science where collaboration with a local team to design and implement and intervention promotes cultural sensitivity and ensures impact, and sustainability [49]. Investing in young children's development has benefits to CHEU and the larger society [18]. This study showed that an intervention based on nurturing care and integrated into PVT clinics, communities and homes in a resource-limited country improved neurodevelopmental scores among CHEU. Our findings support recommendations from WHO and UNICEF that children worldwide, particularly in adverse conditions, receive interventions based on nurturing care [14]. Since our study was conducted, the number of CHEU needing nurturing care in eSwatini remains high. The Ministry of Health recognises the need to strengthen support programmes for CHEU. The country is a signatory to the Global Health Alliance and implementing a nurturing care framework for CHEU is a priority. Improving children's neurodevelopment can reduce disparities by building strong foundations for academic and economic capabilities.

AUTHORS' AFFILIATIONS

[1]Johns Hopkins Bloomberg School of Public Health, Johns Hopkins University, Baltimore, Maryland, USA; [2]Ministry of Health, Kingdom of eSwatini, South Africa; [3]Johns Hopkins Center for Communication Programs, Baltimore, Maryland, USA; [4]mothers2mothers, Cape Town, South Africa; [5]University of Maryland School of Medicine, Baltimore, Maryland, USA; [6]RTI International, Research Triangle Park, North Carolina, USA

COMPETING INTERESTS

The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

AR co-conceived the study, served as a co-principal investigator, oversaw all aspects of the study, interpreted the data, wrote pieces of the article and provided critical comments to the article. XD served as a co-principal investigator from the Ministry of Health in eSwatini, oversaw aspects of the study and provided critical comments to the article. BASN conducted the data analysis, interpreted the data, wrote pieces of the article and provided critical comments to the article.

NS contributed to the study design; coordinated the data collection, data management and preparation of the final report; interpreted the data; wrote pieces of the article; and provided critical comments to the article. DK contributed to the study design, supervised the evaluators and child development specialists, and provided critical comments to the article. FB, ES and KS contributed to the study design, developed the m2m intervention, provided technical oversight of the m2m team in eSwatini that supervised the Mentor Mothers and provided critical comments to the article. FM and NG contributed to the study design, collected the neurodevelopmental data and provided critical comments to the article. LS contributed to the study design, contributed to data management and provided critical comments to the article. MMB served as a co-principal investigator, contributed to the study design, trained the child development specialists, interpreted the data, wrote pieces of the article, provided critical comments and revisions to the article, and coordinated the preparation of the article. All authors provided critical comments on drafts, approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

ACKNOWLEDGEMENTS

We acknowledge the Ministry of Health in eSwatini for their collaboration in the implementation of the study and in the dissemination of the findings; the employees of the participating clinics in eSwatini for their collaboration; the staff of HC3 in eSwatini for their support and collaboration; and the caregivers and children for their participation and enthusiasm.

FUNDING

This study was funded by the United States Agency for International Development with PEPFAR funding [Cooperative Agreement #AID-OAA-A-12-00058] to the Johns Hopkins Center for Communication Programs.

DISCLAIMER

The information provided in this article is not official U.S. Government Information and does not necessarily represent the views or positions of USAID, the United States Government or the Johns Hopkins University.

DATA AVAILABILITY STATEMENT

All the data files can be found in the data catalogue of the University of Maryland at Baltimore.

REFERENCES

1. UNAIDS. AIDSinfo [Internet]. 2020 [cited 2021 Mar 20] http://aidsinfo.unaids.org.
2. Slogrove AL, Powis KM, Johnson LF, Stover J, Mahy M. Estimates of the global population of children who are HIV-exposed and uninfected, 2000–18: a modelling study. Lancet Glob Health. 2020;8(1):e67–75.
3. Chaudhury S, Williams PL, Mayondi GK, Leidner J, Holding P, Tepper V, et al. Neurodevelopment of HIV-exposed and HIV-unexposed uninfected children at 24 months. Pediatrics. 2017;140(4):e20170988.
4. Boivin MJ, Maliwichi-Senganimalunje L, Ogwang LW, Kawalazira R, Sikorskii A, Familiar-Lopez I, et al. Neurodevelopmental effects of ante-partum and post-partum antiretroviral exposure in HIV-exposed and uninfected children versus HIV-unexposed and uninfected children in Uganda and Malawi: a prospective cohort study. Lancet HIV. 2019;6(8):e518–30.
5. Springer PE, Slogrove AL, Kidd M, Kalk E, Bettinger JA, Esser MM, et al. Neurodevelopmental and behavioural outcomes of HIV-exposed uninfected and HIV-unexposed children at 2–3 years of age in Cape Town, South Africa.AIDS Care. 2020;32(4):411–9.
6. Rotheram-Borus MJ, Wynn A, Stewart J, Almirol E, Weichle TW, Tubert J, et al. Outcomes of HIV-exposed but uninfected children in South Africa over 5 years. AIDS. 2021;35(2):347–9.
7. Wedderburn CJ, Yeung S, Rehman AM, Stadler JA, Nhapi RT, Barnett W, et al. Neurodevelopment of HIV-exposed uninfected children in South Africa: outcomes from an observational birth cohort study. Lancet Child Adolesc Health. 2019;3(11):803–13.
8. Young JM, Bitnun A, Read SE, Smith ML. Neurodevelopment of HIV-exposed uninfected children compared with HIV-unexposed uninfected children during early childhood. Dev Psychol. 2022;58(3):551–9.
9. Madlala HP, Myer L, Malaba TR, Newell ML. Neurodevelopment of HIV-exposed uninfected children in Cape Town, South Africa. PLoS One. 2020;15(11):e0242244.
10. McHenry MS, McAteer CI, Oyungu E, McDonald BC, Bosma CB, Mpofu PB, et al. Neurodevelopment in young children born to HIV-infected mothers: a meta-analysis. Pediatrics. 2018;141(2):e20172888.
11. Wedderburn CJ, Weldon E, Bertran-Cobo C, Rehman AM, Stein DJ, Gibb DM, et al. Early neurodevelopment of HIV-exposed uninfected children in the era of antiretroviral therapy: a systematic review and meta-analysis. Lancet Child Adolesc Health. 2022;6(6):393–408.
12. Ntozini R, Chandna J, Evans C, Chasekwa B, Majo FD, Kandawasvika G, et al. Early child development in children who are HIV-exposed uninfected compared to children who are HIV-unexposed: observational sub-study of a cluster-randomized trial in rural Zimbabwe. J Int AIDS Soc. 2020;23(5):e25456.
13. Bornstein MH, Putnick DL, Esposito G. Continuity and stability in development. Child Dev Perspect. 2017;11(2):113–9.
14. WHO/UNICEF. Nurturing care for early childhood development: a framework for helping children survive and thrive to transform health and human potential. Geneva: World Health Organization; 2018.
15. Black MM, Behrman JR, Daelmans B, Prado EL, Richter L, Tomlinson M, et al. The principles of Nurturing Care promote human capital and mitigate adversities from preconception through adolescence. BMJ Glob Health. 2021;6(4):e004436.
16. Murray L, De Pascalis L, Tomlinson M, Vally Z, Dadomo H, MacLachlan B, et al. Randomized controlled trial of a book-sharing intervention in a deprived South African community: effects on carer–infant interactions, and their relation to infant cognitive and socioemotional outcome. J Child Psychol Psychiatry. 2016;57(12):1370–9.
17. Zuckerman B, Elansary M, Needlman R. Book sharing: in-home strategy to advance early child development globally. Pediatrics. 2019;143(3):e20182033.
18. Black MM, Walker SP, Fernald LC, Andersen CT, DiGirolamo AM, Lu C, et al. Early childhood development coming of age: science through the life course. Lancet. 2017;389(10064):77–90.
19. Aboud FE, Yousafzai AK. Global health and development in early childhood. Annu Rev Psychol. 2015;66:433–57.
20. Trude AC, Richter LM, Behrman JR, Stein AD, Menezes AM, Black MM. Effects of responsive caregiving and learning opportunities during pre-school ages on the association of early adversities and adolescent human capital: an analysis of birth cohorts in two middle-income countries. Lancet Child Adolesc Health. 2021;5(1):37–46.

21. Boivin MJ, Bangirana P, Nakasujja N, Page CF, Shohet C, Givon D, et al. A year-long caregiver training program to improve neurocognition in preschool Ugandan HIV-exposed children. J Dev Behav Pediatr. 2013;34(4):269.
22. Boivin MJ, Nakasujja N, Familiar I, Murray SM, Sikorskii A, Awadu J, et al. Effect of caregiver training on neurodevelopment of HIV-exposed uninfected children and caregiver mental health: a Ugandan cluster randomized controlled trial. J Dev Behav Pediatr. 2017;38(9):753.
23. mothers2mothers (m2m). Ending HIV is just the start [Internet]. [Cited 2021 Jun 21] https://m2m.org/.
24. Igumbor JO, Ouma J, Otwombe K, Musenge E, Anyanwu FC, Basera T, et al. Effect of a Mentor Mother Programme on retention of mother−baby pairs in HIV care: a secondary analysis of programme data in Uganda. PLoS One. 2019;14(10):e0223332.
25. StataCorp. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP; 2011.
26. Attanasio OP, Fernandez C, Fitzsimons EO, Grantham-McGregor SM, Meghir C, Rubio-Codina M. Using the infrastructure of a conditional cash transfer program to deliver a scalable integrated early child development program in Colombia: cluster randomized controlled trial. BMJ. 2014;349:g5785.
27. Mullen EM. Mullen Scales of Early Learning Manual. American Guidance Service; 1995.
28. World Health Organization. WHO Multicentre Growth Reference Study [Internet]. 2021 [cited 2021 Jun 21] https://www.who.int/tools/child-growth-standards/who-multicentre-growth-reference-study.
29. Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression: development of the 10-item Edinburgh Postnatal Depression Scale. Br J Psychiatry. 1987;150(6):782–6.
30. Mokwena KE, Mbatha NL. Social and demographic factors associated with postnatal depression symptoms among HIV-positive women in primary healthcare facilities, South Africa. Healthcare. 2021;9:65.
31. Lawrie T, Hofmeyr G, De Jager M, Berk M. Validation of the Edinburgh Postnatal Depression Scale on a cohort of South African women. S Afr Med J. 1998;88(10):1340–4.
32. Hamadani JD, Tofail F, Hilaly A, Huda SN, Engle P, Grantham-McGregor SM. Use of family care indicators and their relationship with child development in Bangladesh. J Health Popul Nutr. 2010;28(1):23.
33. Kariger P, Frongillo EA, Engle P, Britto PMR, Sywulka SM, Menon P. Indicators of family care for development for use in multicountry surveys. J Health Popul Nutr. 2012;30(4):472.
34. Bradley RH, Caldwell BM, Corwyn RF. The Child Care HOME Inventories: assessing the quality of family child care homes. Early Child Res Q. 2003;18(3):294–309.
35. Roberts MY, Kaiser AP. The effectiveness of parent-implemented language interventions: a meta-analysis. Am J Speech Lang Pathol. 2011;20(3):180–99.
36. Kuhl PK. Early language learning and literacy: neuroscience implications for education. Mind Brain Educ. 2011;5(3):128–42.
37. Fernald A, Marchman VA, Weisleder A. SES differences in language processing skill and vocabulary are evident at 18 months. Dev Sci. 2013;16(2):234–48.
38. Weber AM, Diop Y, Gillespie D, Ratsifandrihamanana L, Darmstadt GL. Africa is not a museum: the ethics of encouraging new parenting practices in rural communities in low-income and middle-income countries. BMJ Glob Health. 2021;6(7):e006218.
39. Hair NL, Hanson JL, Wolfe BL, Pollak SD. Association of child poverty, brain development, and academic achievement. JAMA Pediatr. 2015;169(9):822–9.
40. Boyce WT, Levitt P, Martinez FD, McEwen BS, Shonkoff JP. Genes, environments, and time: the biology of adversity and resilience. Pediatrics. 2021;147(2):e20201651.
41. Målqvist M, Clarke K, Matsebula T, Bergman M, Tomlinson M. Screening for antepartum depression through community health outreach in Swaziland. J Community Health. 2016;41(5):946–52.
42. Christodoulou J, Rotheram-Borus MJ, Bradley AK, Tomlinson M. Home visiting and antenatal depression affect the quality of mother and child interactions in South Africa. J Am Acad Child Adolesc Psychiatry. 2019;58(12):1165–74.
43. Suryawanshi O, 4th, Pajai S. A comprehensive review on postpartum depression. Cureus. 2022;14(12):e32745.
44. Munodawafa M, Mall S, Lund C, Schneider M. Process evaluations of task sharing interventions for perinatal depression in low and middle income countries (LMIC): a systematic review and qualitative meta-synthesis. BMC Health Serv Res. 2018;18(1):1–10.
45. Romeo RR, Leonard JA, Robinson ST, West MR, Mackey AP, Rowe ML, et al. Beyond the 30-million-word gap: children's conversational exposure is associated with language-related brain function. Psychol Sci. 2018;29(5):700–10.
46. Schmitz K, Basera TJ, Egbujie B, Mistri P, Naidoo N, Mapanga W, et al. Impact of lay health worker programmes on the health outcomes of mother−child pairs of HIV exposed children in Africa: a scoping review. PLoS One. 2019;14(1):e0211439.
47. Khumalo PN, Katirayi L, Ashburn K, Chouraya C, Mpango L, Mthethwa N, et al. 'There are no more secrets': acceptability of a family-centered model of care for HIV positive children in Eswatini. BMC Health Serv Res. 2020;20(1):1–9.
48. Toledo G, Cote HCF, Adler C, Thorne C, Goetghebuer T. Neurological development of children who are HIV-exposed and uninfected. Dev Med Child Neurol. 2021;63(10):1161–70.
49. Bauer MS, Damschroder L, Hagedorn H, Smith J, Kilbourne AM. An introduction to implementation science for the non-specialist. BMC Psychol. 2015;3(1):32.

SUPPORTING INFORMATION

Additional information may be found under the Supporting Information tab for this article:

Table S1 Intervention content

Table S2 Estimated mean MSEL changes (95% CIs) from the linear mixed model over 9 and 18 months, adjusting for site and child random effects, and arm by timepoint interaction terms

Table S3 Number and percentage of children with z-scores less than −2 on anthropometry, based on WHO standards

Table S4 Predictors of composite MSEL score from the linear mixed model

Table S5 Mediation effects of family care indicators on the relation between study arm and the composite MSEL score

Powis KM et al. *Journal of the International AIDS Society* 2023, **26**(S4):e26165
http://onlinelibrary.wiley.com/doi/10.1002/jia2.26165/full | https://doi.org/10.1002/jia2.26165

JIAS JOURNAL OF THE INTERNATIONAL AIDS SOCIETY

RESEARCH ARTICLE

Lower academic performance among children with perinatal HIV exposure in Botswana

Kathleen M. Powis[1,2,3,§], Lesedi Lebanna[4], Sara Schenkel[1], Gosego Masasa[3], Samuel W. Kgole[3], Martha Ngwaca[3], Coulson Kgathi[3], Paige L. Williams[5], Amy L. Slogrove[6], Roger L. Shapiro[2,3], Shahin Lockman[2,3,7], Mompati O. Mmalane[3], Joseph M. Makhema[3], Jennifer Jao[3,8] and Adam R. Cassidy[3,9]

[§]**Corresponding author**: Kathleen M. Powis, Department of Internal Medicine and Pediatrics, Massachusetts General Hospital, 125 Nashua Street, Office 8426, Boston, MA 02114, USA. Tel: +1 617 643 2054. (kpowis@mgh.harvard.edu)

Abstract

Introduction: Studies have reported a higher risk of suboptimal neurodevelopment among children who are HIV-exposed uninfected (HEU) compared to children HIV-unexposed uninfected (HUU). Actual academic performance among school-aged children by HIV exposure status has not been studied.

Methods: Academic performance in Mathematics, Science, English, Setswana and overall among children enrolled in the Botswana-based FLOURISH study who were attending public primary school and ranging in age from 7.1 to 14.6 years were compared by HIV exposure status using a Cochran-Mantel-Haenszel test. Lower academic performance was defined as a grade of "C" or lower (≤60%). Unadjusted and adjusted logistic regression models were fit to assess for an association between HIV exposure and lower academic performance.

Results: Between April 2021 and December 2022, 398 children attending public primary school enrolled in the FLOURSH study, 307 (77%) were HEU. Median age was 9.4 years (IQR 8.9–10.2). Only 17.9% of children HEU were breastfeed versus 100% of children HUU. Among children HEU, 80.3% had foetal exposure to three-drug antiretroviral treatment, 18.7% to zidovudine only and 1.0% had no antiretroviral exposure. Caregivers of children HEU were older compared to caregivers of children HUU (median 42 vs. 36 years) and more likely to have no or primary education only (15.0% vs. 1.1%). In unadjusted analyses, children HEU were more likely to have lower overall academic performance compared to their children HUU (odds ratio [OR]: 1.96 [95% confidence interval (CI): 1.16, 3.30]), and lower performance in Mathematics, Science and English. The association was attenuated after adjustment for maternal education, caregiver income, breastfeeding, low birth weight and child sex (aOR: 1.86 [95% CI: 0.78, 4.43]).

Conclusions: In this Botswana-based cohort, primary school academic performance was lower among children HEU compared to children HUU. Biological and socio-demographic factors, including child sex, appear to contribute to this difference. Further research is needed to identify modifiable contributors, develop screening tools to identify the risk of poor academic performance and design interventions to mitigate risk.

Keywords: academic performance; Botswana; children; HIV-exposed uninfected; neurodevelopment; primary school

Received 24 January 2023; **Accepted** 23 August 2023

1 | INTRODUCTION

As the HIV epidemic has matured globally, successful scale-up and access to three-drug antiretroviral treatment (ART) among pregnant and breastfeeding persons living with HIV (PLHIV) has dramatically reduced the rate of infant HIV acquisition, from 24% of births in 2010 to 12% in 2021 globally, with high burden settings achieving rates of under 4%, including Botswana, Eswatini and South Africa [1]. Despite laudable gains towards eliminating infant HIV acquisition, the number of infants born to PLHIV has not changed substantially in the last decade, with over one million infants born annually with perinatal HIV exposure [1]. UNAIDS estimates the population of children under 15 years-of-age born HIV-exposed uninfected to be 16 million in 2022, while the population of similarly aged children living with HIV was estimated at 1.5 million [1].

Starting life HIV-free has not ensured that children with perinatal HIV exposure who remain uninfected achieve comparable health, growth or neurodevelopment outcomes compared to children born in the absence of perinatal HIV exposure. While findings are inconsistent, many studies report a higher risk of infectious morbidity and mortality, poorer growth outcomes and developmental delays among children HIV-exposed uninfected (HEU) compared to children HIV-unexposed uninfected (HUU) [2–13]. The aetiology of this higher risk among children HEU is multifactorial, encompassing both biological and social determinants of health, including altered immunity early in life [14–18], a proinflammatory state in infancy [19–21], higher risk of preterm birth [22, 23], suboptimal duration of breastfeeding [3, 24], poor maternal health [25] and household food insecurity [26].

Biological and socio-demographic factors have been associated with neurodevelopmental delays in children, regardless of their HIV exposure status [27–33]. However published research from high HIV burden settings employing a variety of neurodevelopmental assessment tools has reported a higher risk of poorer neurodevelopmental outcomes, including poorer neurocognitive functioning [11, 34], gross motor delays [34, 35] and lagging language skills [34, 35] among children HEU compared to children HUU. The collective body of published work on neurodevelopmental outcomes of children HEU has relied on neurodiagnostic testing to assess for differences between children HEU and those who are HUU. While testing results offer important data, actual academic performance has been closely linked to a person's physical and mental health and their ability to contribute productively to society [36]. However, actual academic performance has not specifically been evaluated in children who are HEU compared to those who are HUU.

Using data from a prospective birth cohort study in Botswana, the FLOURISH (**F**ollowing **L**ongitudinal **O**utcomes to **U**nderstand, **R**eport, **I**ntervene and **S**ustain **H**ealth Outcomes for Infants, Children, and Adolescents who are HIV-Exposed Uninfected) study, we sought to evaluate differences in actual academic performance by child HIV exposure status in a subset of children attending public primary school where curriculum is standardised nationally, as are testing, and grading.

2 | METHODS

2.1 | Study population, design and ethical considerations

The FLOURISH study is an ongoing prospective observational Botswana-based study being conducted by Botswana Harvard Health Partnership (BHP). Children HEU and those HUU are being recruited after previous participation in a BHP birth cohort study, including the Mma Bana [37], Mpepu [38] and Tshipidi [39] studies, all of which have been previously described. The Mma Bana study enrolled treatment naïve pregnant PLHIV with CD4 cell counts ≥200 cells/mm^3, randomizing participants to one of two ART regimens between 26- and 34-weeks gestation, as well as pregnant PLHIV with CD4 cell counts <200 cells/mm^3 who were between 18- and 34-weeks gestation and already receiving the first-line ART regimen per Botswana national treatment guidelines [37]. The Mpepu study, investigating any potential survival benefit with long-term use of cotrimoxazole for infants HEU, allowed for study enrolment in pregnancy or as late as the infant's 34th day of life, as infants were not randomised to cotrimoxazole or placebo until between 30 and 34 days of life under the original study protocol [38]. The Tshipidi study enrolled both PLHIV and those who were seronegative during pregnancy or within 7 days of the infant's birth [39].

Since the curriculum in Botswana public schools is standardised by the Department of Curriculum Development within Botswana's Ministry of Education and Skills Development, and examinations are standardised by the Botswana Examinations Council, as are grading criteria, the academic performance of children attending public schools was analysed overall and in the subjects of Mathematics, Science, English and Setswana, the native language of Botswana. Children who attended private schools were excluded from the analysis, as private schools in Botswana are not required to abide by requirements established by Botswana's Department of Curriculum Development or the Botswana Examinations Council. Additionally, children participating in special education were excluded. If a mother enrolled in a prior BHP study was HIV uninfected during the previous study but subsequently acquired HIV prior to enrolment in the FLOURISH study, the child was excluded from the academic performance analysis. While the FLOURISH study recruits children and adolescents of all ages from prior BHP studies, fewer prior BHP studies involved enrolment of children HUU. Therefore, in order to have an appropriately sized comparator group, only grade levels where at least 15% of FLOURISH participants were children HUU were included in the analysis, restricting the analysis to participants attending primary education grades designated as standard 3 through 6, where annual progression would be expected to have children 7 years-of-age through 12 years-of-age in these grades, depending on a child's date of birth at the start of a school year. All adult participants provided written informed consent, on their own behalf and that of their child's, for study participation. For children ≥7 years of age, assent is also obtained from the child. The FLOURISH study protocol was approved by the Botswana Health Research and Development Committee, as was well Mass General Brigham Institution Review Board.

2.2 | Confirmation of HIV status

All biological mothers not known to be living with HIV at the completion of the prior BHP study in which they participated, and all children participating in the FLOURISH study undergo HIV testing and counselling upon enrolment into the FLOURISH study to confirm HIV status as a condition of study enrolment. Only pairs where the child has a negative HIV test are eligible for continued participation in the FLOURISH study.

2.3 | Historical maternal-child database

A harmonised maternal-child database exists, housing common data elements for key historical BHP maternal-child research studies, including the studies from which the FLOURISH study is recruiting. Maternal data elements include but are not limited to HIV status, date of enrolment, timing of enrolment, either in pregnancy or within 34 days of giving birth, age at enrolment, obstetric history and socio-demographic information at time of enrolment. For women living with HIV at the time of the prior BHP study, if originally collected, the database includes CD4 cell count and HIV-1 viral load at time of enrolment, either during pregnancy or within 34 days of giving birth, timing of ART initiation, either prior to conception or during pregnancy, date of ART initiation (if known) and ART taken in pregnancy as none, zidovudine (AZT) only or a three-drug ART regimen. Harmonised child data, if originally collected, includes gestational age at birth, sex, and infant feeding mode (breast vs. formula). Children who participated in the Mma Bana, Mpepu and Tshipidi studies are now of school age and the historically collected maternal-child data has been used in this analysis of academic performance.

2.4 | Primary outcome—academic performance

At enrolment, grades from the child's latest school report card are abstracted, including subject grades and the child's overall grade. Academic performance was assessed for grades in Mathematics, Science, English, Setswana and the overall grade. Lower academic performance was defined as a grade of C or lower (≤60%). Academic performance was analysed for eligible children enrolled in the FLOURISH study between 30 April 2021 and 31 December 2022.

2.5 | Exposures of interest

The primary exposure of interest was foetal HIV exposure. Other potential exposures associated with childhood neurodevelopment with implications for school performance evaluated as potential predictors of academic performance included child preterm birth (<37 weeks completed gestational age), child sex and ever being breastfed (variables abstracted from the maternal-child database); and maternal education level, maternal positive screen for depression or anxiety (using the Patient Health Questionnaire [PHQ9] and General Anxiety Disorder-7 [GAD7] screening tools) and proxies for household poverty, including caregiver reported income, absence of electricity in the home and report of household food insecurity in the last 12 months (collected in the FLOURISH study), with the latter two assumed, a priori, to be associated with academic performance, as well [32, 40–42].

2.6 | Statistical analysis

Baseline caregiver and child characteristics were compared by child HIV exposure status using Wilcoxon Rank Sum tests for continuous variables and Chi-squared or Fisher's exact tests for categorical or ordinal variables. School grades, by subject and overall, were dichotomised with grades of A or B categorised as higher academic performance and grades of C or lower categorised as lower academic performance. A Cochran-Mantel-Haenszel test was used to compare academic performance by HIV exposure status, by subject and overall. Unadjusted and adjusted logistic regression models were fit to assess the association between HIV exposure status and lower overall academic performance. Covariates in unadjusted models with a *p*-value of ≤0.20 were included in the adjusted model. Logistic regression models were also fit to assess associations between maternal HIV disease status and treatment with overall academic performance in the subset of children HEU. Analyses were performed with SAS, version 9.4 (SAS Institute, Inc).

3 | RESULTS

Between 30 April 2021 and 31 December 2022, 413 children ranging in age from 7.1 to 14.6 years were enrolled in the FLOURISH study and were attending standard 3 through standard 6 primary education. Eight children were attending private school, including five (1.2%) who were HEU and three (3.0%) who were HUU, and these eight were excluded from the analysis of public school academic achievement. Another four children were enrolled in the FLOURISH study with a mother who was HIV uninfected at the time of participation in the original BHP study, but since the biological mother had subsequently acquired HIV prior to enrolment in the FLOURISH study, these children were excluded from the academic achievement analysis. Finally, three children, including two HEU, were participating in special education curriculum. The analysis of academic performance among FLOURISH study participants attending standard 3 through standard 6 includes 398 children, of whom 373 (94.7%) were of appropriate age for grade level, while the remainder 25 (6.3%) were older than what would be expected for grade level, including 20 (6.5%) children who were HEU and five (5.5%) who were HUU.

The characteristics of caregivers and children are presented in Table 1. Caregivers of children HEU were older on average compared to caregivers of children HUU (median age 41.9 vs. 36.0 years), with 97% of all caregivers, regardless of a child's HIV exposure status, being the biological mother of the child. Caregivers of children HEU more often had no formal education or had a primary school education only and less often had completed tertiary education than caregivers of children HUU. A higher proportion of caregivers of children HEU were married or cohabiting compared to caregivers of children HUU. Few children HEU had ever breastfed, while 100% of children HUU had been breastfed. Children HEU were also younger than children HUU (median 9.3 years-of-age vs. 9.9).

Children HEU had higher odds of lower academic performance in Science (2.23 [95% confidence interval (CI) 1.31, 3.80]), Mathematics (1.73 [95% CI 1.03, 2.93]), English (1.83 [95% CI 1.09, 3.08]) and overall (1.96 [95% CI 1.16, 3.30]) compared to children HUU. For Setswana, academic performance did not differ significantly by HIV exposure status (1.25 [95% CI 0.75, 2.10]).

In unadjusted analysis, child HIV exposure status was significantly associated with an increased risk of lower overall academic performance, as was an absence of maternal formal education or highest level as primary school compared to secondary or tertiary education, and male sex of the child (Table 2). The presence of caregiver depression or anxiety and the three proxy markers of poverty, including household income, absence of household electricity or food insecurity in the last year, were not significantly associated with a higher risk of lower overall academic performance. After adjustment for low maternal education, caregiver income, sex at birth, low birth weight and breastfeeding status, the association between HIV exposure and academic performance was

Table 1. Caregiver and child characteristics by child HIV exposure status

Maternal characteristics	**Caregivers of children HEU (*n* = 307)**	**Caregivers of children HUU (*n* = 91)**	***p*-value**
Median caregiver age at enrolment (IQR)	41.9 (37.0–45.7)	36.0 (32.8–41.5)	<0.0001
Highest maternal education level			<0.0001
No or primary school	46 (15.0%)	1 (1.1%)	
Junior or senior secondary school	232 (75.6%)	63 (70.0%)	
Tertiary school	29 (9.4%)	29 (28.9%)	
Marital status # (%)			0.05
Single	168 (54.7%)	61 (68.5%)	
Married/co-habiting	125 (40.7%)	28 (31.5%)	
Divorced	5 (1.7%)	0 (NA)	
Widowed	9 (2.9%)	0 (NA)	
Maternal monthly income			0.002
None	91 (30.5%)	25 (28.1%)	
$1–$50	33 (11.1%)	10 (11.2%)	
$51–$100	51 (17.1%)	9 (10.1%)	
$101–$500	110 (36.9%)	30 (33.7%)	
>$500	14 (4.4%)	16 (16.9%)	
Electricity in home # (%)	269 (87.6%)	81 (89.0%)	0.86
Household food insecurity reported in the last 12 months prior to enrolment # (%)	100 (33.1%)	22 (24.4%)	0.15
Biological mother as caregiver # (%)	297 (96.7%)	90 (98.9%)	0.47
Original BHP study			<0.0001
Mma Bana	5 (1.6%)	0 (NA)	
Mpepu	241 (78.5%)	0 (NA)	
Tshipidi	61 (19.9%)	91 (100%)	
Community			<0.0001
Gaborone (city)	182 (59.3%)	48 (52.8%)	
Lobatse (town)	26 (8.5%)	0 (NA)	
Mochudi (village)	27 (8.8%)	43 (47.2%)	
Molepolole (village)	72 (23.5%)	0 (NA)	
ARV treatment/prophylaxis in pregnancy # (%)			NA
None	3 (1.0%)	NA	
Zidovudine only	56 (18.7%)	NA	
Three-drug antiretroviral treatment regimen	240 (80.3%)	NA	
Median CD4+ cell count at enrolment in original study	475 (353–626)	NA	NA
Virally suppressed at enrolment in original study # (%)	94 (40.9%)	NA	NA
Median viral load at enrolment in original study for participants with unsuppressed viral load (IQR)	4781 (390–25,539)	NA	NA
Child characteristics	**HEU (*n* = 307)**	**HUU (*n* = 91)**	
Median age of school-age children in years	9.3 (8.8–10.1)	9.9 (9.2–10.4)	0.001
Male # (%)	155 (50.5%)	52 (57.1%)	0.28
Preterm # (%)	37 (12.3%)	10 (11.0%)	0.85
Low birth weight (≤2500 grams)	58 (18.9%)	6 (6.7%)	0.005
Ever breastfed # (%)	55 (17.9%)	91 (100%)	<0.0001

Note: Missing variables: Highest educational level—one caregiver of a child HUU; Marital status—two caregivers of children HUU; Income: nine caregivers of children HEU and two caregivers of children HUU; Household food insecurity—five missing for households of children HEU and one missing from household of a child HUU; Antiretroviral treatment/prophylaxis in pregnancy; eight caregivers of children HEU; CD4+ cell count: two for caregivers of children HEU; Viral load: 77 for caregivers of children HEU; Preterm: five missing for children HEU; Low birth weight—one for a child HUU.

Abbreviations: BHP, Botswana Harvard Health Institute Partnership; HEU, HIV-exposed uninfected; HUU, HIV-unexposed uninfected; IQR, interquartile range; NA, not applicable.

Table 2. Logistic regression model of factors associated with lower academic performance

	Unadjusted models		Adjusted model	
Covariates of interest	**Odds ratio (95% CI)**	***p*-value**	**Odds ratio (95% CI)**	***p*-value**
HEU versus HUU	1.96 (1.16, 3.30)	0.01	1.86 (0.78, 4.43)	0.16
Low maternal education[a]	2.40 (1.03, 5.60)	0.04	1.86 (0.77, 4.49)	0.17
Caregiver depression/anxiety at enrolment[b]	1.07 (0.49, 2.32)	0.87		
No caregiver income or income ≤$100 USD per month	1.75 (1.09, 2.81)	0.02	1.57 (0.96, 2.56)	0.07
Absence of household electricity	1.48 (0.70, 3.14)	0.31		
Household food insecurity in the last year[c]	0.82 (0.50, 1.36)	0.44		
Male child	1.80 (1.12, 2.89)	0.02	1.92 (1.17, 3.16)	0.01
Preterm birth[d]	1.43 (0.67, 3.03)	0.36		
Low birthweight (<2500 grams)	1.71 (0.84, 3.50)	0.14	1.61 (0.77, 3.367)	0.21
Never breastfed	1.38 (0.86, 2.22)	0.19	0.82 (0.37, 1.79)	0.61

Note: Covariates in unadjusted analyses with a *p*-value ≤0.20 were included in the adjusted model.
Abbreviations: HEU, HIV-exposed uninfected; HUU, HIV-unexposed uninfected; CI, confidence interval; USD, United States Dollar.
[a]Low maternal education was defined as no or primary education only.
[b]Maternal depression was evaluated using the PHQ9 screening tool and anxiety via the GAD7 screening tool.
[c]Household food insecurity was defined as being present if a caregiver reported that in the last 12 months the household ever had to cut the size of meals or skip meals because there was not enough food in the household.
[d]Preterm birth was defined as a birth before 37.0 weeks completed gestational age.

attenuated, (adjusted OR = 1.86, 95% CI 0.78, 4.43), with male sex being the only significant predictor of lower overall academic performance.

Maternal HIV-related covariates were evaluated to assess for association with overall lower academic achievement only among the 307 children HEU. Using data collected from the biological mother during the original BHP study, enrolment $CD4^+$ cell count (OR 0.75 [95% CI 0.13, 4.18]), detectable pregnancy viral load (OR 1.06 [95% CI 0.54, 2.06]) and absence of receiving a three-drug ART regimen in pregnancy (OR 0.88 [95% CI 0.44, 1.77]) were not found to be associated with lower academic performance.

4 | DISCUSSION

In an analysis of actual academic performance among FLOURISH participants attending public primary school, children HEU were more likely to have lower academic performance in Mathematics, Science, English and overall compared to children HUU. However, in adjusted analysis, the association between HIV exposure status and academic performance was attenuated and only male child was associated with lower academic performance. The fact that a significant statistical association was not found between HIV exposure status and academic performance may reflect inadequate power to detect a true association. Larger studies of actual academic performance would be beneficial. Interestingly, when the covariate breastfeeding was removed from the model, HIV exposure was noted to be significantly associated with lower academic performance, highlighting the known protective effect of breastfeeding on neurodevelopment [29]. Among children HEU, maternal $CD4^+$ cell count <200 cells/mm^3, detectable viral load at the time of entry in the original BHP study, and absence of receiving a three-drug ART regimen in pregnancy, three potentially biological etiologies, were not significantly associated with lower overall academic performance. This is the first study to compare actual academic performance between school-age children by HIV exposure status. This is an important approach, as performance in school, from childhood through young adulthood, has been shown to be closely associated with a person's physical and mental health, as well as their ability to successfully integrate into society [36].

Various studies have been published on cognitive outcomes, comparing children who are HEU to those who are HUU, with mixed findings. Benki-Nugent and colleagues evaluated neurocognitive functioning in a cohort of Kenyan children ages 5–12 years, including 56 children HEU and 65 HUU, employing multiple standardised neuropsychological tests [11]. Children HEU had significantly lower mean z-scores for global cognitive ability, short-term memory, attention and processing speed after adjusting for child age and sex, caregiver age, caregiver education, child nutritional status, household food security and orphanhood [11]. In a Canadian cohort, early academic achievement was measured utilizing the Word Reading, Spelling, and Math Computation subtests of the Wide Range Achievement Test—Fourth Edition (WRAT4) [43] among 110 children HEU and 43 children HUU. While children HEU scored within the average range on these three measures, mean scores were significantly lower compared to children HUU in word reading and math computation [12]. Interestingly, the Tshipidi study, the BHP study in which a portion of our FLOURISH caregiver-child pairs participated, found no difference in neurodevelopmental outcomes at 24 months of life between children HEU and those who were HUU [39]. Our study, although not relying on a standardised battery of neurocognitive testing instruments, provides a pragmatic approach to assessing academic achievement. Participants in the FLOURISH study live in the same communities, regardless of their HIV exposure status. The curriculum is standardised nationally, developed by the Department of Curriculum Development within Botswana's Ministry of Education and Skills Development. Additionally, testing by subject matter is standardised by the Botswana Examinations Council, which also has established national standards for grading of test results. Although prior published studies comparing neurodevelopmental outcomes between children HEU and those who are HUU have relied on a battery of standardised testing instruments [35, 44, 45], it is critically important to evaluate actual academic performance, as this can be expected to exert a more direct influence on a child's self-esteem, self-confidence and enthusiasm for learning.

There are many strengths of the FLOURISH study, and some limitations as well. FLOURISH study participants being re-enrolled after historical participation in birth cohort studies conducted by BHP have allowed us to leverage detailed prospectively collected data on their mother's pregnancy and their health, feeding practices and socio-demographic history. The study design minimises misclassification of a child's HIV exposure status in infancy and their current HIV status. Participants reside in the same communities. Additionally, the fact that the curriculum in public schools in Botswana is standardised by grade level and subject, as is testing and grading is a major strength of this study. However, as in any observational study, there is the potential for unmeasured confounders. For example, data on maternal alcohol and substance use in pregnancy, although rare, were not collected historically. Given the cross-sectional design of this study, with grades collected at study enrolment, some of the children's grades would have reflected an entire school year, while others may have only represented the first semester. While it is possible that a lower grade in the first semester could motivate a student, caregivers or a teacher to intervene, the FLOURISH data highlight the fact that children HEU were disproportionately more likely to have lower grades in key subjects and overall. The FLOURISH study has enrolled fewer children HUU and, for this analysis, all were from a single prior BHP study, Tshipidi. Tshipidi children were recruited from two of the four communities from which FLOURISH participants were recruited, Gaborone and Mochudi. In a separate sensitivity analysis restricted to children recruited from Gaborone and Mochudi only, the findings were similar, both for individual subjects and overall academic performance. It is challenging to disentangle the association between breastfeeding and academic performance, given that 100% of children HUU were breastfed, while only 18% of children HEU ever breastfed. Unfortunately, we do not have historical data collected on the duration of breastfeeding for all participants. Further research is needed to understand associations between the duration of exclusive and overall breastfeeding and academic performance. In this analysis, we selected household income, report of food insecurity in the last 12 months and absence of electricity in the home as markers of poverty, with the latter two independently associated with lower academic performance [32, 40–42]. In unadjusted analysis, only household income was associated with lower academic performance and there was a high prevalence of households with electricity at 87.9%. Future studies should explore the most significant markers of poverty associated with academic performance, as poverty eradication interventions could be designed, tested and implemented to improve academic performance. Finally, we recognise that maternal and family adjustment to a diagnosis of HIV, maternal disclosure to others, including children, and the support received or stigma experienced by a person living with HIV can influence a child's academic performance. We used measures of caregiver mental health, specifically screening instruments for depression, PHQ9, and anxiety, GAD7, as surrogates for maternal adjustment to living with HIV. We acknowledge that this may not have fully captured the impact of a caregiver's experience of living with HIV on a child's academic performance.

Suboptimal neurodevelopmental outcomes, which impact actual academic performance, are influenced by individual, family and societal factors. In this quantitative analysis, societal factors were not measured and limited data were collected on potential familial factors. Future studies of actual academic performance among children HEU would benefit from a multi-level mixed methods study design measuring factors, such as illness of parents or siblings, school absenteeism, bullying, stigma, household internet access and contextually appropriate structural factors, at a minimum. Incorporation of qualitative in-depth interviews structured to capture the impact of individual family dynamics over time which could influence a child's academic performance would also be beneficial.

5 | CONCLUSIONS

In summary, there are a host of psychosocial factors that can influence a child's academic performance. While children who are HEU participating in the Botswana-based FLOURISH study were more likely to have lower academic performance in Mathematics, Science, English and in their overall grade compared to children HUU, only being a male child was significantly associated with observed differences in adjusted analyses. In this cohort, children HEU were significantly less likely to ever have been breastfed, an activity with proven neurodevelopmental benefits. As this is the first study to pragmatically compare academic performance by child HIV exposure status, additional studies are needed to validate our findings. It will be important to identify risk factors amenable to interventions. Additionally, given the large and expanding population of children HEU, screening tools are urgently needed to identify children most at risk for poor academic achievement.

AUTHORS' AFFILIATIONS

[1]Department of Internal Medicine and Pediatrics, Massachusetts General Hospital, Boston, Massachusetts, USA; [2]Department of Immunology and Infectious Diseases, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA; [3]Botswana Harvard Health Partnership, Gaborone, Botswana; [4]Department of Curriculum Development and Evaluation, Botswana Ministry of Basic Education, Gaborone, Botswana; [5]Departments of Biostatistics and Epidemiology, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA; [6]Department of Paediatrics & Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Worcester, South Africa; [7]Division of Infectious Diseases, Brigham and Women's Hospital, Boston, Massachusetts, USA; [8]Department of Pediatrics, Northwestern Feinberg School of Medicine, Chicago, Illinois, USA; [9]Departments

of Psychiatry & Psychology and Pediatric & Adolescent Medicine, Mayo Clinic, Rochester, Minnesota, USA

COMPETING INTERESTS

No authors have competing interests or have conflict of interest against the work being performed in the FLOURISH study.

AUTHORS' CONTRIBUTIONS

KMP conceived of this study, performed the statistical analysis and drafted the initial manuscript. SS prepared the datasets for the analysis. SWK, MM and MN performed data cleaning on anomalous data. PLW and ALS provided guidance on the statistical analysis plan and interpretation. LL, SS, GM, SWK, MN, CK, PLW, ALS, RLS, SL, MOM, JMM, JJ and ARC all provided editorial input in the preparation of the final manuscript.

ACKNOWLEDGEMENTS

We are grateful to the caregiver-child participants of the FLOURISH study and to the FLOURISH study staff, without whom this study would not be possible.

FUNDING

The FLOURISH study is funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (R33 HD103099; Principal Investigators: Powis, Jao, Makhema).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

REFERENCES

1. UNAIDS. Latest Data on HIV 2022. https://aidsinfo.unaids.org/. Accessed 6 Aug 2023.
2. Anderson K, Kalk E, Madlala HP, Nyemba DC, Kassanjee R, Jacob N, et al. Increased infectious-cause hospitalization among infants who are HIV-exposed uninfected compared with HIV-unexposed. AIDS. 2021;35(14):2327–39.
3. le Roux SM, Abrams EJ, Donald KA, Brittain K, Phillips TK, Zerbe A, 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;4(3):220–31.
4. Brennan AT, Bonawitz R, Gill CJ, Thea DM, Kleinman M, Long L, et al. A meta-analysis assessing diarrhea and pneumonia in HIV-exposed uninfected compared with HIV-unexposed uninfected infants and children. J Acquir Immune Defic Syndr. 2019;82(1):1–8.
5. Brennan AT, Bonawitz R, Gill CJ, Thea DM, Kleinman M, Useem J, et al. A meta-analysis assessing all-cause mortality in HIV-exposed uninfected compared with HIV-unexposed uninfected infants and children. AIDS. 2016;30(15):2351–60.
6. Ajibola G, Leidner J, Mayondi GK, van Widenfelt E, Madidimalo T, Petlo C, et al. HIV exposure and formula feeding predict under-2 mortality in HIV-uninfected children, Botswana. J Pediatr. 2018;203:68–75 e2.
7. Tukei VJ, Machekano R, Gill MM, Tiam A, Mokone M, Isavwa A, et al. 24-Month HIV-free survival among HIV-exposed infants in Lesotho: the PEAWIL cohort study. J Int AIDS Soc. 2020;23(12):e25648.
8. Neary J, Langat A, Singa B, Kinuthia J, Itindi J, Nyaboe E, et al. Higher prevalence of stunting and poor growth outcomes in HIV-exposed uninfected than HIV-unexposed infants in Kenya. AIDS. 2022;36(4):605–10.
9. Aizire J, Sikorskii A, Ogwang LW, Kawalazira R, Mutebe A, Familiar-Lopez I, et al. Decreased growth among antiretroviral drug and HIV-exposed uninfected versus unexposed children in Malawi and Uganda. AIDS. 2020;34(2):215–25.
10. Fowler MG, Aizire J, Sikorskii A, Atuhaire P, Ogwang LW, Mutebe A, et al. Growth deficits in antiretroviral and HIV-exposed uninfected versus unexposed children in Malawi and Uganda persist through 60 months of age. AIDS. 2022;36(4):573–82.
11. Benki-Nugent SF, Yunusa R, Mueni A, Laboso T, Tamasha N, Njuguna I, et al. Lower neurocognitive functioning in HIV-exposed uninfected children compared with that in HIV-unexposed children. J Acquir Immune Defic Syndr. 2022;89(4):441–7.
12. Young JM, Bitnun A, Read SE, Smith ML. Early academic achievement of HIV-exposed uninfected children compared to HIV-unexposed uninfected children at 5 years of age. Child Neuropsychol. 2021;27(4):532–47.
13. Prendergast AJ, Evans C. Children who are HIV-exposed and uninfected: evidence for action. AIDS. 2023;37(2):205–15.
14. Jalbert E, Ghosh T, Smith C, Amaral FR, Mussi-Pinhata MM, Weinberg A. Impaired functionality of antigen presenting cells in HIV-exposed uninfected infants in the first six months of life. Front Immunol. 2022;13:960313.
15. Afran L, Jambo KC, Nedi W, Miles DJC, Kiran A, Banda DH, et al. Defective monocyte enzymatic function and an inhibitory immune phenotype in human immunodeficiency virus-exposed uninfected African infants in the era of antiretroviral therapy. J Infect Dis. 2022;226(7):1243–55.
16. Dzanibe S, Lennard K, Kiravu A, Seabrook MSS, Alinde B, Holmes SP, et al. Stereotypic expansion of T regulatory and Th17 cells during infancy is disrupted by HIV exposure and gut epithelial damage. J Immunol. 2022;208(1):27–37.
17. Gabriel B, Medin C, Alves J, Nduati R, Bosire RK, Wamalwa D, et al. Analysis of the TCR repertoire in HIV-exposed but uninfected infants. Sci Rep. 2019;9(1):11954.
18. Williams ME, Janse Van Rensburg A, Loots DT, Naude PJW, Mason S. Immune dysregulation is associated with neurodevelopment and neurocognitive performance in HIV pediatric populations—a scoping review. Viruses. 2021;13(12):2543.
19. Dirajlal-Fargo S, Mussi-Pinhata MM, Weinberg A, Yu Q, Cohen R, Harris DR, et al. HIV-exposed-uninfected infants have increased inflammation and monocyte activation. AIDS. 2019;33(5):845–53.
20. Bertran-Cobo C, Wedderburn CJ, Robertson FC, Subramoney S, Narr KL, Joshi SH, et al. A neurometabolic pattern of elevated myo-inositol in children who are HIV-exposed and uninfected: a South African Birth Cohort Study. Front Immunol. 2022;13:800273.
21. Sevenoaks T, Wedderburn CJ, Donald KA, Barnett W, Zar HJ, Stein DJ, et al. Association of maternal and infant inflammation with neurodevelopment in HIV-exposed uninfected children in a South African birth cohort. Brain Behav Immun. 2021;91:65–73.
22. Elenga N, Djossou FEL, Nacher M. Association between maternal human immunodeficiency virus infection and preterm birth: a matched case–control study from a pregnancy outcome registry. Medicine (Baltimore). 2021;100(4):e22670.
23. Shinar S, Agrawal S, Ryu M, Walmsley S, Serghides L, Yudin MH, et al. Perinatal outcomes in women living with HIV-1 and receiving antiretroviral therapy—a systematic review and meta-analysis. Acta Obstet Gynecol Scand. 2022;101(2):168–82.
24. Ndiaye A, Suneson K, Njuguna I, Ambler G, Hanke T, John-Stewart G, et al. Growth patterns and their contributing factors among HIV-exposed uninfected infants. Matern Child Nutr. 2021;17(2):e13110.
25. Ruck C, Reikie BA, Marchant A, Kollmann TR, Kakkar F. Linking susceptibility to infectious diseases to immune system abnormalities among HIV-exposed uninfected infants. Front Immunol. 2016;7:310.
26. Baroncelli S, Galluzzo CM, Liotta G, Andreotti M, Mancinelli S, Mphwere R, et al. Immune activation and microbial translocation markers in HIV-exposed uninfected Malawian infants in the first year of life. J Trop Pediatr. 2019;65(6):617–25.
27. Herz J, Bendix I, Felderhoff-Muser U. Peripheral immune cells and perinatal brain injury: a double-edged sword? Pediatr Res. 2022;91(2):392–403.
28. Arpino C, Compagnone E, Montanaro ML, Cacciatore D, De Luca A, Cerulli A, et al. Preterm birth and neurodevelopmental outcome: a review. Childs Nerv Syst. 2010;26(9):1139–49.
29. Bar S, Milanaik R, Adesman A. Long-term neurodevelopmental benefits of breastfeeding. Curr Opin Pediatr. 2016;28(4):559–66.
30. Wall-Wieler E, Roos LL, Gotlib IH. Maternal depression in early childhood and developmental vulnerability at school entry. Pediatrics. 2020;146(3):e20200794.
31. Bell MF, Bayliss DM, Glauert R, Ohan JL. Developmental vulnerabilities in children of chronically ill parents: a population-based linked data study. J Epidemiol Community Health. 2019;73(5):393–400.
32. Gallegos D, Eivers A, Sondergeld P, Pattinson C. Food insecurity and child development: a state-of-the-art review. Int J Environ Res Public Health. 2021;18(17):8990. https://doi.org/10.3390/ijerph18178990
33. Larson CP. Poverty during pregnancy: its effects on child health outcomes. Paediatr Child Health. 2007;12(8):673–7.
34. le Roux SM, Donald KA, Brittain K, Phillips TK, Zerbe A, Nguyen KK, et al. Neurodevelopment of breastfed HIV-exposed uninfected and HIV-unexposed children in South Africa. AIDS. 2018;32(13):1781–91.
35. Ntozini R, Chandna J, Evans C, Chasekwa B, Majo FD, Kandawasvika G, et al. Early child development in children who are HIV-exposed uninfected compared to children who are HIV-unexposed: observational sub-study of a cluster-randomized trial in rural Zimbabwe. J Int AIDS Soc. 2020;23(5):e25456.

36. Zajacova A, Lawrence EM. The relationship between education and health: reducing disparities through a contextual approach. Annu Rev Public Health. 2018;39:273–89.
37. Shapiro RL, Hughes MD, Ogwu A, Kitch D, Lockman S, Moffat C, et al. Antiretroviral regimens in pregnancy and breast-feeding in Botswana. N Engl J Med. 2010;362(24):2282–94.
38. Lockman S, Hughes M, Powis K, Ajibola G, Bennett K, Moyo S, et al. Effect of co-trimoxazole on mortality in HIV-exposed but uninfected children in Botswana (the Mpepu Study): a double-blind, randomised, placebo-controlled trial. Lancet Glob Health. 2017;5(5):e491–500.
39. Chaudhury S, Williams PL, Mayondi GK, Leidner J, Holding P, Tepper V, et al. Neurodevelopment of HIV-exposed and HIV-unexposed uninfected children at 24 months. Pediatrics. 2017;140(4):e20170988.
40. Jyoti DF, Frongillo EA, Jones SJ. Food insecurity affects school children's academic performance, weight gain, and social skills. J Nutr. 2005;135(12):2831–9.
41. Zhang Q, Appau S, Lord Kodom P. Energy poverty, children's wellbeing and the mediatiating role of academic performance: evidence from China. Energy Econ. 2011;97.
42. Rajaona Daka K, Ballet J. Children's education and home electrification: a case study in northwestern Madagascar. Energy Policy. 2011;39(5): 2866–74.
43. Wilkinson G, Robertson G. Wide Range Achievement Test Psychological Assessment Resources. 2006.
44. Madlala HP, Myer L, Malaba TR, Newell ML. Neurodevelopment of HIV-exposed uninfected children in Cape Town, South Africa. PLoS One. 2020;15(11):e0242244.
45. Cassidy AR, Williams PL, Leidner J, Mayondi G, Ajibola G, Makhema J, et al. In utero efavirenz exposure and neurodevelopmental outcomes in HIV-exposed uninfected children in Botswana. Pediatr Infect Dis J. 2019;38(8): 828–34.

Bulterys MA et al. *Journal of the International AIDS Society* 2023, **26**(S4):e26159
http://onlinelibrary.wiley.com/doi/10.1002/jia2.26159/full | https://doi.org/10.1002/jia2.26159

JIAS
JOURNAL OF THE INTERNATIONAL AIDS SOCIETY

COMMENTARY

Neurodevelopment among children exposed to HIV and uninfected in sub-Saharan Africa

Michelle A. Bulterys[1,2,§], Irene Njuguna[2,3], Mary Mahy[4], Laurie A. Gulaid[5], Katheen M. Powis[6,7,8], Catherine J. Wedderburn[9,10] and Grace John-Stewart[1,2,11,12]

[§]**Corresponding author**: Michelle A. Bulterys, 3980 15th Ave NE, Seattle, WA 98195, USA. Tel: +1 (626) 375-8610. (mbult@uw.edu)

Abstract

Introduction: The population of 16 million children exposed to HIV and uninfected (CHEU) under 15 years of age continues to expand rapidly, and the estimated prevalence of CHEU exceeds 20% in several countries in sub-Saharan Africa with high HIV prevalence. Some evidence suggests that CHEU experience suboptimal neurodevelopmental outcomes compared to children born to women without HIV. In this commentary, we discuss the latest research on biologic and socio-behavioural factors associated with neurodevelopmental outcomes among CHEU.

Discussion: Some but not all studies have noted that CHEU are at risk of poorer neurodevelopment across multiple cognitive domains, most notably in language and motor skills, in diverse settings, ages and using varied assessment tools. Foetal HIV exposure can adversely influence infant immune function, structural brain integrity and growth trajectories. Foetal exposure to antiretrovirals may also influence outcomes. Moreover, general, non-CHEU-specific risk factors for poor neurodevelopment, such as preterm birth, food insecurity, growth faltering and household violence, are amplified among CHEU; addressing these factors will require multi-factorial solutions. There is a need for rigorous harmonised approaches to identify children at the highest risk of delay. In high-burden HIV settings, existing maternal child health programmes serving the general population could adopt structured early child development programmes that educate healthcare workers on CHEU-specific risk factors and train them to conduct rapid neurodevelopmental screening tests. Community-based interventions targeting parent knowledge of optimal caregiving practices have shown to be successful in improving neurodevelopmental outcomes in children and should be adapted for CHEU.

Conclusions: CHEU in sub-Saharan Africa have biologic and socio-behavioural factors that may influence their neurodevelopment, brain maturation, immune system and overall health and wellbeing. Multidisciplinary research is needed to disentangle complex interactions between contributing factors. Common environmental and social risk factors for suboptimal neurodevelopment in the general population are disproportionately magnified within the CHEU population, and it is, therefore, important to draw on existing knowledge when considering the socio-behavioural pathways through which HIV exposure could impact CHEU neurodevelopment. Approaches to identify children at greatest risk for poor outcomes and multisectoral interventions are needed to ensure optimal outcomes for CHEU in sub-Saharan Africa.

Keywords: CHEU; children who are HIV-exposed uninfected; HEU; neurodevelopment; perinatal HIV exposure; sub-Saharan Africa

Received 27 January 2023; **Accepted** 21 August 2023

1 | INTRODUCTION

Successful prevention of vertical infant HIV acquisition has resulted in an expanding population of 16 million children exposed to HIV and uninfected (CHEU) under 15 years of age, according to the 2023 UNAIDS Spectrum estimates [1–3]. CHEU represent over three-quarters of all children born to the 1.3 million women living with HIV who give birth annually worldwide, the majority of whom reside in sub-Saharan Africa [1, 4]. UNAIDS estimates the prevalence of CHEU among all children <15 years in the population exceeds 20% in several sub-Saharan African countries, with over one million CHEU born every year (Figure 1) [1, 4]. CHEU are at higher risk of adverse health outcomes, including suboptimal neurodevelopment, compared to children who are HIV-unexposed and uninfected (CHUU) [1, 4–17]. A recent meta-analysis of eight high-quality studies combining neurodevelopment data from ~5000 CHEU and CHUU, primarily from sub-Saharan Africa, found CHEU had significantly lower scores in expressive language and gross motor domains by age 2 years across a variety of settings and assessment tools [6, 11, 18–26]. Even subtle early neurodevelopment impairments can

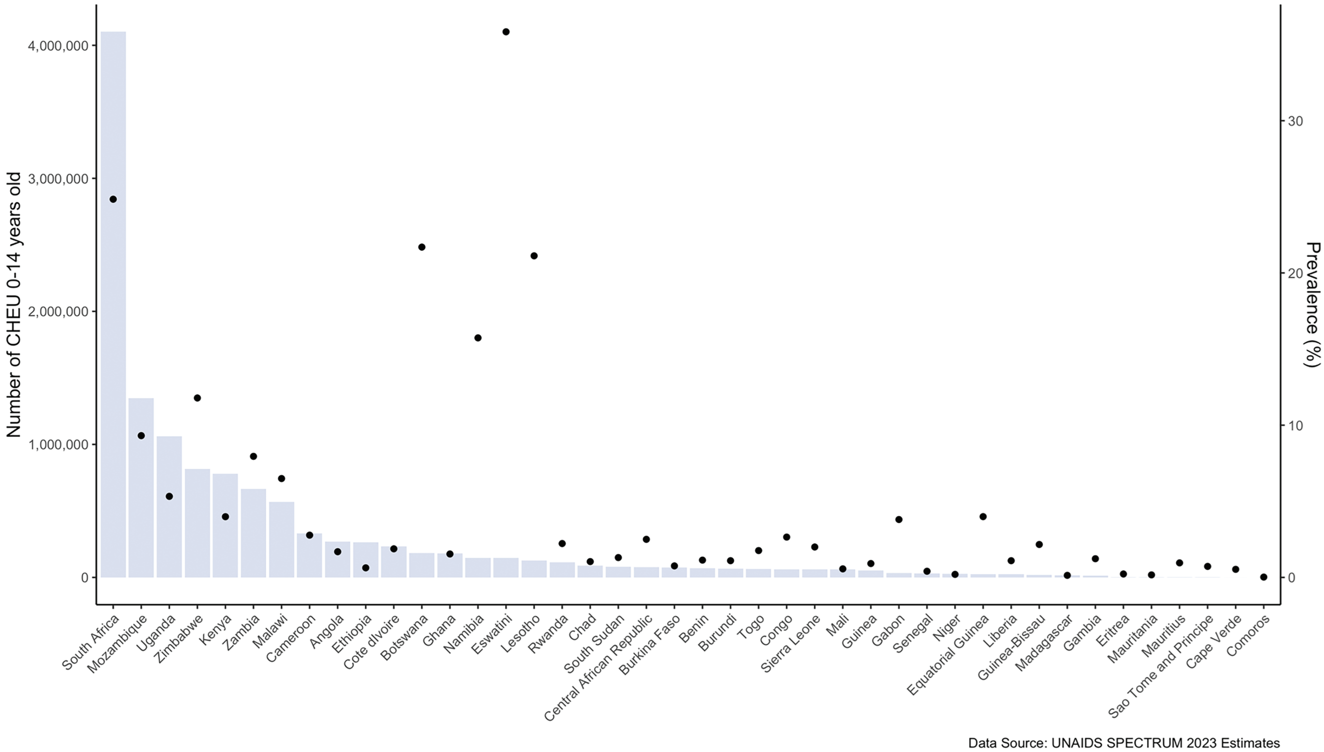

Figure 1. Double-axis figure of the number of CHEU aged 0–14 years, and prevalence of CHEU, by sub-Saharan African country (UNAIDS 2023 estimates).
This double-axis figure depicts the (x axis) number of children exposed to HIV and uninfected (CHEU), 0–14 years old, and the (y axis) prevalence of CHEU among the child population aged 0–14 years, by sub-Saharan African country. Figure by Drs. Michelle Bulterys and Mary Mahy, using UNAIDS 2023 estimates.

have lifelong physical and mental wellbeing implications. Early interventions in the first 1000 days of life, from conception through a child's second birthday, can greatly improve outcomes [27–31]. This commentary discusses potential biologic and socio-behavioural mechanistic pathways that could synergistically impact neurodevelopment among CHEU and synthesises existing literature on the key ingredients for cultivating optimal neurodevelopment for CHEU (Figure 2).

2 | DISCUSSION

2.1 | *In-utero* exposure to HIV and the intrauterine environment

Infant brain development *in utero* may be influenced by exposures to infectious pathogens or to drugs, and both may play a role in the context of maternal HIV, but these mechanistic pathways have yet to be fully established. High levels of HIV viremia among mothers during pregnancy have been associated with poorer expressive language and motor skills among CHEU [32]. HIV antigen and ribonucleic acid are detectable in placental and foetal membranes and it is possible that exposure to the HIV virus leads to inflammatory changes that influence neurodevelopment [33, 34]. The HIV virus can alter vaginal microbiota which, in turn, has also been associated with child neurodevelopmental delay [35]. Pregnant women with HIV exhibit six times higher incidence of endometrial, placental and amniotic infections, such as cytomegalovirus, which could impact neurodevelopment among CHEU [13, 36–38]. Maternal immune activation, immunosuppression, lower transfer of passively transferred antibodies and altered cell-mediated immune function may play a role in modifying neurodevelopmental outcomes [10, 13, 16, 39–42]. Additionally, maternal folic acid and iron deficiency during pregnancy have been associated with neurodevelopment and may be altered by perinatal exposure to HIV, but have not been adequately studied among CHEU [43]. Moreover, CHEU may themselves have immunologic changes that affect their neurodevelopment that warrant exploration [10, 44–46].

2.2 | Antiretroviral therapy exposure

There are inconsistent and limited data on the influence of antiretroviral therapy (ART) exposure on CHEU neurodevelopment [11, 18, 47, 48]. Foetal ART exposure has been associated with subtle but significantly reduced immune function through 8 years [49, 50]. However, studies were subject to substantial confounding, as CHEU with foetal ART exposure were likely systematically different from CHEU born without the use of maternal ART. Some but not all studies have found ART exposure to be associated with substantial ART drug levels, febrile seizures, mitochondrial dysfunction

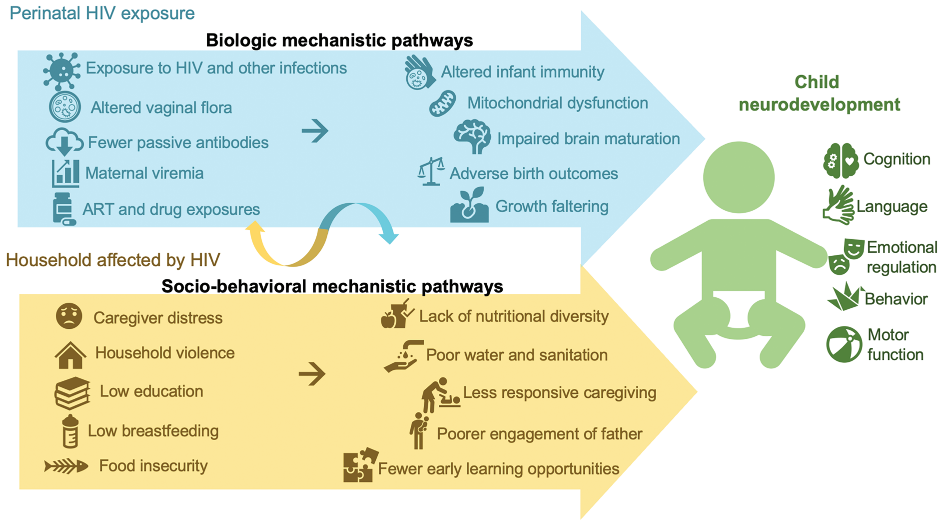

Figure 2. Biologic and socio-behavioural mechanistic pathways through which CHEU status might impact neurodevelopment. **This conceptual model summarises the potential biologic and socio-behavioural mechanistic pathways through which perinatal HIV exposure might impact child neurodevelopment among children exposed to HIV and uninfected (CHEU).**

and neurologic disorders in CHEU [51–54]. Although some studies reported that a longer duration of foetal exposure to atazanavir-based regimens was associated with lower language scores at 12 months, other studies at 24 months found no notable differences [32, 55–57]. In Botswana, foetal exposure to efavirenz (EFV)-based regimens was associated with neurodevelopmental deficits among 2-year-old CHEU, compared to non-EFV-based regimens [58]. It is also critical to understand the safety of evolving HIV treatments during pregnancy; the World Health Organisation (WHO)'s recommendation to transition all individuals living with HIV to dolutegravir (DTG)-based regimens provided a unique opportunity to assess the impact of foetal DTG exposure on CHEU neurodevelopment [59]. A recent multi-site prospective longitudinal cohort of Kenyan CHEU found that compared to foetal exposure to an EFV-based maternal ART, a DTG-based regimen was associated with better gross motor scores at 1 year (Bulterys et al., included in this supplement). To date, there are scant neurodevelopment data following foetal exposure to long-acting ART. With any observational study, unmeasured confounding could bias results; but this collective body of literature suggests that maternal ART could play a role in CHEU neurodevelopment. Ultimately, the benefits of ART for maternal HIV treatment and prevention of vertical transmission greatly outweigh the risks of rare and modest adverse outcomes. However, employing rigorous scientific practices to identify the safest drugs for use in pregnancy and the postnatal period for women living with HIV remains important [57].

2.3 | Brain maturation and imaging studies

Rapid brain growth in the first 1000 days of life is vital for developing healthy cognitive systems [60, 61]. A recent magnetic resonance imaging (MRI) study in South Africa observed that ART-exposed newborns had significantly lower volumes of total grey matter and size of the caudate nucleus, a key component of the basal ganglia, than CHUU [60]. These structures are fundamental for brain function, and alterations have been associated with neurologic disorders (e.g. autism spectrum disorder, attention-deficit disorders and schizophrenia) [61–64]. This association was strongest among mothers with lower CD4 cell counts in pregnancy [60], indicating that more advanced HIV viremia and corresponding immune abnormalities may be driving some differences. Separately, another South African study found smaller basal ganglia nuclei in CHEU [65], most notably associated with maternal ART initiation during pregnancy compared to pre-pregnancy and higher HIV viremia, suggesting that ART may be protective due to its effect on maternal immune health [65]. Other MRI studies have detected significantly altered metabolites in the basal ganglia, including choline (regulator of mood and intelligence) and creatine (regulator of energy production) among older CHEU [66–68], while diffusion tensor imaging has revealed altered white matter microstructural integrity (essential for visuospatial and memory cognition) among CHEU [69, 70]. Finally, a recent magnetic resonance spectroscopy study suggests perinatal HIV exposure to be associated with neurometabolic patterns indicative of neuroinflammation, which may increase the risk of neurodevelopmental delay [71]. It will be important to pair cutting-edge neuroimaging research, leveraging scalable low-field MRI technologies, with contextually appropriate neurodevelopment assessments to determine whether neuroimaging could represent the earliest signal of suboptimal neurodevelopmental outcomes for which interventions could be developed and tested.

2.4 | Birth outcomes

CHEU are twice as likely as CHUU to be born preterm (<37 weeks gestational age) and have low birth weight (<2500 grams), both of which are associated with increased risk of poorer neurodevelopment [10, 13, 23, 45, 72–75]. In South

Africa, preterm birth modified the relationship between perinatal HIV exposure and poorer neurodevelopment; preterm CHEU had five times higher odds of delay compared to preterm CHUU [23]. Similarly, in a Kenyan cohort of CHEU, preterm birth was significantly associated with poorer gross motor scores at 1 year (Bulterys et al., included in this supplement). Among pregnant Ugandan women living with HIV, an increased risk of preterm birth was associated with maternal weight gain of less than 0.1 kg per week during gestation, highlighting the importance of supporting maternal nutrition during pregnancy [76]. Research is needed to identify modifiable predictors of preterm birth among CHEU.

2.5 | Growth and nutrition

CHEU have higher prevalence of childhood stunting, wasting and microcephaly than CHUU, and growth faltering could lie on the pathway between HIV exposure and neurodevelopmental delay [77]. It is unclear whether suboptimal growth outcomes are amplified among the CHEU population, or simply a result of higher frequencies of exposures like preterm birth among CHEU [78–82]. Exclusive, prolonged breastfeeding has been shown to improve child growth and neurodevelopmental outcomes [20, 83]. However, despite increased exclusive and longer breastfeeding durations in CHEU than CHUU in some South African and Kenyan settings, evidence has shown that CHEU remain at higher risk of undernutrition, poorer growth and infectious morbidity [77, 84]. Poor maternal nutrition while lactating, despite optimal breastfeeding practices, could be one potential mechanism that explains growth faltering among breastfed CHEU [77, 85]. Households affected by HIV in sub-Saharan Africa face multifactorial health and social disparities, including greater food insecurity and lower access to safe water, sanitation and hygiene (WASH), compared to the general population [20, 86], which significantly predict poorer neurodevelopment [32, 46, 55, 87]. In the Zimbabwean SHINE Trial, CHEU randomised to a combined food supplementation and WASH intervention performed significantly better on neurodevelopmental assessments compared to the standard of care; however, children randomised to either food supplementation or WASH alone did not exhibit neurodevelopmental improvements, demonstrating the importance of multi-factorial interventions [88, 89]. Vigilant growth monitoring and nutritional support should be prioritised for CHEU, particularly for those who were born prematurely.

2.6 | Home environment and caregiving

Beyond the biologic pathways described above, universal risk factors for child neurodevelopment, such as poor caregiver mental health, violence and food insecurity in the household, are amplified among CHEU [90–92]. Women living with HIV experience disproportionately high rates of intimate partner violence and food insecurity which considerably threaten a child's neurodevelopment and academic performance [28, 29, 91–104]. These factors can impact a caregiver's ability to care responsively for their children, and likely serve as potential confounders or modifiers along the biological pathways described above [96–98]. Couples affected by HIV also experience relationship dissolution more often than couples in the general population, and pregnant women living with HIV cite often fear of abandonment to be their most prominent barrier to HIV status disclosure [100, 105–107]. On average, HIV serodifferent couples separate five times more often when the female is the one living with HIV compared to the male, and this association was also compounded by financial insecurity [105, 107]. Attributable to many of these social disparities, women living with HIV are at high risk of stress, anxiety, depression and suicidal ideation [29, 108], and studies have consistently found a strong relationship between a mother living with HIV, distress and poorer child neurodevelopment [109–111]. Both paternal absence and poor maternal mental health can reduce the quantity and quality of parent-child interactions, which could impact a child's exposure to responsive caregiving and early learning opportunities [112]. Despite the critical impact of these caregiver factors, mental health, relationship counselling and violence-reduction interventions are rarely implemented in low-resource settings where the healthcare cadre are overtaxed [113]. Thus, caregiver conflict and distress could further contribute to suboptimal neurodevelopment among CHEU, which calls for caregiver-targeted interventions.

2.7 | Programmatic support for CHEU

Sub-Saharan Africa has the highest prevalence in the world of children <5 years at risk of not reaching their developmental potential, and CHEU represent a substantial proportion of this population [114]. Achieving healthy neurodevelopment by age 5 requires culturally contextual, multi-factorial approaches. To address biologic risk factors faced by CHEU, it is critical to optimise maternal health; newer ART regimens promote maternal health through improved safety, ART adherence and viral suppression. The SHINE Trial described above, which tested the effects of improved WASH and food supplementation on CHEU neurodevelopment, only found evidence of benefit in the combined intervention arm [88, 115, 116]. There is a need for further research to inform the development of cross-cutting interventions and normative guidance to best support CHEU.

Not every CHEU will need additional support, so systematic screening is necessary. CHEU are not tracked systematically, and screening may be challenging to implement in already overburdened, resource-limited settings. Incorporating monitoring within existing Maternal and Child Health programmes, in which many HIV-oriented programmes are already housed may be feasible. Ideally, these existing programmes serving the general population could adopt structured neurodevelopment training programmes that educate healthcare workers on CHEU-specific risk factors and train them to conduct rapid neurodevelopmental screening tests to identify children at the highest risk of delay. Accurate and rapid screening tools that can be delivered by healthcare workers as well as lay people in the community are needed. The three most common screening tests used in sub-Saharan Africa are the Ages and Stages Questionnaire, Strengths and Difficulties Questionnaire and Ten Questions Questionnaire; all three have strong interobserver reliability and cover different age bands [117–119].

The WHO and UNICEF currently recommend countries rely on the Nurturing Care Framework to improve early child development [112]. This framework consists of five interdependent domains—health, nutrition, responsive caregiving, safety and early learning opportunities—which have shown to result in optimal neurodevelopment, if adequately provided by caregivers. Delivering this education to caregivers in the first 2 years of life, when CHEU families are actively engaged in Maternal and Child Health care, maximises benefits at a critical time [31, 120, 121]. A large cohort study of 10,500 CHEU, from 23 clinics across Kenya, estimated the incidence of loss-to-follow-up (LTFU) from perinatal care was >20 per 100 child-years [122]. In this study, LTFU was significantly lower among CHEU who received food supplementation compared to those who did not (Hazard Ratio = 0.58) [122]. Food supplementation may incentivise caregivers to remain engaged in care. LTFU was more common among CHEU who were orphaned, malnourished, stunted or wasted, from rural residence, or had >3 siblings, in studies in Kenya, Malawi and Ethiopia [122–124]. Routine neurodevelopmental screenings should coincide with routine paediatric care visits, when children are already receiving immunisations and growth monitoring, to reduce the burden on caregivers and healthcare workers [125]. Mothers attending HIV services could also receive brief materials at each perinatal visit about the importance of at-home stimulation, responsive caregiving, maternal mental health, WASH and diverse nutrition (and if needed, food supplementation) [125].

Existing early child development programmes can be leveraged for CHEU; successful interventions for promoting neurodevelopment in the general population are likely to be effective among CHEU. Clinical trials have demonstrated effectiveness in improving neurodevelopmental outcomes in resource-limited settings and this evidence base should be leveraged and adapted for CHEU. Large meta-analyses of interventions in low-and-middle-income countries found that providing parents with education about responsive interaction, at-home stimulation, and providing a safe and healthy home environment, were more effective in improving neurodevelopmental outcomes than interventions that targeted nutrition, water and sanitation [31, 120, 126, 127]. Interventions to promote responsive caregiving and infant stimulation techniques, such as book-sharing, [128] significantly improve parental knowledge, frequency and quality of interactions, and child neurodevelopment [31, 125, 128]. It is critical to identify the optimal delivery models of caregiver-targeted education in sub-Saharan Africa, which may be adapted for varied regional settings. Video-based interventions are efficient for reducing healthcare worker burden; in clinics with technological capabilities, educational videos for mothers in waiting rooms could improve child neurodevelopmental outcomes [129–132]. There is also a need to reach caregivers who are not engaged in clinical care, through non-clinic, community-based or home-delivered interventions that leverage community health workers and mobile health innovations [133].

In cases of suspected neurodevelopmental disability (as opposed to just delay), healthcare workers need clear and effective referral pathways to connect children to specialists for comprehensive assessments and treatment. Fortunately, there are efficacious evidence-based treatments for children with developmental disabilities in high HIV-burden settings which could be adopted [121, 134, 135]. In settings where specialists are few and costly, simple, community-based interventions can be designed to support families requiring additional support. Iterative input from key stakeholders like in-country HIV and paediatric care decision-makers, health providers and caregivers will be fundamental for designing, delivering and monitoring these programmes. Most importantly, rigorous research that generates local evidence will be critical to secure governmental buy-in and financial support, both essential for the successful implementation and sustainability of such programmes for CHEU.

3 | CONCLUSIONS

Biological and socio-behavioural factors can collectively contribute to child development. CHEU are at disproportionate risk of biologic, social and household factors that may threaten their ability to achieve optimal maturation of their brain, immune system, and overall health and wellbeing. Multidisciplinary research is needed to disentangle the modifiable aspects of and complex interactions between potential contributing factors.

AUTHORS' AFFILIATIONS

[1]Department of Epidemiology, University of Washington, Seattle, Washington, USA; [2]Department of Global Health, University of Washington, Seattle, Washington, USA; [3]Kenyatta National Hospital, Nairobi, Kenya; [4]UNAIDS, Geneva, Switzerland; [5]UNICEF, eastern and southern Africa Regional Office, Nairobi, Kenya; [6]Harvard Medical School, Boston, Massachusetts, USA; [7]Department of Immunology and Infectious Diseases, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA; [8]Department of Internal Medicine and Pediatrics, Massachusetts General Hospital, Boston, Massachusetts, USA; [9]Department of Pediatrics and Child Health and Neuroscience Institute, University of Cape Town, Cape Town, South Africa; [10]Department of Clinical Research, London School of Hygiene & Tropical Medicine, London, UK; [11]Department of Pediatrics, University of Washington, Seattle, Washington, USA; [12]School of Medicine, University of Washington, Seattle, Washington, USA

COMPETING INTERESTS

The authors have no competing interests to disclose.

AUTHORS' CONTRIBUTIONS

The initial topic of this commentary was developed by MAB and GJ-S. MAB led manuscript development with detailed guidance and iterative feedback from IN, MM, LAG, KMP, CJW and GJ-S. All authors reviewed the manuscript and approved it for publication.

ACKNOWLEDGEMENTS

We would like to thank and acknowledge the numerous researchers and clinicians from around the world who contributed to the body of literature summarised here.

REFERENCES

1. Joint United Nations Programme on HIV/AIDS (UNAIDS). UNAIDS Spectrum Estimates. AIDSinfo: people living with HIV receiving ART. 2023 [Cited 2023 Jul 10] https://aidsinfo.unaids.org
2. Joint United Nations Programme on HIV/AIDS (UNAIDS). Quick Start Guide for Spectrum. 2019 [Cited 2023 Jul 2] https://www.unaids.org/sites/default/files/media_asset/QuickStartGuide_Spectrum_en.pdf
3. Mahy M, Brown T, Stover J, Walker N, Stanecki K, Kirungi W, et al. Producing HIV estimates: from global advocacy to country planning and impact measurement. Glob Health Action. 2017;10(sup1):1291169.

4. Slogrove AL, Becquet R, Chadwick EG, Côté HCF, Essajee S, Hazra R, et al. Surviving and thriving-shifting the public health response to HIV-exposed uninfected children: report of the 3rd HIV-exposed uninfected child workshop. Front Pediatr. 2018;6:157.
5. Slogrove A, Powis KM, Johnson LF, Stover J, Mahy M. Estimates of the global population of children who are HIV-exposed and uninfected, 2000–18: a modeling study. Lancet Glob Health. 2020;8(1):67–75.
6. Wedderburn CJ, Yeung S, Rehman AM, Stadler JAM, Nhapi RT, Barnett W, et al. Neurodevelopment of HIV-exposed uninfected children in South Africa: outcomes from an observational birth cohort. Lancet Child Adolesc Health. 2019;3(11):P803–13.
7. McGrath CJ, Nduati R, Richardson BA, Kristal AR, Mbori-Ngacha D, Farquhar C, et al. The prevalence of stunting is high in HIV-1-exposed uninfected infants in Kenya. J Nutr. 2012;142(4):757–63.
8. Kuhn L, Sinkala M, Semrau K, Kankasa C, Kasonde P, Mwiya M, et al. Elevations in mortality associated with weaning persist into the second year of life among uninfected children born to HIV-infected mothers. Clin Infect Dis. 2010;50(3):437–44.
9. Slogrove A. It is a question of equity: time to talk about children who are HIV-exposed and "HIV-free". J Int AIDS Soc. 2021;24(11):e25850.
10. Anderson K, Kalk E, Madlala HP, Nyemba DC, Kassanjee R, Jacob N, et al. Increased infectious-cause hospitalization among infants who are HIV-exposed uninfected compared with HIV-unexposed. AIDS. 2021;35(14):2327–39.
11. McHenry MS, McAteer CI, Oyungu E, Mcdonald BC, Bosma CB, Mpofu PB, et al. Neurodevelopment in young children born to HIV-infected mothers: a meta-analysis. Pediatrics. 2018;141(2):e20172888.
12. Makasa M, Kasonka L, Chisenga M, Sinkala M, Chintu C, Tomkins A, et al. Early growth of infants of HIV-infected and uninfected Zambian women. Trop Med Int Health. 2007;12(5):594–602.
13. Ackerman W 4th, Kwiek JJ. Role of the placenta in adverse perinatal outcomes among HIV-1 seropositive women. J Nippon Med Sch. 2013;80(2):90–4.
14. Slogrove A, Reikie B, Naidoo S, De Beer C, Ho K, Cotton M, et al. HIV-exposed uninfected infants are at increased risk for severe infections in the first year of life. J Trop Pediatr. 2012;58(6):505–8.
15. Moseholm E, Helleberg M, Nordly SB, Rosenfeldt V, Storgaard M, Pedersen G, et al. Hospital admission among HIV-exposed uninfected children compared with HIV-unexposed children. AIDS. 2016;30(17):2697–706.
16. Abu-Raya B, Kollmann TR, Marchant A, MacGillivray DM. The immune system of HIV-exposed uninfected infants. Front Immunol. 2016;7:383.
17. Brennan AT, Bonawitz R, Gill CJ, Thea DM, Kleinman M, Useem J, et al. A meta-analysis assessing all-cause mortality in HIV-exposed uninfected compared with HIV-unexposed uninfected infants and children. AIDS. 2016;30(15)::2351–:60.
18. Wedderburn CJ, Weldon E, Bertran-Cobo C, Rehman AM, Stein DJ, Gibb DM, et al. Early neurodevelopment of HIV-exposed uninfected children in the era of antiretroviral therapy: a systematic review and meta-analysis. Lancet Child Adolesc Health. 2022;6(6):393–408.
19. Benki-Nugent SF, Yunusa R, Mueni A, Laboso T, Tamasha N, Njuguna I, et al. Lower neurocognitive functioning in HIV-exposed uninfected children compared with that in HIV-unexposed children. J Acquir Immune Defic Syndr. 2022;89(4):441–7.
20. Wedderburn CJ, Evans C, Yeung S, Gibb DM, Donald KA, Prendergast AJ. Growth and neurodevelopment of HIV-exposed uninfected children: a conceptual framework. Curr HIV/AIDS Rep. 2019;16(6):501–13.
21. Sherr L, Croome N, Parra Castaneda K, Bradshaw K. A systematic review of psychological functioning of children exposed to HIV: using evidence to plan for tomorrow's HIV needs. AIDS Behav. 2014;18(11):2059–74.
22. Le Doaré K, Bland R, Newell ML. Neurodevelopment in children born to HIV-infected mothers by infection and treatment status. Pediatrics. 2012;130(5):e1326–44.
23. le Roux SM, Donald KA, Brittain K, Phillips TK, Zerbe A, Nguyen KK, et al. Neurodevelopment of breastfed HIV-exposed uninfected and HIV-unexposed children in South Africa. AIDS. 2018;32(13):1781–91.
24. Sirajee RCA, Namasopo S, Opoka RO, Lavoie S, Forgie S, Salami BO, et al. Growth faltering and developmental delay in HIV-exposed uninfected Ugandan infants: a prospective cohort study. J Acquir Immune Defic Syndr. 2021;87(1):730–40.
25. Kerr SJ, Puthanakit T, Vibol U, Aurpibul L, Vonthanak S, Kosalaraksa P, et al. Neurodevelopmental outcomes in HIV-exposed-uninfected children versus those not exposed to HIV. AIDS Care. 2014;26(11):1327–35.
26. Van Rie A, Mupuala A, Dow A. Impact of the HIV/AIDS epidemic on the neurodevelopment of preschool-aged children in Kinshasa, Democratic Republic of the Congo. Pediatrics. 2008;122(1):e123–8.
27. Grantham-McGregor S, Cheung YB, Cueto S, Glewwe P, Richter L, Strupp BJ, et al. Developmental potential in the first 5 years for children in developing countries. Lancet North Am Ed. 2007;369(9555):60–70.
28. Walker SP, Wachs TD, Gardner JM, Lozoff B, Wasserman GA, Pollitt E, et al. Child development: risk factors for adverse outcomes in developing countries. Lancet. 2007;369(9556):145–57.
29. Walker SP, Wachs TD, Grantham-McGregor S, Black MM, Nelson CA, Huffman SL, et al. Inequality in early childhood: risk and protective factors for early child development. Lancet. 2011;378(9799):1325–38.
30. Blair C, Raver CC. Poverty, stress, and brain development: new directions for prevention and intervention. Acad Pediatr. 2016;16(3 Suppl):S30–6.
31. Jeong J, Franchett EE, Ramos de Oliveira CV, Rehmani K, Yousafzai AK. Parenting interventions to promote early child development in the first three years of life: a global systematic review and meta-analysis. PLoS Med. 2021;18(5):e1003602.
32. le Roux SM, Donald KA, Kroon M, Phillips TK, Lesosky M, Esterhuyse L, et al. HIV viremia during pregnancy and neurodevelopment of HIV-exposed uninfected children in the context of universal antiretroviral therapy and breastfeeding: a prospective study. Pediatr Infect Dis J. 2019;38(1):70–5.
33. Backé E, Jiménez E, Unger M, Schafer A, Jauniaux E, Vogel M, et al. Demonstration of HIV-1 infected cells in human placenta by in situ hybridisation and immunostaining. J Clin Pathol. 1992;45(10):871–4.
34. Sewankambo N, Gray RH, Wawer MJ, Paxton L, Mcnairn D, Wabwire-Mangen F, et al. HIV-1 infection associated with abnormal vaginal flora morphology and bacterial vaginosis. Lancet. 1997;350(9077):546–50.
35. Juliana NCA, Suiters MJM, Al-Nasiry S, Morré SA, Peters RPH, Ambrosino E. The association between vaginal microbiota dysbiosis, bacterial vaginosis, and aerobic vaginitis, and adverse pregnancy outcomes of women living in sub-Saharan Africa: a systematic review. Front Public Health. 2020;8:567885.
36. Gompels UA, Larke N, Sanz-Ramos M, Bates M, Musonda K, Manno D, et al. Human cytomegalovirus infant infection adversely affects growth and development in maternally HIV-exposed and unexposed infants in Zambia. Clin Infect Dis. 2012;54(3):434–42.
37. Garcia-Knight MA, Nduati E, Hassan AS, Nkumama I, Etyang TJ, Hajj NJ, et al. Cytomegalovirus viraemia is associated with poor growth and T-cell activation with an increased burden in HIV-exposed uninfected infants. AIDS. 2017;31(13):1809–18.
38. Goldenberg RL, Mudenda V, Read JS, Brown ER, Sinkala M, Kamiza S, et al. HPTN 024 study: histologic chorioamnionitis, antibiotics and adverse infant outcomes in a predominantly HIV-1-infected African population. Am J Obstet Gynecol. 2006;195(4):1065–74.
39. Afran L, Garcia Knight M, Nduati E, Urban BC, Heyderman RS, Rowland-Jones SL. HIV-exposed uninfected children: a growing population with a vulnerable immune system? Clin Exp Immunol. 2014;176(1):11–22.
40. Patel SM, Jallow S, Boiditswe S, Madhi SA, Feemster KA, Steenhoff AP, et al. Placental transfer of respiratory syncytial virus antibody among HIV-exposed, uninfected infants. J Pediatr Infect Dis Soc. 2020;9(3):349–56.
41. Smith C, Jalbert E, de Almeida V, Canniff J, Lenz LL, Mussi-Pinhata MM, et al. Altered natural killer cell function in HIV-exposed uninfected infants. Front Immunol. 2017;8:470.
42. Li W, McHenry M, Oyungu E, Yang J, Xia Y, Syed F, et al. Immune checkpoint dysregulation and immune activation in HIV-exposed uninfected children. J Immunol. 2020;204(1 Supplement):225.6.
43. Ali SS. A brief review of risk-factors for growth and developmental delay among preschool children in developing countries. Adv Biomed Res. 2013;2:91.
44. Mussi-Pinhata MM, Motta F, Freimanis-Hance L, De Souza R, Szyld E, Succi RCM, et al. Lower respiratory tract infections among human immunodeficiency virus-exposed, uninfected infants. Int J Infect Dis. 2010;14(Suppl 3):e176–82.
45. Anderson K, Emmaa K, Madlala HP, Nyemba DC, Jacob N, Slogrove A, et al. Preterm birth and severe morbidity in hospitalized neonates who are HIV exposed and uninfected compared with HIV unexposed. AIDS. 2021;35(6):921–31.
46. Sevenoaks T, Wedderburn CJ, Donald KA, Barnett W, Zar HJ, Stein DJ, et al. Association of maternal and infant inflammation with neurodevelopment in HIV-exposed uninfected children in a South African birth cohort. Brain Behav Immun. 2021;91:65–73.
47. Koren G, Pastuszak A, Ito S. Drugs in pregnancy. N Engl J Med. 1998;338(16):1128–37.
48. Schnoll JG, Temsamrit B, Zhang D, Song H, Ming G-L, Christian KM. Evaluating neurodevelopmental consequences of perinatal exposure to antiretroviral drugs: current challenges and new approaches. J Neuroimmune Pharmacol. 2021;16:113–29.
49. Pacheco SE, McIntosh K, Lu M, Mofenson LM, Diaz C, Foca M, et al. Women and infants transmission study, effect of perinatal antiretroviral drug exposure

on hematologic values in HIV-uninfected children: an analysis of the women and infants transmission study. J Infect Dis. 2006;194(8):1089–97.

50. Bunders MJ, Bekker V, Scherpbier HJ, Boer K, Godfried M, Kuijpers T. Haematological parameters of HIV-1-uninfected infants born to HIV-1-infected mothers. Acta Paediatr. 2005;94(11):1571–7.

51. Barret B, Tardieu M, Rustin P, Lacroix C, Chabrol B, Desguerre I, et al.; for the French Perinatal Cohort Study Group. Persistent mitochondrial dysfunction in HIV-1-exposed but uninfected infants. AIDS. 2003;17(12):1769–85.

52. Brinkman K, ter Hofstede HJ, Burger DM, Smeitink JAM, Koopmans PP. Adverse effects of reverse transcriptase inhibitors: mitochondrial toxicity as common pathway. AIDS. 1998;12(14):1735–44.

53. Dainiak N, Worthington M, Riordan MA, Kreczko S, Goldman L. 3'-Azido-3'-deoxythymidine (AZT) inhibits proliferation in vitro of human haematopoietic progenitor cells. Br J Haematol. 1988;69(3):299–304.

54. Landreau-Mascaro A, Barret B, Mayaux MJ, Tardieu M, Blanche S; for the French Perinatal Cohort Study Group. Risk of early febrile seizure with perinatal exposure to nucleoside analogues. Lancet. 2002;359(9306):583–4.

55. Caniglia EC, Patel K, Huo Y, Williams PL, Kapetanovic S, Rich KC, et al. Atazanavir exposure in utero and neurodevelopment in infants: a comparative safety study. AIDS. 2016;30(8):1267–78.

56. Williams PL, Marino M, Malee K, Brogly S, Hughes MD, Mofenson LM, et al. Neurodevelopment and in utero antiretroviral exposure of HIV-exposed uninfected infants. Pediatrics. 2010;125(2):e250–60.

57. Van Dyke RB, Chadwick EG, Hazra R, Williams PL, Seage GR. The PHACS SMARTT Study: assessment of the safety of in utero exposure to antiretroviral drugs. Front Immunol. 2016;7:199.

58. Cassidy AR, Williams PL, Leidner J, Mayondi G, Ajibola G, Makhema J, et al. In utero efavirenz exposure and neurodevelopmental outcomes in HIV-exposed uninfected children in Botswana. Pediatr Infect Dis J. 2019;38(8):828–34.

59. World Health Organization (WHO). Update on the transition to dolutegravir-based antiretroviral therapy: report of a WHO meeting, 29–30 March 2022. https://www.who.int/publications/i/item/9789240053335; 2022. Accessed on July 10, 2023.

60. Wedderburn CJ, Groenewold NA, Roos A, Yeung S, Fouche J-P, Rehman AM, et al. Early structural brain development in infants exposed to HIV and antiretroviral therapy in utero in a South African birth cohort. J Int AIDS Soc. 2022;25(1):e25863.

61. Gilmore JH, Knickmeyer RC, Gao W. Imaging structural and functional brain development in early childhood. Nat Rev Neurosci. 2018;19(3):123–37.

62. Knickmeyer RC, Gouttard S, Kang C, Evans D, Wilber K, Smith JK, et al. A structural MRI study of human brain development from birth to 2 years. J Neurosci. 2008;28(47):12176–82.

63. Nwosu EC, Robertson FC, Holmes MJ, Cotton MF, Dobbels E, Little F, et al. Altered brain morphometry in 7-year old HIV-infected children on early ART. Metab Brain Dis. 2018;33(2):523–35.

64. Mottahedin A, Ardalan M, Chumak T, Riebe I, Ek J, Mallard C, et al. Effect of neuroinflammation on synaptic organization and function in the developing brain: implications for neurodevelopmental and neurodegenerative disorders. Front Cell Neurosci. 2017;11:190.

65. Ibrahim A, Warton FL, Fry S, Cotton MF, Jacobson SW, Jacobson JL, et al. Maternal ART throughout gestation prevents caudate volume reductions in neonates who are HIV exposed but uninfected. Front Neurosci. 2023;17:1085589.

66. Robertson FC, Holmes MJ, Cotton MF, Dobbels E, Little F, Laughton B, et al. Perinatal HIV infection or exposure is associated with low N-acetylaspartate and glutamate in basal ganglia at age 9 but not 7 years. Front Hum Neurosci. 2018;12:145.

67. Mbugua KK, Holmes MJ, Cotton MF, Ratai E-M, Little F, Hess AT, et al. HIV-associated $CD4^{+}/CD8^{+}$ depletion in infancy is associated with neurometabolic reductions in the basal ganglia at age 5 years despite early antiretroviral therapy. AIDS. 2016;30(9):1353–62.

68. Arsalidou M, Duerden EG, Taylor MJ. The centre of the brain: topographical model of motor, cognitive, affective, and somatosensory functions of the basal ganglia. Hum Brain Mapp. 2013;34(11):3031–54.

69. McHenry MS, Balogun KA, McDonald BC, Vreeman RC, Whipple EC, Serghides L. In utero exposure to HIV and/or antiretroviral therapy: a systematic review of preclinical and clinical evidence of cognitive outcomes. J Int AIDS Soc. 2019;22(4):e25275.

70. Tran LT, Roos A, Fouche J, Koen N, Woods RP, Zar HJ, et al. White matter microstructural integrity and neurobehavioral outcome of HIV-exposed uninfected neonates. Medicine (Baltimore). 2016;95(4):e2577.

71. Bertran-Cobo C, Wedderburn CJ, Robertson FC, Subramoney S, Narr KL, Joshi SH, et al. A neurometabolic pattern of elevated myo-inositol in children who are HIV-exposed and uninfected: a South African Birth Cohort Study. Front Immunol. 2022; 13. https://journals.aai.org/jimmunol/article/204/1_Supplement/225.6/65254/Immune-checkpoint-dysregulation-andimmune

72. Sudfeld CR, Lei Q, Chinyanga Y, Tumbare E, Khan N, Dapaah-Siakwan F, et al. Linear growth faltering among HIV-exposed uninfected children. J Acquir Immune Defic Syndr. 2016;73(2):182–9.

73. Dirajlal-Fargo S, Mussi-Pinhata M, Weinberg A, Yu Q, Cohen R, Harris DR, et al. HIV-exposed-uninfected infants have increased inflammation and monocyte activation. AIDS. 2019;33(5):845–53.

74. Neary J, Langat A, Singa B, Kinuthia J, Itindi J, Nyaboe E, et al. Higher prevalence of stunting and poor growth outcomes in HIV-exposed uninfected than HIV-unexposed infants in Kenya. AIDS. 2022;36(4):605–10.

75. Deichsel EL, Pavlinac PB, Richardson BA, Mbori-Ngacha D, Walson JL, Mcgrath CJ, et al. Birth size and early pneumonia predict linear growth among HIV-exposed uninfected infants. Matern Child Nutr. 2019;15(4):e12861.

76. Koss CA, Natureeba P, Plenty A, Luwedde F, Mwesigwa J, Ades V, et al. Risk factors for preterm birth among HIV-infected pregnant Ugandan women randomized to lopinavir/ritonavir- or efavirenz-based antiretroviral therapy. J Acquir Immune Defic Syndr. 2014;67(2):128–35.

77. Pillay L, Moodley D, Emel LM, Nkwanyana NM, Naidoo K. Growth patterns and clinical outcomes in association with breastfeeding duration in HIV exposed and unexposed infants: a cohort study in KwaZulu Natal, South Africa. BMC Pediatr. 2021;21(183). https://journals.aai.org/jimmunol/article/204/1_Supplement/225.6/65254/Immune-checkpoint-dysregulation-andimmune

78. Ndiaye A, Suneson K, Njuguna I, Ambler G, Hanke T, John-Stewart G, et al. Growth patterns and their contributing factors among HIV-exposed uninfected infants. Matern Child Nutr. 2021;17(2):e13110.

79. le Roux SM, Abrams EJ, Donald KA, Brittain K, Phillips TK, Nguyen KK, 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;3(4):234–44.

80. Deichsel EL, Pavlinac PB, Mbori-Ngacha D, Walson JL, Maleche-Obimbo E, Farquhar C, et al. Maternal diarrhea and antibiotic use are associated with increased risk of diarrhea among HIV-exposed, uninfected infants in Kenya. Am J Trop Med Hyg. 2020;102(5):1001–8.

81. Lane CE, Bobrow EA, Ndatimana D, Ndayisaba GF, Adair LS. Determinants of growth in HIV-exposed and HIV-uninfected infants in the Kabeho Study. Matern Child Nutr. 2019;15(3):e12776.

82. Nyemba DC, Kalk E, Madlala HP, Malaba TR, Slogrove AL, Davies M-A, et al. Lower birth weight-for-age and length-for-age z-scores in infants with in-utero HIV and ART exposure: a prospective study in Cape Town, South Africa. BMC Pregnancy Childbirth. 2021;21(1):354.

83. Filteau S. The HIV-exposed, uninfected African child. Trop Med Int Health. 2009;14(3),276–87.

84. Wambura JN, Marnane B. Undernutrition of HEU infants in their first 1000 days of life: a case in the urban-low resource setting of Mukuru Slum, Nairobi, Kenya. Heliyon. 2019;5(7):e02073.

85. Lutter CK, Daelmans BM, de Onis M, Kothari MT, Ruel MT, Arimond M, et al. Undernutrition, poor feeding practices, and low coverage of key nutrition interventions. Pediatrics. 2011;128(6):e1418–27.

86. Prendergast AJ, Evans C. Children who are HIV-exposed and uninfected: evidence for action. AIDS. 2023;37:205–15.

87. Madlala HP, Myer L, Malaba TR, Newell ML. Neurodevelopment of HIV-exposed uninfected children in Cape Town, South Africa. PLoS One. 2020;15(11):e0242244.

88. Chandna J, Ntozini R, Evans C, Kandawasvika G, Chasekwa B, Majo FD, et al. Effects of improved complementary feeding and improved water, sanitation and hygiene on early child development among HIV-exposed children: substudy of a cluster randomised trial in rural Zimbabwe. BMJ Glob Health. 2020;5(1):e001718.

89. World Health Organization (WHO). Quality health services: a planning guide. 2020.

90. Sherr L, Croome N. Involving fathers in prevention of mother to child transmission initiatives–what the evidence suggests. J Int AIDS Soc. 2012;15(Suppl 2):17378.

91. World Health Organization (WHO). WHO Report: INSPIRE: Seven strategies for Ending Violence Against Children. https://www.who.int/publications/i/item/inspire-seven-strategies-for-ending-violence-against-children; 2016. Accessed on July 10, 2023.

92. Ramos de Oliveira CV, Sudfeld CR, Muhihi A, Mccoy DC, Fawzi WW, Masanja H, et al. Association of exposure to intimate partner violence with maternal depressive symptoms and early childhood socioemotional development among mothers and children in rural Tanzania. JAMA Netw Open. 2022;5(12):e2248836.

93. Overbeek M, de Schipper JC, Willemen A, Lamers-Winkelman F, Schuengel C. Mediators and treatment factors in intervention for children exposed to interparental violence. J Clin Child Adolesc Psychol. 2017;46:411–27.
94. Garriga A, Pennoni F. The causal effects of parental divorce and parental temporary separation on children's cognitive abilities and psychological wellbeing according to parental relationship quality. Soc Indic Res. 2020; 161. https://www.researchgate.net/publication/343241355_The_Causal_Effects_of_Parental_Divorce_and_Parental_Temporary_Separation_on_Children%27s_Cognitive_Abilities_and_Psychological_Wellbeing_According_to_Parental_Relationship_Quality
95. Xerxa Y, Rescorla LA, Serdarevic F, Van Ijzendorn MH, Jaddoe VW, Verhulst FC, et al. The complex role of parental separation in the association between family conflict and child problem behavior. J Clin Child Adolesc Psychol. 2020;49(1):79–93.
96. Chawla A, Chan A. Intimate partner violence associated with poor socioemotional development in children. 2023.
97. Bulterys MA, King'e M, Njuguna I, Chebet D, Moraa H, Gomez L, et al. Predictors of neurodevelopment in HIV-exposed uninfected infants. Conference on Retroviruses and Opportunistic Infections (CROI). 2022.
98. Wagman JA, Charvat B, Thoma ME, Ndyanabo A, Nalugoda F, Ssekasanvu J, et al. Intimate partner violence as a predictor of marital disruption in rural Rakai, Uganda: a longitudinal study. Int J Public Health. 2016;61(8):961–70.
99. Dagnew GW, Asresie MB, Fekadu GA, Gelaw YM. Factors associated with divorce from first union among women in Ethiopia: further analysis of the 2016 Ethiopia demographic and health survey data. PLoS One. 2020;15(12):e0244014.
100. Porter L, Hao L, Bishai D, Serwadda D, Wawer MJ, Lutalo T, et al. HIV status and union dissolution in sub-Saharan Africa: the case of Rakai, Uganda. Demography. 2004;41(3):465–82.
101. Bhatia DS, Harrison AD, Kubeka M, Milford C, Kaida A, Bajunirwe F, et al. The role of relationship dynamics and gender inequalities as barriers to HIV-serostatus disclosure: qualitative study among women and men living with HIV in Durban, South Africa. Front Public Health. 2017;5:188.
102. Choko AT, Kumwenda MK, Johnson CC, Sakala DW, Chikalipo MC, Fielding K, et al. Acceptability of woman-delivered HIV self-testing to the male partner, and additional interventions: a qualitative study of antenatal care participants in Malawi. J Int AIDS Soc. 2017;20(1):21610.
103. Garcia J, Hromi-Fiedler A, Mazur RE, Marquis G, Sellen D, Lartey A, et al. Persistent household food insecurity, HIV, and maternal stress in peri-urban Ghana. BMC Public Health. 2013;13:215.
104. Hatcher AM, Weiser SD, Cohen CR, Hagey J, Weke E, Burger R, et al. Food insecurity and intimate partner violence among HIV-positive individuals in rural Kenya. Am J Prev Med. 2021;60(4):563–8.
105. Mackelprang RD, Bosire R, Guthrie BL, Choi RY, Liu A, Gatuguta A, et al. High rates of relationship dissolution among heterosexual HIV-serodiscordant couples in Kenya. AIDS Behav. 2014;18(1):189–93.
106. Floyd S, Crampin AC, Glynn JR, Mwenebabu M, Mnkhondia S, Ngwira B, et al. The long-term social and economic impact of HIV on the spouses of infected individuals in northern Malawi. Trop Med Int Health. 2008;13(4):520–31.
107. Bulterys MA, Mujugira A, Nakyanzi A, Wyatt MA, Kamusiime B, Kasiita V, et al. "Him leaving me—that is my fear now": a mixed methods analysis of relationship dissolution between Ugandan pregnant and postpartum women living with HIV and their male partners. AIDS Behav. 2023;27:1776–92.
108. Skeen S, Tomlinson M, Macedo A, Croome N, Sherr L. Mental health of carers of children affected by HIV attending community-based programmes in South Africa and Malawi. AIDS Care. 2014;26Suppl 1 (1):S11–21.
109. Sherr L, Skeen S, Hansels IS, Tomlinson M, Macedo A. The effects of caregiver and household HIV on child development: a community-based longitudinal study of young children. Child Care Health Dev. 2016;42(6):890–9.
110. Sherr L, Cluver LD, Betancourt TS, Kellerman SE, Richter LM, Desmond C. Evidence of impact: health, psychological and social effects of adult HIV on children. AIDS. 2014;28(Suppl 3):S251–9.
111. Laurenzi CA, Hunt X, Skeen S, Sundin P, Weiss RE, Kosi V, et al. Associations between caregiver mental health and young children's behaviour in a rural Kenyan sample. Glob Health Action. 2021;14(1):1861909.
112. WHO, UNICEF. NURTURING CARE for Early Childhood Development: a framework for helping children survive and thrive to transform health and human potential. 2018.
113. Glover V. Maternal depression, anxiety and stress during pregnancy and child outcome; what needs to be done. Best Pract Res Clin Obstet Gynaecol. 2014;28(1):25–35.
114. Black MM, Walker SP, Fernald LC, Andersen CT, Digirolamo AM, Lu C, et al. Early childhood development coming of age: science through the life course. Lancet North Am Ed. 2017;389(10064):77–90.
115. Prendergast AJ, Chasekwa B, Evans C, Mutasa K, Mbuya MNN, Stoltzfus RJ, et al. 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(2):77–90.
116. Humphrey JH, Mbuya MNN, Ntozini R, Moulton LH, Stoltzfus RJ, Tavengwa NV, et al. 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(1):e132–47.
117. Squires J, Bricker D. Ages & Stages Questionnaires®, Third Edition (ASQ®-3): A Parent-Completed Child Monitoring System. Baltimore, MD: Paul H. Brookes Publishing Co., Inc.; 2009.
118. Obradović J, Willoughby MT. Studying executive function skills in young children in low- and middle-income countries: progress and directions. Child Dev Perspect. 2019;13(4):227–34.
119. Semrud-Clikeman M, Romero RA, Prado EL. Selecting measures for the neurodevelopmental assessment of children in low- and middle-income countries. Child Neuropsychol. 2017;23(17):761–802.
120. Grantham-McGregor SM, Fernald LC, Kagawa RM, Walker S. Effects of integrated child development and nutrition interventions on child development and nutritional status. Ann N Y Acad Sci. 2014;1308:11–32.
121. Smythe T, Zuurmond M, Tann CJ, Gladstone M, Kuper H. Early intervention for children with developmental disabilities in low and middle-income countries—the case for action. Int Health. 2021;13(3):222–31.
122. Braitstein P, Katshcke A, Shen C, Sang E, Nyandiko W, Ochieng VO, et al. Retention of HIV-infected and HIV-exposed children in a comprehensive HIV clinical care programme in Western Kenya. Trop Med Int Health. 2010;15(7):833–41.
123. Wubneh CA, Belay GM, Yehualashet FA, Tebeje NB, Mekonnen BD, Endalamaw A. Lost to follow-up and predictors among HIV-exposed infants in northwest Ethiopia. Infect Dis Ther. 2021;10(1):229–39.
124. Ioannidis JP, Taha TE, Kumwenda N, Broadhead R, Mtimavalye L, Miotti P, et al. Predictors and impact of losses to follow-up in an HIV-1 perinatal transmission cohort in Malawi. Int J Epidemiol. 1999;28(4):769–75.
125. Sadoo S, Nalugya R, Lassman R, Kohli-Lynch M, Chariot G, Davies HG, et al. Early detection and intervention for young children with early developmental disabilities in western Uganda: a mixed methods evaluation. BMC Pediatr. 2021;22(158).
126. Zhang L, Ssewanyana D, Martin MC. Supporting child development through parenting interventions in low- to middle-income countries: an updated systematic review. Front Public Health. 2021;9:671988.
127. Yousafzai AK, Aboud FE. Review of implementation processes for integrated nutrition and psychosocial stimulation interventions. Ann N Y Acad Sci. 2014;1308(1):33–45.
128. Murray L, De Pascalis L, Tomlinson M, Vally Z, Dadomo H, Maclachlan B, et al. Randomized controlled trial of a book-sharing intervention in a deprived South African community: effects on carer–infant interactions, and their relation to infant cognitive and socioemotional outcome. J Child Psychol Psychiatry. 2016;57(12):1370–9.
129. Chang SM, Grantham-McGregor SM, Powell CA, Vera-Hernández M, Lopez-Boo F, Baker-Henningham H, et al. Integrating a parenting intervention with routine primary health care: a cluster randomized trial. Pediatrics. 2015;136(2):272–80.
130. Hendricks M, Nair G, Staunton C, Pather M, Garrett N, Baadjies D, et al. Impact of an educational video as a consent tool on knowledge about cure research among patients and caregivers at HIV clinics in South Africa. J Virus Erad. 2018;4(2):103–7.
131. Wang Y, Neary J, Zhai X, Otieno A, O'malley G, Moraa H, et al. Pediatric HIV pre-test informational video is associated with higher knowledge scores compared to counselor-delivered information. AIDS Behav. 2022;26(11):3775–82.
132. Wagner AD, Njuguna IN, Neary J, Lawley KA, Louden DKN, Tiwari R, et al. Demand creation for HIV testing services: a systematic review and meta-analysis. PLoS Med. 2023;20(3):e1004169.
133. Singla DR, Kumbakumba E, Aboud FE. Effects of a parenting intervention to address maternal psychological wellbeing and child development and growth in rural Uganda: a community-based, cluster randomised trial. Lancet Glob Health. 2015;3(8):e458–69.
134. Salomone E, Pacione L, Shire S, Brown FL, Reichow B, Servili C. Development of the WHO caregiver skills training program for developmental disorders or delays. Front Psychiatry. 2019;10:769.
135. Tann CJ, Kohli-Lynch M, Nalugya R, Sadoo S, Martin K, Lassman R, et al. Surviving and thriving: early intervention for neonatal survivors with developmental disability in Uganda. Infants Young Child. 2021;34(1):17–32.

le Roux SM et al. *Journal of the International AIDS Society* 2023, **26**(S4):e26152
http://onlinelibrary.wiley.com/doi/10.1002/jia2.26152/full | https://doi.org/10.1002/jia2.26152

JIAS JOURNAL OF THE INTERNATIONAL AIDS SOCIETY

RESEARCH ARTICLE

Children of a syndemic: co-occurring and mutually reinforcing adverse child health exposures in a prospective cohort of HIV-affected mother-infant dyads in Cape Town, South Africa

Stanzi M. le Roux[1,§], Elaine J. Abrams[2,3], Allison Zerbe[2], Tamsin K. Phillips[1] and Landon Myer[1]

[§]**Corresponding author**: Stanzi M. le Roux, Division of Epidemiology & Biostatistics, School of Public Health, University of Cape Town, Anzio Road, Observatory 7925, Cape Town, South Africa. (stanzi.leroux@uct.ac.za)

Abstract

Introduction: Several HIV-related syndemics have been described among adults. We investigated syndemic vulnerability to hazardous drinking (HD), intimate partner violence (IPV) and household food insecurity (HFIS) in breastfed children born without HIV in urban South Africa. We compared those who were perinatally HIV exposed (CHEU) to those who were not (CHU), under conditions of universal maternal antiretroviral therapy (ART) and breastfeeding.

Methods: A prospective cohort of pregnant women living with HIV (WLHIV), and without HIV, were enrolled and followed with their infants for 12 months postpartum (2013–2017). All WLHIV initiated antenatal efavirenz-based ART. Measurements of growth (~3 monthly), infectious cause hospitalisation, ambulatory childhood illness (2-week recall) and neurodevelopment (BSID-III, measured at ~12 months' age) were compared across bio-social strata using generalised linear regression models, with interaction terms; maternal data included interview-based measures for HD (AUDIT-C), IPV (WHO VAW) and HFIS.

Results: Among 872 breastfeeding mother-infant pairs (n = 461 CHEU, n = 411 CHU), WLHIV (vs. HIV negative) reported more unemployment (279/461, 60% vs. 217/411, 53%; $p = 0.02$), incomplete secondary education (347/461, 75% vs. 227/411, 55%; $p < 0.0001$), HD (25%, 117/459 vs. 7%, 30/411; $p < 0.0001$) and IPV (22%, 101/457 vs. 8%, 32/411; $p < 0.0001$) at enrolment; and HFIS at 12 months (45%, 172/386 vs. 30%, 105/352; $p > 0.0001$). There were positive interactions between maternal HIV and other characteristics. Compared to food secure CHU, the mean difference (95% CI) in weight-for-age Z-score (WAZ) was 0.06 (−0.14; 0.25) for food insecure CHU; −0.26 (−0.42; −0.10) for food secure CHEU; and −0.43 (−0.61; −0.25), for food insecure CHEU. Results were similar for underweight (WAZ < −2), infectious-cause hospitalisation, cognitive and motor delay. HIV-IPV interactions were evident for ambulatory diarrhoea and motor delay. There were HIV-HD interactions for odds of underweight, stunting, cognitive and motor delay. Compared to HD-unexposed CHU, the odds ratios (95% CI) of underweight were 2.31 (1.11; 4.82) for HD-exposed CHU; 3.57 (0.84; 15.13) for HD-unexposed CHEU and 6.01 (2.22; 16.22) for HD-exposed CHEU.

Conclusions: These data suggest that maternal HIV-related syndemics may partly drive excess CHEU health risks, highlighting an urgent need for holistic maternal and family care and support alongside ART to optimise the health of CHEU.

Keywords: HIV; perinatology; vertical transmission; syndemic; social determinants of health; Africa

Additional information may be found under the Supporting Information tab of this article.

Received 8 February 2023; **Accepted** 14 August 2023

1 | INTRODUCTION

In 2021, the global population of children who are perinatally HIV exposed but HIV negative (CHEU) was almost 16 million, with another one million CHEU born annually [1, 2]. The largest number of CHEU live in sub-Saharan Africa, predominantly in South Africa where an estimated 20% of the under-15 population are CHEU [1, 3]. Prior to the widespread availability of universal maternal antiretroviral therapy (ART), predominantly formula-fed CHEU were reported to have excess risks of mortality, infectious morbidity, growth restriction and developmental delays compared to HIV-negative children who are perinatally HIV unexposed (CHU) [4, 5]. Emerging data suggest that while the magnitude of these historic risk differences is substantially diminished under conditions of universal maternal ART with optimal breastfeeding, some risk differential remains [6–10]. In regions with large numbers of CHEU, even small increases in risk are likely to adversely impact child health at a population level [9]. Understanding the drivers of these residual differences is necessary for the creation and implementation of effective public health interventions, in turn promoting child health in high HIV burden settings.

The syndemic model of health seeks to assess the co-occurrence of and interactions between social determinants of health, biological factors and disease outcomes within the context of inequality and deprivation [11]. Reflecting the high incidence of HIV among people who are marginalised and poor, several HIV-related syndemics have been described among women living with HIV (WLHIV), including interrelationships between hazardous use of alcohol, household food insecurity (HFIS) and intimate partner violence (IPV), which in turn exacerbate HIV disease severity, adversely affect adherence to ART and increase the risk of mental health challenges [12–14]. Each of these maternal factors is also known to increase the risks of adverse health outcomes among children globally, including CHEU [15–17]. In a prospective cohort study comparing breastfeeding CHEU to CHU over the first year of life in the context of universal, maternal efavirenz-based ART, we previously reported small but clinically meaningful increased risks of growth restriction, early infectious cause hospitalisation, ambulatory childhood illness, cognitive delay and motor delay [6–8]. Previously, we noted the independent effects of individual psychosocial, behavioural and economic factors on child health outcomes. This secondary analysis investigates the potential role of maternal HIV-related syndemic relationships in the previously reported adverse health outcomes among CHEU (Figure S1).

2 | METHODS

2.1 | Study design and enrolment

We conducted a secondary analysis of data collected in two linked, prospective cohort studies, conducted in parallel at the Gugulethu Midwife and Obstetric Unit, a primary care centre in an impoverished community of peri-urban Cape Town, South Africa (enrolment, June 2013–April 2016; follow-up through March 2017). At the first antenatal visit, the MCH-ART (**M**aternal and **C**hild **H**ealth **A**nti-**R**etroviral **T**herapy) study enrolled WLHIV who were initiating ART during pregnancy; the HU2 (**H**IV-**u**nexposed **u**ninfected) study enrolled pregnant women who tested HIV negative. Details regarding the study methodology have been published elsewhere [6–8, 18]. Briefly, women were followed up through delivery, and with their HIV-negative, breastfeeding infants, until at least 12 months postpartum (visits at 6 weeks; 3 monthly from 3 to 12 months). Apart from HIV-specific measures, study follow-up, procedures and measurements were identical for both studies, utilising the same study site, materials and staff.

2.2 | Study measurements

2.2.1 | Maternal measures

At enrolment and during follow-up, demographic, psychosocial and behavioural data were collected by trained study counsellors administering standardised, locally validated, questionnaires in private rooms. All questionnaires were translated into both isiXhosa and Afrikaans, and administered in the participant's language of choice. We used the Alcohol Use Disorders Identification Test (AUDIT) [19] to measure maternal alcohol use ("hazardous drinking," HD defined as AUDIT consumption score $\geq$3); the Edinburgh Postnatal Depression Scale [20] to estimate probable maternal depression (EPDS score $\geq$13); and the World Health Organisation Violence against Women (VAW) questionnaire for IPV (any psychological, physical or sexual violence) [21]. At the 12-month visit, we also assessed HFIS (defined as "has, or is at risk of food insecurity" vs. no food insecurity) using a questionnaire (reference period, "ever") previously used in South Africa, adapted from the Household Food Insecurity Access Scale, Food and Nutrition Technical Assistance Project and the Community Childhood Hunger Identification Project Index [22]. To minimise participant time commitments for interim study visits, the psychosocial/behavioural tools (AUDIT, EPDS and VAW) were only administered at pre-specified visits. This analysis focuses primarily on potential syndemic factors measured at the first antenatal visit, and at 12 months postpartum, the only time points when all three of these tools were administered at the same study visit (other time points of measurement are shown in tables).

2.2.2 | Child health measures

Measurement and quality assurance information have previously been published in detail for each of the key child health outcomes [6–8]. In summary, trained counsellors conducted supervised anthropometric measurements using calibrated tools at each study visit [6]. We used anthropometric software (Intergrowth-21st Project and WHO Multicentre Growth Reference Study as indicated) to generate Z-scores (adjusted for age, sex and gestation) for weight-for-age (WAZ), length-for-age (LAZ) and head circumference-for-age (HCAZ). We measured infectious morbidity through (1) hospitalisation data abstracted from Provincial Health Data Centre databases [23] with diagnoses based on the International Classification of Diseases, 10th edition; and (2) point prevalence (2-week recall) of ambulatory childhood illness (presumed lower respiratory tract illness, RTI; diarrhoeal illness) at each study visit, using questions from the Demographic and Health Survey (DHS) [7, 24]. A trained clinician assessed neurodevelopment using the Bayley Scales of Infant Development (3rd edition, BSID-III) on a subset of study participants at approximately 12 months of age [8, 25, 26].

2.3 | Statistical methodology

Sample size calculations for the primary analyses were based on direct comparisons of CHEU to CHU with >80% power to detect *a priori*-defined clinically meaningful differences (definitions and achieved power shown in Table S1) [6–8].

A syndemic is defined as "population-level clustering of social and health problems," with three main characteristics: (a) the presence of adverse contextual and social factors which drive disease concentration; (b) the clustering of diseases within a specific population; and (c) adverse disease interaction, where concurrent (bidirectional or co-occurring) factors (biological, social or behavioural) increase morbidity or mortality [11]. Accordingly, we described the social circumstances of our study population, in which context the following inter-related hypotheses were tested, derived from syndemic theory (Figure S1):

(i) HD, IPV and HFIS are more common among women who are HIV positive than women who are HIV negative (clustering of potential syndemic factors)

(ii) Maternal HIV, HD, IPV and HFIS have independent adverse effects on the health of CHEU and CHU (direct effects on child health)

(iii) There is positive interaction (synergistic risk exacerbation of adverse child health outcomes) between maternal HIV and at least one of the examined co-factors (HD, IPV or HFIS), which result in differences that may have an impact on either an individual or population level, for at least one of the following outcomes ("potentially meaningful" differences defined below):

- Child growth (>0.2 absolute difference in Z-score, or relative increase of >1.2 for Z-score < 2)
- Infectious morbidity (odds ratio or risk ratio of >1.5 for any of the defined measures)
- Neurodevelopmental delay (absolute difference of >5 composite score, or relative increase of >1.2 in the odds ratio for cognitive or motor delay, defined as composite score < 85)

We used standard data exploration techniques and generalised linear regression models with outcome-specific link functions, correcting for repeat measures with random effects models or generalised estimating equations. Approaches followed those utilised in the original publications where possible [6–8]. In all original analyses, choices of third variables were based on *a priori*-specified directed acyclic graphs; where more than one variable measuring the same construct was available, we were guided by Akaike's Information Criterion. The HFIS questionnaire we utilised categorised households as being "not at risk," "at risk for food insecurity" or "food insecure." In exploratory analyses, there were little differences between the "at risk" and "food insecure" groups; for best model fit, we created a binary variable combining these two groups. To accommodate multiple imputation for infectious morbidity analyses, we used logistic regression analysis for dichotomous hospitalisation and ambulatory infectious illness variables, a simplified approach compared to the analyses used in the original publication. We used both interaction (product) terms and indicator variables in regression analyses to test hypothesis (iii), and calculated Rothman's interaction contrast (IC) and relative excess risk due to interaction ($RERI_{RR}$) to clearly demonstrate the direction and scale of interactions [27]. All analyses were completed using Stata 16 (StataCorp); we also used GraphPad Prism version 9.0 (GraphPad Software, www.graphpad.com) and DeepVenn software for additional data visualizstion [28].

2.3.1 | *Missing data*

Less than 1% of mother-child pairs had at least one potential syndemic factor missing at the antenatal enrolment visit; 16% (137/872) had at least one factor missing at the 12 months' postpartum visit, including food security data. Differences by the availability of HFIS data are shown in Table S2, stratified by maternal HIV status. To maximise efficiency, we used multiple imputation (chained equations) [29] in the Stata 16 multiple imputation package (StataCorp) to impute 20 datasets for regression modelling (details shown in Table S3), combining analytic estimates using Rubin's rules [30].

2.4 | Ethics

The University of Cape Town Faculty of Health Sciences' Research Ethics Committee approved the MCH-ART and HU2 studies. Both studies conform to the Declaration of Helsinki; all women provided written, informed consent.

3 | RESULTS

Overall, 872 mother-child pairs contributed to this analysis (CHEU, $n = 461$; CHU, $n = 411$); 717 (82%) completed 12 months of postnatal follow-up (Figure S2). There were minimal differences between those who contributed and did not contribute data at 12 months (Table S2).

Overall, most women were living in informal housing, without running water and/or flushable toilets inside the home at study enrolment (Table 1). Compared to HIV-negative women, WLHIV were more likely to be unemployed (279/461, 60% vs. 217/411, 53%; $p = 0.02$) and have incomplete secondary education (347/461, 75% vs. 227/411, 55%; $p < 0.0001$, Table 1). Co-distributions of maternal factors are shown in Table S3.

3.1 | Clustering of potential maternal syndemic factors at enrolment and over time

At antenatal enrolment, WLHIV (vs. HIV-negative women) reported more HD (25% [117/459] vs. 7% [30/411], $p < 0.0001$) and IPV (22% [101/457] vs. 8% [32/411], $p < 0.0001$), Table 2. One in three WLHIV with HD also reported concurrent IPV (38%, 44/116), compared to one in five of WLHIV without HD (17%, 57/341); absolute risk difference (RD) 21% (95% CI 11%–31%). This difference was smaller among HIV-negative women (prevalence of IPV among women reporting any vs. no HD, 20% vs. 7%; RD 13%, 95% CI −1% to 28%). For both HD and IPV independently, risks at enrolment predicted risks at 12 months postpartum: the prevalence of HD at 12 months (12% overall, Table 2) was five times higher among women who had also reported any (vs. no) HD at enrolment (37% vs. 7%; relative risk, RR 5.27; 95% CI 3.66–7.59); similar results were seen for IPV at 12 months (comparing those with vs. without IPV at enrolment:

Table 1. Maternal and infant characteristics, by maternal HIV status

	Total (*N* = 872)	Women who are HIV positive, and CHEU (*n* = 461)	Women who are HIV negative, and CHU (*n* = 411)	Missing, pre-imputation	Missing, after imputation[a]
MATERNAL CHARACTERISTICS					
Demographics and household characteristics					
Age in years, mean (SD)	28 (6)	28 (5)	27 (6)	0	n/a
Married/cohabiting	373 (43%)	189 (41%)	184 (45%)	0	0
Incomplete secondary education	574 (66%)	347 (75%)	227 (55%)	0	0
Unemployed	496 (57%)	279 (60%)	217 (53%)	0	0
Informal housing	438 (50%)	242 (52%)	196 (48%)	0	0
No flushable toilet inside home	580 (67%)	335 (73%)	245 (60%)	0	0
No running water inside home	468 (54%)	272 (59%)	196 (48%)	0	0
Lives in a formal, brick home, with flushable toilet and running water inside the home					
No, lacks at least one of the above	592 (68%)	336 (73%)	256 (62%)		
Yes, has all three	280 (32%)	125 (27%)	155 (38%)		
Household crowding (≥10 people)	40 (5%)	28 (6%)	12 (3%)	0	0
Maternal HIV-related measures at enrolment and delivery					
CD4 cell count at ART initiation (cells/mm^3)	–	354 (249–527)	–	12	n/a
Log_{10} HIV viral load at ART initiation (copies/ml)	–	4.0 (3.3–4.5)	–	0	n/a
Log_{10} HIV viral load at delivery (copies/ml)		1.6 (1.6–1.6)		0	n/a
HIV viral load <50 copies/ml at delivery	–	352 (76%)	–	0	n/a
INFANT CHARACTERISTICS					
Gestational age at ART initiation (weeks)	–	22 (17–27)	–	0	n/a
Gestational age at delivery (weeks)	39 (38–40)	39 (38–40)	39 (38–40)	0	0
Preterm (<37)	94 (11%)	56 (12%)	38 (9%)	0	n/a
Weight-for-age Z-score at birth	−0.13 (−0.84; 0.51)	−0.21 (−0.93; 0.37)	−0.05 (−0.72; 0.64)	0	0
Small-for-gestational-age (birthweight <10th centile)[b]	90 (10%)	51 (11%)	39 (10%)	0	n/a
Male sex	428 (49%)	232 (50%)	196 (48%)	0	n/a
Early introduction of breastfeeding (within first hour of life)[c]	788/867 (91%)	400/459 (87%)	388/408 (95%)	5	0
Duration of EBF (months)[c]	1.4 (0.1–3.0)	1.4 (0.2–3.5)	1.2 (0.1–3.0)	0	0
Duration of any breastfeeding (months)[c]	6.1 (1.5–12.0)	3.9 (1.4–12.0)	9.0 (3.0–12.0)	0	0

Note: Results are *n* (column %) with *p*-value from chi^2 test; mean (SD) with *p*-value from *t*-test for normally distributed variables; or median (interquartile range, IQR) with *p*-value from Kruskal–Wallis.
Abbreviations: ART, antiretroviral therapy; CHEU, children who were perinatally HIV exposed but are HIV negative; CHU, children who were perinatally HIV unexposed and are HIV negative; EBF, exclusive breastfeeding; ml, millilitre; mm^3, cubic millimetre; SD, standard deviation.
[a]n/a, not applicable (variables not included in imputation model); post imputation missing values not used if maternal or child death occurred.
[b]Birth weight percentile based on Intergrowth-21st reference standards.
[c]Maternal report (24-hour recall); exclusive breastfeeding defined as only breast milk and prescribed medicine.

RR 4.0, 95% CI 2.61–6.27), and when stratified by HIV status (data not shown). At enrolment and over time, the prevalence of probable or possible maternal depression (as measured by the EPDS at threshold values of 13, and of 10) did not vary substantially by HIV status (Table 2). At 12 months, 45% (172/386) of WLHIV experienced or were at risk of HFIS, compared to 30% (105/352) of HIV-negative women ($p < 0.0001$, Table 2). WLHIV were notably more likely to report frequent household hunger (due to lack of resources) than HIV-negative women (based on responses to the three questions directly addressing hunger: 72/386, 19% vs. 6/352, 2%), suggesting severe food insecurity [31].

Table 2. Maternal psychosocial and behavioural factors at antenatal enrolment and over time, by maternal HIV status[a]

	Total (*N* = 872)	Women who are HIV positive (*n* = 461)	Women who are HIV negative (*n* = 411)	*p*-value	Missing, pre-imputation	Missing, after imputation[b]
Alcohol Use Disorder Identification Tool (AUDIT) measurements						
Total score						
At first antenatal visit, study enrolment[c]	0 (0–1)	0 (0–4)	0 (0–0)	0.0001	2	n/a
At ∼34 weeks' gestation[d]	0 (0–0)	0 (0–0)	0 (0–0)	0.0001	32	n/a
At 6 months postpartum[e]	0 (0–0)	0 (0–0)	0 (0–0)	0.072	123	n/a
At 12 months postpartum[c]	0 (0–0)	0 (0–0)	0 (0–0)	0.16	132	n/a
Hazardous drinking (defined as AUDIT consumption score ≥3)						
At first antenatal visit, study enrolment[c]	147/870 (17%)	117/459 (25%)	30/411 (7%)	<0.0001	2	0
At ∼34 weeks' gestation[d]	43/840 (5%)	40/455 (9%)	3/385 (1%)	<0.0001	32	n/a
At 6 months postpartum[e]	50/749 (7%)	40/403 (10%)	10/346 (3%)	<0.0001	123	n/a
At 12 months postpartum[c]	92/740 (12%)	57/387 (15%)	35/353 (10%)	0.047	132	n/a
World Health Organisation "Violence against Women" questionnaire measurements						
Any intimate partner violence[f]						
At first antenatal visit, study enrolment[c]	133/868 (15%)	101/457 (22%)	32/411 (8%)	<0.0001	4	0
At 7 days' (neonatal) visit[d]	41/871 (5%)	31/461 (7%)	10/410 (2%)	0.003	1	n/a
At 12 months postpartum[c]	68/739 (9%)	40/388 (10%)	28/351 (8%)	0.27	133	16
Edinburgh Postnatal Depression Scale (EPDS)						
Total score						
Enrolment (antenatal first booking)[g]	3 (1–7)	4 (1–8)	2 (1–6)	0.018	2	n/a
At 6 weeks postpartum[g]	1 (0–4)	3 (0–5)	1 (0–2)	0.0001	51	n/a
At 12 months postpartum[g]	1 (0–4)	2 (0–6)	0 (0–2)	0.0001	133	n/a
Probable depression: EPDS total score ≥13						
Enrolment (antenatal first booking)[g]	75/870 (9%)	46/459 (10%)	29/411 (7%)	0.12	2	0
At 6 weeks postpartum[g]	31/821 (4%)	19/435 (4%)	12/386 (3%)	0.34	51	n/a
At 12 months postpartum[g]	43/739 (6%)	22/386 (6%)	21/353 (6%)	0.88	133	16

(*Continued*)

Table 2. (Continued)

	Total (N = 872)	Women who are HIV positive (n = 461)	Women who are HIV negative (n = 411)	p-value	Missing, pre-imputation	Missing, after imputation[b]
Possible depression: EPDS total score ≥10						
Enrolment (antenatal first booking)[g]	145/870 (17%)	88/459 (19%)	57/411 (14%)	0.036	2	n/a
At 6 weeks postpartum[g]	57/821 (7%)	38/435 (9%)	19/386 (5%)	0.032	51	n/a
At 12 months postpartum[g]	65/739 (9%)	38/386 (10%)	27/353 (8%)	0.29	133	n/a
Household food security at 12 months' visit[h]				<0.0001	134	16
No food insecurity	461/738 (63%)	214/386 (55%)	247/352 (70%)			
Has/is at risk of food insecurity	277/738 (37%)	172/386 (45%)	105/352 (30%)			
Combination indicator				<0.0001	138	n/a
For hazardous drinking (enrolment), IPV (enrolment) and/or household food insecurity (12 months)						
Has none of the above	346/734 (47%)	133/382 (35%)	213/352 (61%)			
Has one of the above	283/734 (39%)	161/382 (42%)	122/352 (35%)			
Has two of the above	81/734 (11%)	67/382 (18%)	14/352 (4%)			
Has all three of the above	24/734 (3%)	21/382 (5%)	3/352 (1%)			

Note: Results are n (column %) with p-value from chi^2 test; mean (SD) with p-value from t-test for normally distributed variables; or median (interquartile range, IQR) with p-value from Kruskal–Wallis.

Abbreviations: EPDS, Edinburgh Postnatal Depression Scale; HEU, HIV-exposed uninfected; HU, HIV-unexposed uninfected; SD, standard deviation.

[a]Limited to mothers of children who tested HIV negative at the most recent test.

[b]n/a, not applicable (no imputed datapoints used, as the variable was not included in the imputation or primary analysis models).

[c]With reference to the preceding 12 months.

[d]With reference to the time since mother identified her pregnancy.

[e]With reference to the time since birth of the infant.

[f]Any physical, sexual or psychological violence.

[g]With reference to the preceding week.

[h]Based on 10-item questionnaire adapted from the Household Food Insecurity Access Scale (HFIAS), Food and Nutrition Technical Assistance Project (FANTA) and the Community Childhood Hunger Indentification Project Index (CCHIP).

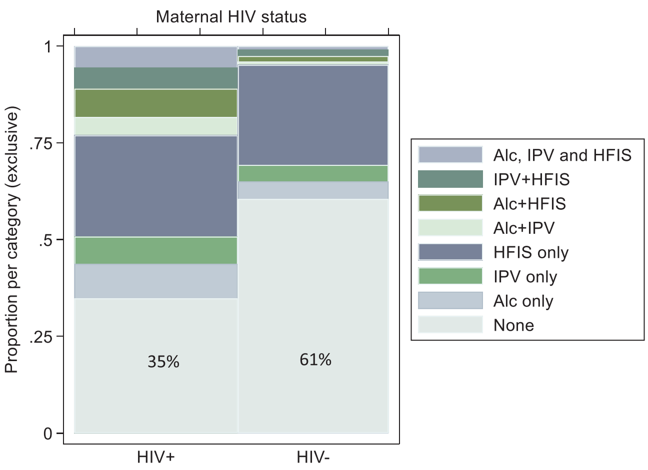

Figure 1. Spine plot showing distributions of maternal hazardous drinking ("Alc"), intimate partner violence (IPV), and household food insecurity (HFIS), by maternal HIV status.

At 12 months, concurrent HD or IPV predicted increased risks of HFIS: the relative risk for HFIS was 1.56 (95% CI 1.26–1.94) when HD was also reported; and 1.78 (95% CI 1.43–2.20) for HFIS when IPV was also reported. Two-thirds of WLHIV had at least one of the potential syndemic factors (HD, IPV or HFIS), compared to only a third of HIV-negative women (Table 2 and Figure 1). Proportional Venn diagrams for the overlap of these factors are shown in Figures S3a–c.

3.2 | Individual effects of potential maternal syndemic factors on child outcomes

Complete results from crude and adjusted regression models estimating individual effects of maternal HIV status, HD, IPV and HFIS on all pre-specified child outcomes are shown in Tables S5–S9. The strongest relationships relevant to the current analysis were noted for absolute differences in WAZ; and relative differences in underweight, infectious admission hospitalisation in early infancy (7 days to 3 months), cognitive delay and motor delay (Table 3). Adjusting for HD, IPV and HFIS, maternal HIV predicted lower WAZ, increased risks of underweight, infectious hospitalisation and cognitive delay. In the same multivariable regression models, HD predicted lower WAZ and higher odds of underweight; IPV was associated with increased odds of motor delay; and HFIS with increased odds of cognitive and motor delay (Table 3).

3.3 | Combined effects of potential maternal syndemic factors on child outcomes

Epidemiologic interaction estimates (IC and $RERI_{RR}$) are shown in Table S10. Across child health outcomes, the strongest evidence for positive interaction effects was for *maternal HIV status* (exposed, HIV+ vs. unexposed, HIV−) and *household food insecurity (HFIS)* (HFIS+ vs. HFIS−); these effects were most evident for WAZ, underweight, infectious hospitalisation and developmental delay (Table 4 and Tables S5–S9). For example, using food-secure CHU (HIV−|HFIS−)

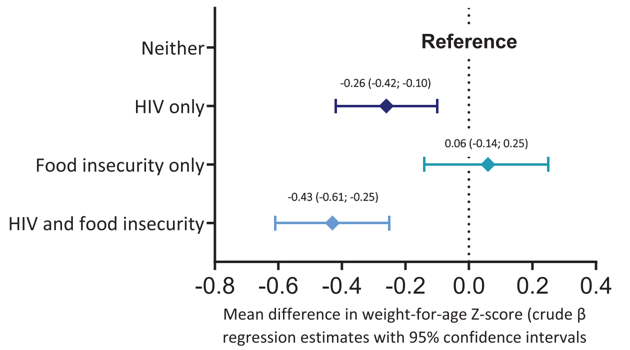

Figure 2. Mean differences in weight-for-age Z-scores, by categories of maternal HIV status and household food security: interaction forest plots on linear scale.

as reference, food-secure CHEU (HIV+|HFIS−) had WAZ −0.26 (95% CI −0.42 to −0.10) and CHEU with food insecurity (HIV+|HFIS+) had WAZ −0.43 (95% CI −0.61; −0.25), whereas CHU with food insecurity (HIV−|HFIS+) had a similar WAZ to the reference (HIV−|HFIS+), WAZ 0.06 (95% CI −0.14; 0.25), Figure 2 and Table 4. That is, whereas exposure to only HFIS was not associated with WAZ deficit (mean difference 0.06), exposure to only HIV was associated with some WAZ deficit (−0.26), and double exposure (HFIS and HIV) was associated with a substantial WAZ deficit (−0.43), which was greater than the sum of the effects of the individual exposures (−0.26 + 0.06 = −0.20, compared to −0.43) [27]. Similar results were seen for the odds of being underweight (Figure 3a), infectious cause hospitalisation in early infancy (Figure 3b), cognitive delay (Figure 3c) and motor delay (Figure 3d); (Table 4 and Tables S5–S9). There were also suggestions of positive HIV-HFIS interactions on HCAZ, microcephaly and hospitalisation beyond the first 72 hours, although precision was limited (Tables S4–S9).

Precision was also limited for subgroup comparisons by exposure categories for *maternal HIV status* (HIV+ vs. HIV−) and *hazardous drinking* (HD+ vs. HD−, as reported at study enrolment). The concurrent exposure of HD exacerbated the adverse effects of HIV exposure on mean weight (Table S5): compared to children exposed to neither (HIV−|HD−), those exposed to HIV only (HIV+|HD−) had WAZ −0.28 (95% CI −0.41; −0.14) and HD only (HIV−|HD+) had WAZ −0.28 (95% CI −0.65; 0.08), while those with both exposures (HIV+|HD+) had WAZ −0.61 (95% CI −0.81; −0.40). There was also evidence of interaction between exposures to HIV and HD on the odds of underweight when comparing HIV exposure only (HIV+|HD−), HD exposure only (HIV−|HD+) and both exposures (HIV+|HD+) to neither exposure (HIV−|HD−): odds ratio, OR (95% CI) of 2.31 (1.11; 4.82), 3.57 (CI 0.84; 15.13) and 6.01 (2.22; 16.22), respectively (Tables S6 and S10). Similar results were seen for LAZ and ambulatory diarrhoea, but not for other measures of infectious morbidity or for developmental delay (Tables S5–S7).

Exposure to both *HIV and IPV* predicted substantially higher odds of ambulatory childhood illness and motor delay than either exposure by itself (positive interaction), albeit with low

Table 3. Estimates of absolute and relative differences in selected child growth, infectious morbidity and neurodevelopmental outcomes by maternal HIV status, hazardous drinking, IPV and household food security status

	WAZ Mean (SD)		Underweight (WAZ<−2)		Any infectious cause hospitalisation (age 7 days to 3 months)[a]		Composite cognitive score <85: delay[b]		Composite motor score <85: delay[b]	
Population outcome average/ prevalence	0.18 (1.18) over repeat measures		3% (155/4332 measurement events)		5% (40/849 with data)		7% (34/525 with assessments)		6% (32/510 with assessments)	
	β (95% CI)	aβ (95% CI)	OR (95% CI)	aOR (95% CI)	OR (95% CI)	aOR (95% CI)	OR (95% CI)	aOR (95% CI)	OR (95% CI)	aOR (95% CI)
HIV	−0.34	−0.28	2.73	2.20	3.30	3.31	2.19	2.23	2.01	1.39
	(−0.47; −0.21)	(−0.41; −0.15)	(1.37; 5.44)	(1.09; 4.46)	(1.55; 7.02)	(1.52; 7.21)	(1.08; 4.44)	(1.06; 4.68)	(0.97; 4.12)	(0.64; 3.05)
Hazardous drinking	−0.41	−0.30	3.44	2.53	0.85	0.47	0.66	0.46	2.18	1.35
	(−0.59; −0.23)	(−0.49; −0.10)	(1.57; 8.00)	(1.098; 5.93)	(0.35; 2.07)	(0.18; 1.28)	(0.23; 1.93)	(0.15; 1.43)	(0.97; 4.90)	(0.55; 3.32)
IPV	−0.23	−0.09	1.65	1.04	1.43	1.33	0.94	0.88	3.03	2.35
	(−0.41; −0.05)	(−0.27; 0.10)	(0.70; 3.91)	(0.40; 2.65)	(0.64; 3.19)	(0.58; 3.06)	(0.32; 2.77)	(0.29; 2.72)	(1.33; 6.89)	(1.09; 4.90)
Food insecurity[c]	−0.11	−0.06	1.87	1.50	1.53	1.34	2.27	2.09	2.67	2.31
	(−0.24; 0.02)	(−0.19; 0.06)	(0.91; 3.82)	(0.76; 2.95)	(0.78; 3.00)	(0.68; 2.67)	(1.13; 4.59)	(1.02; 4.29)	(1.29; 5.54)	(1.09; 4.90)

Note: Estimates from multi-variable models are adjusted for maternal HIV status, hazardous drinking at enrolment, IPV at enrolment and household food insecurity at 12 months.
Abbreviations: aβ, adjusted mean difference from linear regression; aOR, adjusted odds ratio from logistic regression; CI, confidence interval; IPV, intimate partner violence; SD, standard deviation; WAZ, weight-for-age Z-score.

[a]Hospitalisation data obtained from electronic provincial hospital databases, infectious cause classification based on ICD10 codes and checked by infectious disease specialist paediatrician.

[b]Composite score <85 per domain at approximately 12 months of age, using Bailey Scales of Infant Development, 3rd edition.

[c]Has or is at risk of household food insecurity at 12 months, based on questionnaire adapted from the Household Food Insecurity Access Scale (HFIAS), Food and Nutrition Technical Assistance Project (FANTA) and the Community Childhood Hunger Indentification Project Index (CCHIP).

Table 4. Summarised comparison of child growth, infectious morbidity and neurodevelopmental outcomes by maternal HIV status and household food security status: estimates and measures of interaction effects

	WAZ Mean (SD)		Underweight (WAZ<−2)		Any infectious cause hospitalisation (age 7 days to 3 months)[a]		Composite cognitive score <85: delay[b]		Composite motor score <85: delay[b]	
Study population outcome average/ prevalence	**0.18 (1.18) over repeat measures**		**3% (155/4332 measurement events)**		**5% (40/849 with data)**		**7% (34/525 with assessments)**		**6% (32/510 with assessments)**	
Regression coefficients	**β (95% CI)**	***p***	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***
Categories of exposure to HIV and food security										
No HIV, food secure	Ref		Ref		Ref		Ref		Ref	
HIV, food secure	−0.26 (−0.42; −0.10)	0.001	1.35 (0.56; 3.27)	0.51	2.69 (1.00; 7.22)	0.05	1.33 (0.46; 3.84)	0.60	1.26 (0.40; 3.96)	0.69
No HIV, food insecure	0.06 (−0.14; 0.25)	0.55	0.41 (0.11; 1.52)	0.18	0.95 (0.18; 5.07)	0.95	1.34 (0.44; 4.12)	0.61	1.84 (0.62; 5.47)	0.27
HIV and food insecure	−0.43 (−0.61; −0.25)	<0.0001	3.90 (1.67; 9.11)	0.002	3.87 (1.45; 10.29)	0.007	3.69 (1.54; 8.84)	0.003	3.96 (1.58; 9.91)	0.003
Interaction model[c]										
HIV versus no HIV	−0.26 (−0.42; −0.10)	0.001	1.35 (0.56; 3.27)	0.51	2.69 (1.00; 7.22)	0.05	1.33 (0.46; 3.83)	0.60	1.26 (0.40; 3.96)	0.69
Food insecure versus secure, no HIV	0.06 (−0.15; 0.25)	0.55	0.41 (0.11; 1.52)	0.18	0.95 (0.18; 5.07)	0.94	1.34 (0.44; 4.12)	0.61	1.84 (0.62; 5.47)	0.27
Interaction term	−0.23 (−0.48; 0.02)	0.068	7.05 (1.43; 34.70)	0.16	1.52 (0.24; 9.60)	0.65	2.07 (0.46; 9.29)	0.34	1.70 (0.37; 7.84)	0.50

(*Continued*)

Table 4. (Continued)

	WAZ Mean (SD)		Underweight (WAZ<−2)		Any infectious cause hospitalisation (age 7 days to 3 months)[a]		Composite cognitive score <85: delay[b]		Composite motor score <85: delay[b]	
Study population outcome average/ prevalence	**0.18 (1.18) over repeat measures**		**3% (155/4332 measurement events)**		**5% (40/849 with data)**		**7% (34/525 with assessments)**		**6% (32/510 with assessments)**	
Regression coefficients	**β (95% CI)**	***p***	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***
Interaction contrast (IC)[d]	n/a		12%		2%		−6%		6%	
$RERI_{RR}$[e]	n/a		1.49		1.10		−1.33		1.54	
Multiplicative interaction measure[f]	n/a		3.68		1.38		0.19		1.57	
Evidence of interaction on additive scale	Yes, positive		Yes, positive		Yes, positive		Yes, negative		Yes, positive	
Evidence of interaction on multiplicative scale	n/a		Yes, positive		Yes, positive		Yes, positive		Yes, positive	

Note: Proportions are expressed as percentages to facilitate interpretation in clinical terms; epidemiological measures of interaction only calculable on binary data. Has or is at risk of household food insecurity, based on questionnaire adapted from the Household Food Insecurity Access Scale (HFIAS), Food and Nutrition Technical Assistance Project (FANTA) and the Community Childhood Hunger Indentification Project Index (CCHIP).

Abbreviations: CI, confidence interval; n/a, not applicable; OR, odds ratio; $RERI_{RR}$, relative excess risk due to interaction, also referred to as interaction contrast ratio (ICR); SD, standard deviation; WAZ, weight-for-age Z-score.

[a]Hospitalisation data obtained from electronic provincial hospital databases, infectious cause classification based on ICD10 codes and checked by infectious disease specialist paediatrician.

[b]Composite score <85 per domain at approximately 12 months of age, using Bailey Scales of Infant Development, 3rd edition.

[c]Models including only HIV and binary indicator for household food insecurity, with interaction term (Z-scores analysis accounting for repeat measures; model choice based on data type).

[d]Indicator for the differences in proportions between the four exposure groups (formula, $p_{11} - p_{10} - p_{01} + p_{00}$, where p_{11} indicates risk of binary outcome in group exposed to both HIV and food insecurity; p_{10}, exposure to HIV only; p_{01}, exposure to food insecurity only; and p_{00}, exposed to neither). Measures interaction on the additive scale: >0 indicates positive interaction, <0 indicates negative interaction. Interpretable as magnitude of interaction on additive scale (absolute differences in risk); can be approximated by the difference in mean Z-scores indicated by interaction term in linear regression model.

[e]$RERI_{RR}$ tests interaction on the additive scale, based on calculated risk ratios; interpretation: <0, negative interaction; $RERI_{RR}$>0, positive interaction ($RERI_{RR}$ measures departure from additive effects, in terms of direction but not magnitude as baseline group risks may vary between groups).

[f]Measures the extent to which, on the risk ratio scale, the effect of both exposures together exceeds the product of the effects of the two exposures considered separately; if <1, negative interaction; >1, positive; can be approximated by the interaction term of logistic regression if rare disease assumption holds (here, OR in interaction terms are likely an overestimation).

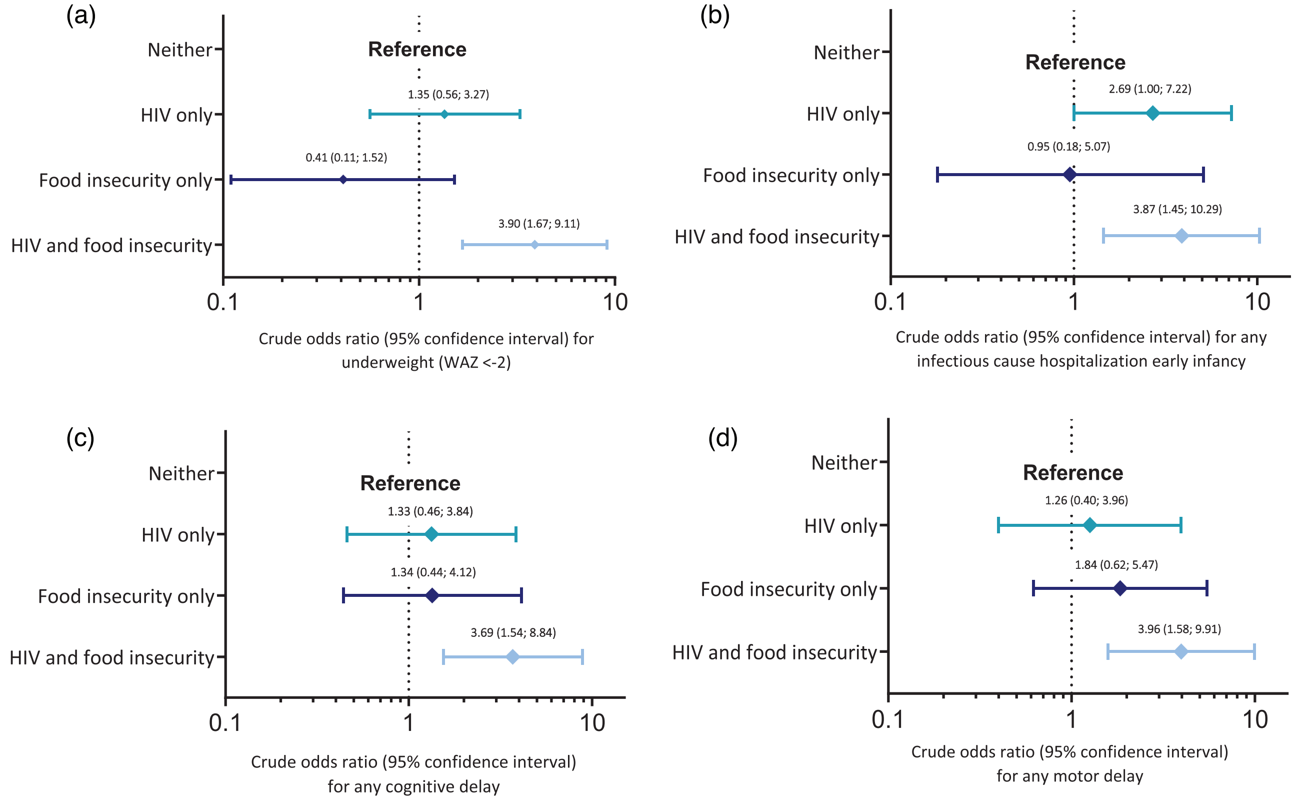

Figure 3. Relative odds (odds ratios) of child health outcomes, by categories of maternal HIV status and household food security: interaction forest plots on logarithmic scale. (a) Odds ratios for underweight (weight-for-age Z-score < −2) during follow-up. (b) Odds ratios for infectious cause hospitalisation between ages 7 days and 3 months. (c) Odds ratios for any cognitive delay (Bayley Scales of Infant Development, 3rd edition, composite score). (d) Odds ratios for any motor delay (Bayley Scales of Infant Development, 3rd edition, composite score).

precision (Tables S7 and S 9). Compared to children with neither exposure (HIV−|IPV−), those with HIV exposure only (HIV+|IPV−) had double the odds of RTI (OR 2.53; 95% CI 1.64; 3.90); those with IPV exposure only (HIV−|IPV+) had similar odds (OR 0.32; 95% CI 0.04; 2.39); and those with both exposures (HIV+|IPV+) had three-fold higher odds (OR 3.27; 95% CI 1.85; 5.78). Results were similar for ambulatory diarrhoea (Table S7). Compared to neither exposure (HIV−|IPV−), odds for motor delay was incrementally increased for HIV exposure only (HIV+|IPV−), IPV exposure only (HIV−|IPV+) and both exposures (HIV+|IPV+) with OR (95% CI) of 1.61 (0.70; 3.75), 2.14 (0.45; 10.21) and 4.68 (1.72; 12.72), respectively.

3.4 | Sensitivity analyses

Results from complete-case analysis using pre-imputation data approximated those from analyses based on imputed datasets. Limiting all outcomes and exposures to the 12-month time point did not alter any inferences. Results were also unchanged when varying the choice of time point for measurements of exposure to maternal alcohol use, depression or IPV (data not shown).

4 | DISCUSSION

We provide unique insights into the syndemic vulnerability from HD, IPV and HFIS in WLHIV and their HIV-negative children, with data to support all three criteria of a syndemic: (a) adverse contextual and social factors; (b) disease clustering; and (c) adverse disease interaction [11]. We described a population of women and children living in adverse socio-economic conditions, within a country known for its stark social inequality, a legacy of extreme racism and ongoing structural violence [32]. Notably, HFIS was the most prevalent maternal syndemic co-factor for both WLHIV and HIV-negative women, with many households experiencing hunger [31]. WLHIV also had greater risks of other adverse exposures than HIV-negative women across socio-economic measures. Within this context, there was marked clustering of maternal HIV with HD, IPV and HFIS at enrolment and over time, with evidence of bi-directional relationships. In turn, these factors individually affected child health outcomes, in both crude and adjusted analyses. Moreover, we found evidence for interaction with HIV for each of the examined syndemic co-factors, on one or more of the examined child outcomes. The strongest interaction effects were seen between maternal HIV and HFIS. Taken together, these data support our *a priori* hypotheses, suggesting a maternal HIV, alcohol, violence and food insecurity syndemic with adverse consequences for CHEU health.

Although concurrence of and interactions between the maternal factors included in this analysis have been reported in several adult-focused studies [14, 33], the impact on child health is less well understood. To our knowledge, this is the first study to systematically seek evidence of HIV-related syndemic interactions on a maternal level, with impact measured on a child health level, following current syndemic theory [11]. Cross-generational syndemic vulnerability has been described in non-HIV-related work, demonstrating the complex web of interactions that can persist over generations, driving psychological and cardiometabolic disease [34]. While our findings require corroboration in other HIV-specific settings, these results align with growing evidence for the developmental origins of the health and disease hypothesis, strengthened by recent advances in neuro-imaging and epigenetic research [35, 36].

These data demonstrate a clear need for multi-faceted interventions to optimise child health in high HIV burden settings, in addition to breastfeeding with ART for maternal HIV. There are a growing number of adult-focused studies evaluating individual- and community-level interventions to reduce alcohol abuse, IPV and/or food insecurity. Community mobilisation, screening with counselling, motivational interviews, housing interventions, cognitive behaviour therapy and microfinance interventions have proven efficacy, although results have varied by setting and duration of effect [33, 37, 38]. In addition to policy-level decision-making around water security and agricultural practices, household-level interventions, including home gardens, food rations and other economic strengthening approaches, can mitigate food insecurity [31, 39–41]. However, there are limited published data available on the effects similar single or multi-component interventions may have on the health of CHEU. The South African-based Philani Intervention Programme, utilising a "Mentor-Mother" community field worker approach, has demonstrated improvements in maternal mental health and child cognitive and physical growth [42]. The feasibility and success of this programme highlights a potential avenue for implementation of and linkage to additional interventions for HD, IPV and HFIS in a similar context. In turn, such multi-faceted programmes would align with the Sustainable Development Goals, which seek to bring "Health in All Policies" [43].

Several key exposures evaluated in this analysis were measured with self-report, increasing the risk of information bias, even when utilising validated tools [27]. Reassuringly, as the same measurement tools were used for both groups of women, any resulting bias would tend towards the null [27]. The food insecurity findings would have been strengthened by repeated measurement, and the use of more than one tool. Our study is also limited by the small sub-group sample sizes, most notably the low prevalence of probable maternal depression overall, and of HD in HIV-negative women. Further research into this field should ideally explore maternal mental health effects in greater detail while incorporating larger sample sizes, for which purpose individual-patient-data meta-analysis may prove useful. Furthermore, a full appreciation of syndemic effects requires both individual- and population-level data [11]. Our findings may not be generalisable to settings with different socio-economic and political structures. Changes in HIV treatment policies have occurred since the completion of our study, most notably the shift from efavirenz-based to dolutegravir-based ART for pregnant women. In turn, the health trajectories of CHEU in our study cohort may not be generalisable to CHEU whose mothers received dolutegravir in pregnancy. Nonetheless, it is unlikely that the adverse consequences of exposure to maternal psychosocial/behavioural factors would differ meaningfully by the type of antenatal ART regimen. Additionally, the background estimates of maternal alcohol use, IPV and HFIS have increased substantially since the COVID-19 pandemic, including in South Africa [44]. Given the worsening international economic milieu, it is likely that our (pre-COVID-19) results underestimate the current syndemic vulnerability of HIV-affected families.

Of the syndemic co-factors evaluated in this work, the most time-critical and salient aspect requiring urgent attention is the extreme burden of food insecurity. There has been a devastating post-2020 increase in food insecurity globally, with worsening conditions predicted under current rates of climate change [31]. Africa—where most CHEU live—has been identified as the continent with the greatest risk of hunger for the present and the foreseeable future [31]. Optimising CHEU health cannot be achieved without addressing the dire living conditions many HIV-affected families experience daily, including the enduring spectre of child hunger.

5 | CONCLUSIONS

Syndemic interactions between maternal HIV, HD, IPV and HFIS may partly drive the residual health discrepancies between CHEU and CHU. These data support the importance of holistic maternal and family care and support alongside ART to optimise CHEU child health.

AUTHORS' AFFILIATIONS

[1]Division of Epidemiology & Biostatistics, School of Public Health, University of Cape Town, Cape Town, South Africa; [2]Mailman School of Public Health, ICAP at Columbia University, Columbia University, New York, New York, USA; [3]Department of Pediatrics, Vagelos College of Physicians & Surgeons, Columbia University, New York, New York, USA

COMPETING INTERESTS

The authors have no competing interests to declare.

AUTHOR CONTRIBUTIONS

SMLR (corresponding author) was responsible for the conceptualisation and implementation of the HU2 study; assisted with the collection of data; conducted the analyses; wrote the first draft of the manuscript and confirms that she had full access to all the data and takes final responsibility for the decision to submit for publication. LM and EJA conceived the MCH-ART and HU2 studies, and were responsible for study design, funding, implementation and overall leadership. TKP was the study coordinator for the MCH-ART study and was responsible for data management and oversight. AZ was the senior MCH-ART study manager and provided oversight of all study administration processes. All authors contributed to and approved the final manuscript.

ACKNOWLEDGEMENTS

The authors thank the funding agencies, research staff and clinical staff who supported this work, and the families who participated in the study.

FUNDING

Funding for this study was provided by PEPFAR through NICHD under Cooperative Agreement 1R01HD074558. Additional funding comes from the Elizabeth Glaser Pediatric AIDS Foundation, South African Medical Research Council (Clinician-Researcher PhD Scholarship), the Fogarty Foundation (NIH Fogarty International Center Grant #5R25TW009340) and the Office of AIDS Research. TKP was supported by the Fogarty International Center of the National Institutes of Health under Award Number K43TW011943.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

REFERENCES

1. UNAIDS. AIDSinfo. Global data on HIV epidemiology & response. [Cited 2022 Jul 15] https://aidsinfo.unaids.org/.
2. Slogrove AL, Powis KM, Johnson LF, Stover J, Mahy M. Estimates of the global population of children who are HIV-exposed and uninfected, 2000–18: a modelling study. Lancet Glob Health. 2020;8(1):e67–e75.
3. Statistics South Africa. Mid-year population estimates. 2022 [Cited 2022 Feb 3] https://www.statssa.gov.za/?p = 15601.
4. le Roux SM, Abrams EJ, Nguyen K, Myer L. Clinical outcomes of HIV-exposed, HIV-uninfected children in sub-Saharan Africa. Trop Med Int Health. 2016;21(7):829–45.
5. Evans C, Jones CE, Prendergast AJ. HIV-exposed, uninfected infants: new global challenges in the era of paediatric HIV elimination. Lancet Infect Dis. 2019;16(6):e92–e107.
6. le Roux SM, Abrams EJ, Donald KA, Brittain K, Phillips TK, Nguyen KK, 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;3(4):234–44.
7. le Roux SM, Abrams EJ, Donald KA, Brittain K, Phillips TK, Zerbe A, 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;4(3):220–31.
8. le Roux SM, Donald KA, Brittain K, Phillips TK, Zerbe A, Nguyen KK, et al. Neurodevelopment of breastfed HIV-exposed uninfected and HIV-unexposed children in South Africa. AIDS. 2018;32(13):1781–91.
9. Prendergast AJ, Evans C. Children who are HIV-exposed and uninfected: evidence for action. AIDS. 2023;37(2):205–15.
10. Evans C, Chasekwa B, Ntozini R, Majo FD, Mutasa K, Tavengwa N, et al. Mortality, human immunodeficiency virus (HIV) transmission, and growth in children exposed to HIV in rural Zimbabwe. Clin Infect Dis. 2021;72(4):586–94.
11. Singer M, Bulled N, Ostrach B, Mendenhall E. Syndemics and the biosocial conception of health. Lancet. 2017;389(10072):941–50.
12. Singer M. Toward a critical biosocial model of ecohealth in Southern Africa: the HIV/AIDS and nutrition insecurity syndemic. Ann Anthropol Pract. 2011;35(1):8–27.
13. Laurenzi C, Field S, Honikman S. Food insecurity, maternal mental health, and domestic violence: a call for a syndemic approach to research and interventions. Matern Child Health J. 2020;24(4):401–4.
14. Lee JS, Bainter SA, Tsai AC, Andersen LS, Stanton AM, Magidson JF, et al. Intersecting relationships of psychosocial and structural syndemic problems among people with HIV in South Africa: using network analysis to identify influential problems. AIDS Behav. 2023;27(6):1741–56.
15. Richter LM, Daelmans B, Lombardi J, Heymann J, Boo FL, Behrman JR, et al. Investing in the foundation of sustainable development: pathways to scale up for early childhood development. Lancet. 2017;389(10064):103–18.
16. Victora CG, Christian P, Vidaletti LP, Gatica-Domínguez G, Menon P, Black RE. Revisiting maternal and child undernutrition in low-income and middle-income countries: variable progress towards an unfinished agenda. Lancet. 2021;397(10282):1388–99.
17. Rod NH, Bengtsson J, Elsenburg LK, Taylor-Robinson D, Rieckmann A. Hospitalisation patterns among children exposed to childhood adversity: a population-based cohort study of half a million children. Lancet Public Health. 2021;6(11):e826–35.
18. Myer L, Phillips TK, Zerbe A, Ronan A, Hsiao NY, Mellins CA, et al. Optimizing antiretroviral therapy (ART) for maternal and child health (MCH): rationale and design of the MCH-ART study. J Acquir Immune Defic Syndr. 2016;72(Suppl 2):S189–96.
19. WHO. AUDIT. The Alcohol Use Disorders Identification Test. Guidelines for use in primary care. 2nd ed. World Health Organization, Department of Mental Health and Substance Dependence; 2001.
20. Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale. Br J Psychiatry. 1987;150:782–86.
21. García-Moreno C, Jansen HA, Ellsberg M, Heise L, Watts CH. WHO multi-country study on women's health and domestic violence against women: initial results on prevalence, health outcomes and women's responses. Geneva: World Health Organization; 2005.
22. Labadarios D, McHiza ZJ, Steyn NP, Gericke G, Maunder EM, Davids YD, et al. Food security in South Africa: a review of national surveys. Bull World Health Organ. 2011;89(12):891–99.
23. Boulle A, Heekes A, Tiffin N, Smith M, Mutemaringa T, Zinyakatira N, et al. Data Centre Profile: the provincial health data centre of the Western Cape Province, South Africa. Int J Popul Data Sci. 2019;4(2):1143.
24. Statistics South Africa. South Africa Demographic and Health Survey 2016: Key Indicator Report [Cited 2018 Sept 11] https://www.statssa.gov.za/publications/Report%2003-00-09/Report%2003-00-092016.pdf.
25. le Roux SM, Donald KA, Kroon M, Phillips TK, Lesosky M, Esterhuyse L, et al. HIV viremia during pregnancy and neurodevelopment of HIV-exposed uninfected children in the context of universal antiretroviral therapy and breastfeeding: a prospective study. Pediatr Infect Dis J. 2019;38(1):70–75.
26. Bayley N. Bayley Scales of Infant and Toddler Development—Third Edition. Pearson Clinical Assessments. San Antonio, TX: Psychological Corporation; 2006.
27. Lash TL, VanderWeele TJ, Haneuse S, Rothman KJ. Modern epidemiology. 4th ed. Philadelphia, PA: Wolters Kluwer; 2021.
28. Hulsen T. DeepVenn–a web application for the creation of area-proportional Venn diagrams using the deep learning framework Tensorflow. js. arXiv preprint arXiv:221004597. 2022.
29. van Buuren S, Boshuizen HC, Knook DL. Multiple imputation of missing blood pressure covariates in survival analysis. Stat Med. 1999;18(6):681–94.
30. Rubin DB. Multiple imputation for nonresponse in surveys. John Wiley & Sons; 2004.
31. FAO, IFAD, UNICEF, WFP, WHO. The state of food security and nutrition in the world, 2022: repurposing food and agricultural policies to make healthy diets more affordable. Rome: FAO; 2022.
32. Farmer PE, Nizeye B, Stulac S, Keshavjee S. Structural violence and clinical medicine. PLoS Med. 2006;3(10):e449.
33. Mitchell J, Wight M, Van Heerden A, Rochat TJ. Intimate partner violence, HIV, and mental health: a triple epidemic of global proportions. Int Rev Psychiatry. 2016;28(5):452–63.
34. Slagboom MN, Crone MR, Reis R. Exploring syndemic vulnerability across generations: a case study of a former fishing village in the Netherlands. Social Sci Med. 2022;295:113122.
35. Cavalli G, Heard E. Advances in epigenetics link genetics to the environment and disease. Nature. 2019;571(7766):489–99.
36. Wu Y, Espinosa KM, Barnett SD, Kapse A, Quistorff JL, Lopez C, et al. Association of elevated maternal psychological distress, altered fetal brain, and offspring cognitive and social-emotional outcomes at 18 months. JAMA Netw Open. 2022;5(4):e229244.
37. Yakubovich AR, Bartsch A, Metheny N, Gesink D, O'Campo P. Housing interventions for women experiencing intimate partner violence: a systematic review. Lancet Public Health. 2022;7(1):e23–e35.
38. Madhombiro M, Musekiwa A, January J, Chingono A, Abas M, Seedat S. Psychological interventions for alcohol use disorders in people living with HIV/AIDS: a systematic review. Syst Rev. 2019;8(1):244.
39. Exavery A, Charles J, Barankena A, Bajaria S, Minja E, Mulikuza J, et al. Impact of household economic strengthening intervention on food security among caregivers of orphans and vulnerable children in Tanzania. PLoS One. 2022;17(2):e0264315.
40. Fahey CA, Njau PF, Dow WH, Kapologwe NA, McCoy SI. Effects of short-term cash and food incentives on food insecurity and nutrition among HIV-infected adults in Tanzania. AIDS. 2019;33(3):515–24.
41. Motbainor A, Arega Z, Tirfie M. Comparing level of food insecurity between households with and without home gardening practices in Zege, Amhara region, North West Ethiopia: community based study. PLoS One. 2022;17(12):e0279392.
42. Tomlinson M, Rotheram-Borus MJ, Scheffler A, le Roux I. Antenatal depressed mood and child cognitive and physical growth at 18-months in South Africa: a

cluster randomised controlled trial of home visiting by community health workers. Epidemiol Psychiatr Sci. 2018;27(6):601–10.
43. United Nations. Sustainable Development Goals [Cited 2019 Aug 18] https://www.un.org/sustainabledevelopment/sustainable-development-goals/.
44. Abrahams Z, Boisits S, Schneider M, Prince M, Lund C. The relationship between common mental disorders (CMDs), food insecurity and domestic violence in pregnant women during the COVID-19 lockdown in Cape Town, South Africa. Soc Psychiatry Psychiatr Epidemiol. 2022;57(1):37–46.

SUPPORTING INFORMATION

Additional information may be found under the Supporting Information tab for this article:

Figure S1: Schematic representation of hypothesised maternal HIV-related syndemics and pathways to adverse child health consequences.

Figure S2: Study flow diagram.

Figure S3: a) Proportional Venn diagram demonstrating overlap between maternal HIV status, hazardous drinking, and intimate partner violence; b). Proportional Venn diagram demonstrating overlap between maternal HIV status, hazardous drinking, and household food insecurity; c) Proportional Venn diagram demonstrating overlap between maternal HIV status, intimate partner violence, and household food insecurity.

Table S1: Sample size calculations1 for primary study analyses on child health outcomes.

Table S2: Characteristics of mother-infant pairs who completed follow-up and contributed household food insecurity data at 12 months' study visit vs those who did not, stratified by maternal HIV status.

Table S3: Methodological aspects of multiple imputation overall and by outcome.

Table S4: Interrelationships between maternal sociodemographic and behavioural factors: percentage of total study population with two potentially adverse maternal or household factors.

Table S5: Mean differences in Z-scores by maternal characteristics: results from random effects linear regression models with repeat measures.

Table S6: Relative odds (odds ratios) for underweight, stunting, and microcephaly over time, by maternal characteristics: results from random effects logistic regression models with repeat measures.

Table S7: Relative odds (odds ratios) for infectious morbidity events, by maternal characteristics: results from logistic regression models.

Table S8: Mean differences in BSID-III composite developmental scores, by maternal characteristics, at approximately 12 months of age: results from linear regression models.

Table S9: Relative odds (odds ratios) of developmental delay (BSID-III composite score <85), by maternal characteristics, at approximately 12 months of age: results from logistic regression models.

Table S10: Interaction on the additive and/or the multiplicative scale: testing variation in exposure effects by strata of maternal HIV status, hazardous drinking, intimate partner violence, and household food insecurity, using crude risk ratios and epidemiological measures of interaction.

Bukasa LL et al *Journal of the International AIDS Society* 2023, **26**(S4):e26150
http://onlinelibrary.wiley.com/doi/10.1002/jia2.26150/full | https://doi.org/10.1002/jia2.26150

JIAS JOURNAL OF THE INTERNATIONAL AIDS SOCIETY

COMMENTARY

Setting the research agenda: involving parents in research on children who are HIV-free

Laurette L. Bukasa[1,§,#], Angelina Namiba[2,#], Matilda Brown[2], Estelle Ndu'ngu[2], Mercy Nangwale[2], Gillian Letting[2], Patricia Chirwa[2], Claire Thorne[1] and Shema Tariq[3,4]

[§]**Corresponding author**: Laurette L. Bukasa, Population, Policy and Practice Research & Teaching Department, UCL Great Ormond Street Institute of Child Health, 30 Guilford Street, London WC1N 1EH, UK. (l.bukasa@ucl.ac.uk)

Abstract

Introduction: There is growing interest in health, developmental and survival outcomes of children who are born HIV-free to women living with HIV (children born HIV-free). To date, the research agenda has been largely determined by researchers, funders and policy makers, with limited involvement of parents, who are key stakeholders. Researchers at UCL Great Ormond Street Institute of Child Health in partnership with community-based organisation 4M Network of Mentor Mothers conducted two workshops with parents in March 2022 to establish research priorities for children born HIV-free, and key considerations for methodological approaches both to research and engagement with the affected communities.

Discussion: When exploring research on children born HIV-free, we consider the following: what aspects of current research are aligned with women and parents' priorities, what is missing and what approaches would be preferred. A holistic approach to research on children born HIV-free should be prioritised, focussing on a breadth of outcomes and how they intersect. Secondary use of existing data sources should be maximised to facilitate this, with a view of monitoring the long-term effects of fetal antiretroviral drug exposure alongside other key health and developmental outcomes. Involving and engaging with parents, and children where possible, must be at the heart of research design to maximise relevance and impact of findings for the affected communities. Potential barriers to engaging with individuals who were children born HIV-free include parental disclosure and individuals not identifying as a child born HIV-free to a mother living with HIV. Stigma-free language must be incorporated into the vocabulary of researchers and other stakeholders, avoiding reference to exposure; we propose the term "children born HIV-free."

Conclusions: Mothers and parents living with HIV should be involved in research about their children born HIV-free and are key in identifying research priorities so that findings may translate into an impact on their children's health and wellbeing. Meaningful involvement of women living with HIV through trusted community partners is an effective mechanism by which to elicit views on research about their children.

Keywords: public engagement; co-production; women; children; community; HIV

Received 23 January 2023; **Accepted** 14 August 2023

1 | INTRODUCTION

Successes in preventing vertical transmission (VT) have led to substantially fewer children being born with HIV [1]. In parallel, the number of children who are born HIV-free to women living with HIV* (*children born HIV-free will henceforth refer to children born to women living with HIV who remain HIV-free throughout childhood) has increased to an estimated 15 million globally, with more than half living in just four sub-Saharan African countries [2]. In the UK, there are approximately 900 pregnancies in women living with HIV each year with a VT rate <0.4% since 2012 among diagnosed women [3].

The first 1000 days of life (conception to approximately 24 months) is a critical period of development for children, where factors relating to the maternal and external environment can play an important role in modifying life-long risk of health and developmental outcomes [4]. Children born HIV-free develop in an intrauterine environment where HIV, antiretroviral drugs and other factors, such as anxiety and depression, affect the mother in pregnancy [5]. Growing evidence from predominantly low- and middle-income settings suggests that children born HIV-free may have sub-optimal health and survival outcomes compared with children born to women without HIV [6–9]. Specific antiretrovirals [10, 11], HIV viral factors [12, 13] and adverse birth outcomes, such as preterm birth [14], may contribute to these divergent outcomes, but many questions remain.

The multilevel response to improve outcomes for children born HIV-free have included interventions to reduce mortality, support programmatic scale-up and effectiveness of prevention of VT programmes, and minimise health and developmental disparities within a framework where children are alive, HIV-free and thriving [15]. With progress being made to improve survival and reduce VT rates globally [16], the research landscape is increasingly focussed on children thriving. Recent findings have demonstrated that in addition to existing evidence on increased morbidity, developmental delay may disproportionately affect children born HIV-free in sub-Saharan Africa [17, 18]. This could involve pathways relating to indirect effects of maternal HIV, such as adverse maternal mental health, that is depression and stress [17, 19] and possible direct effects of exposure to maternal HIV, co-infections and Antiretroviral therapy (ART) in utero [20], although no data exist for the UK.

There is growing recognition of the importance of including pregnant people and parents living with HIV at all stages of research, beyond being research participants, in accordance with equitable research principles and UNAIDS policy for greater involvement of people living with HIV [21, 22]. Successful examples of co-production in research and policy-making exist; such as the inclusion of mothers living with HIV in the study team and the advisory board of the NOURISH-UK study on HIV and infant feeding [23] and community-led WHO consultation with women living with HIV when preparing updates to guidelines [24]. However, there are areas of research where women living with HIV are excluded from participating and shaping research. For example, pregnant and breastfeeding women have been routinely excluded from clinical research on antiretroviral drugs, perpetuating the widening evidence gap on drug safety during this period [25]; when enabled to contribute to discussions on this topic, women had strong views that challenged long-standing protocols and advocated for them to make informed choices about participation [26]. Communities can have differing views on research to researchers, yet parents living with HIV are rarely involved in shaping research on children born HIV-free, despite often being the main caregivers with key insights into their children's health. Even less common is the involvement of children born HIV-free themselves, although models for meaningful involvement of children and young adults living with HIV exist [27].

Researchers at UCL conducting research on children born HIV-free in the UK and 4M Network of Mentor Mothers convened two workshops in March 2022 with six biological mothers of children born HIV-free from Black ethnic backgrounds to explore components for a research agenda in the UK and globally. Building on the outcomes of these discussions, we provide key learnings for stakeholders involved in research on children born HIV-free.

2 | DISCUSSION

In our workshops, six parents living with HIV established themes for research on children born HIV-free, including priorities, an infrastructure for utilising existing data source, language preferences and approaches (Figure 1).

2.1 | Outcomes of interest

There has been long-standing recognition of the need to monitor the longer-term health and development of children born HIV-free in the UK, in the context of routine discharge from clinical care after confirmation of HIV-free status at approximately 24 months of age [28, 29]. The primary concern for families affected by HIV in the UK was the potential adverse effects associated with early life exposures to antiretrovirals, and there was explicit support for researchers to address the significant knowledge gaps that still exist. In view of this, parents expressed a preference for a wide range of outcomes to be investigated, regardless of perceived severity. For example, dental conditions may not be considered a severe adverse outcome by researchers, yet parents are concerned about such conditions as they are common and impact their children's wellbeing. An exploration of the long-term health effects or benefits of breastfeeding was also identified as a key outcome; breast/chestfeeding is less common in high-income settings like the UK, but increasingly becoming the infant feeding option of choice [30, 31]. Limited data on the effects of neonatal HIV post-exposure prophylaxis (PEP) [32] should also be addressed. This is particularly salient given the increasing prevalence of breast/chestfeeding among people with HIV [33], prolonging exposure to ART through human milk and infant PEP for the duration of breast/chestfeeding in some settings [34].

Sub-optimal immune system development and increased risk and severity of infectious diseases have been reported in cohorts of children born HIV-free both in high-income and low-income settings, although not specifically in the UK [35, 36]. Parents observed that their children born HIV-free may experience infections more often than other children, with particular mention of tonsilitis. Increased frequency and severity of infections in children born HIV-free may have multidimensional impacts beyond health, such as poor school attendance which can lead to social service involvement. This highlights the potential upstream effects of poorer health in childhood on later life, mediated by educational attainment. Engaging parents can yield an understanding of the individual-level impact of findings on infections and immune system development of children born HIV-free.

2.2 | Utilising existing data and pioneering data linkages

When considering data collection methods, secondary use of administrative data (information generated when interacting with public services [37]) was desirable for several reasons, including efficiency, cost, and robust ethical and data governance processes. A key advantage among parents was the potential for linkage using multiple datasets that could facilitate a broader understanding of health and developmental outcomes among children born HIV-free. For example, there is conflicting evidence regarding neurodevelopmental outcomes in children born HIV-free in low- and middle-income countries [20, 38] but there are no data for the UK context at present.

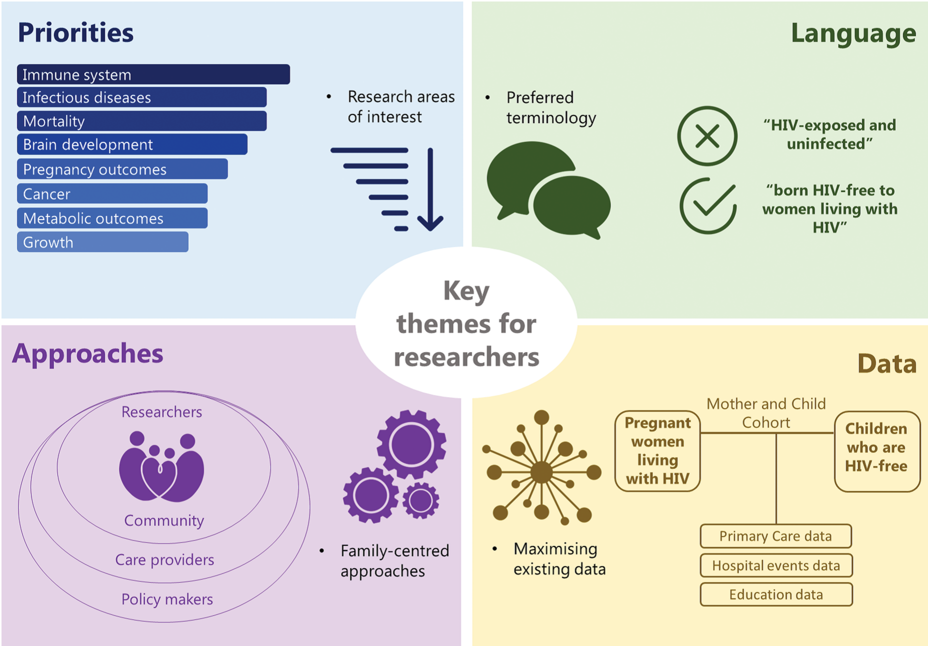

Figure 1. Key themes for research on children born HIV-free. Top left corner shows the group priority research areas, top right corner illustrates terminology preferences, bottom left corner illustrates a family-centred approach to research and engagement with other stakeholders and bottom right corner shows a data infrastructure to explore outcomes.

Linking health and educational records would enable an investigation of possible disparities in educational attainment and explore potential drivers. Similarly, primary care data could be valuable for understanding health from pregnancy through to childhood as the main entry point to clinical care pathways, containing information on morbidity (less severe than hospital events), prescriptions and vaccinations.

Utilising existing data sources to explore health and developmental outcomes among children born HIV-free minimises the burden on the affected communities to contribute to research as participants. Currently, much of the data from this population come from prospective observational cohort studies that require follow-up visits and are associated with costs in both time and money to participants and their families. In addition, the perceived burden of follow-up may act as a barrier to recruitment, threatening the feasibility of studies [39] that are already limited in their capacity to address long-term outcomes with respect to research funding. However, these benefits for secondary use of existing data should be considered alongside its limitations including limited scope to explore beyond what has already been collected.

2.3 | Language and terminology

The use of language for people living with HIV has evolved, with greater recognition of its power to perpetuate stigma and discrimination [40]. There is now a commitment among many key stakeholders, including researchers and clinicians, to adopt terms that are destigmatising and people-centred, illustrated by the People First Charter [41]. Parent(s), who have experienced this evolution first-hand, place great importance on getting the language right from the outset for children born HIV-free. Terms such as "uninfected" can be viewed as clinical and stigmatising, and the use of acronyms such as "CHEU" (children who are HIV-exposed but uninfected) dehumanising when engaging in dialogue about children born HIV-free. There was a preference for terms such as "children born without HIV," "children born HIV-free" or "children who are HIV-free" among parents, and while current terminology used among stakeholders (children who are HIV-exposed and uninfected) adhere to the People First Charter [42], greater consideration should be given by researchers to how they refer to this population.

2.4 | A family-centred approach for setting the research agenda

2.4.1 | *Women and pregnancy*

Exploring outcomes of children born HIV-free within the context of the woman and mother could offer an alternative perspective on inequalities within and between populations:

"For a healthy pregnancy, birth and child, a woman must be physically and mentally well."

Maternal mental health in the context of HIV in pregnancy is an underdeveloped area of research in the UK. Women living with HIV are disproportionately affected by mental health difficulties [43, 44], driven in part by social disadvantage [44, 45]. Investigating the impact of maternal mental health on pregnancy and both short- and long-term child outcomes may elucidate pathways that may be driving health and developmental inequalities and reveal opportunities for potential interventions in similar settings where evidence of developmental differences have been observed [46].

The persistence of adverse parental mental health can affect children born HIV-free directly and indirectly; direct effects include children being more likely to be absent from school or display behavioural problems [47], and indirect effects could include the risk of HIV-related death among parents experiencing mental health difficulties [48], which could, in turn, increase the risk of adverse childhood experiences (i.e. parental bereavement) among children born HIV-free, analogous to their counterparts living with HIV [49, 50].

2.4.2 | *Engaging children born HIV-free*

Parents identified children born HIV-free as experts-by-experience who should be involved in research. However, engaging children born HIV-free is associated with several challenges.

Firstly, parents need to talk about their HIV status to their children, but rates of parental disclosure are low globally [51, 52]. While there are benefits of this sharing for the parent-child relationship [53], it is conditional upon an acceptance of the parent's HIV status themselves, which could involve overcoming self-stigma, cultural and family-related factors. Even if a child or young adult is aware of their parent(s)' HIV status, opportunities to involve them in discussions about research are limited. There is a lack of community-based organisations for this population in the UK and beyond, and the absence of routine population-level clinical follow-up of children born HIV eliminates the possibility of approaching them opportunistically. However, children and young adults can be identified through their family members living with HIV; for example, HIV-free siblings of young people with perinatally acquired HIV were recruited as controls in the UK's AALPHI study [54].

Furthermore, those who are HIV-free and aware of their HIV-free status may not perceive themselves as different from children who were born to women without HIV. Engaging a population that do not consider themselves as at risk of adverse outcomes or do not identify as "HIV-exposed" is a significant barrier to the co-production of research on children born HIV-free. A driving factor for children and young adult's dissociation from being "HIV-free" could be related to HIV-associated stigma and fear of bullying if their parent(s)' status became common knowledge. Researchers must also consider the capacity for children and young adults to engage with and become involved with research. Some will also be navigating social and economic disadvantage which can be prevalent in communities affected by HIV [55, 56], as well as potential illness within their families.

There are likely to be varying perspectives on being "HIV-free" among children and young adults born to women living with HIV, highlighting the importance of involving them in discussions around the research agenda from inception, as their views on research and its relevance to their lives may differ to their parents [57].

2.5 | Maximising research impact

Research on children born HIV-free can be poorly disseminated to communities which minimises impact. When considering stakeholder groups for dissemination of research findings, children and/or young adults born HIV-free should be prioritised along with their parent(s) living with HIV. Children born HIV-free should be given access to information on research at an appropriate age of comprehension [58] using specific content created for them, and efforts made to engage within settings in which they feel comfortable, that is podcasts, social media or attending youth events. Parents living with HIV should be disseminating findings alongside researchers as self-advocates, particularly in health and social care settings. Dissemination strategies must be co-produced with children born HIV-free and their parents to target appropriate key stakeholders, and to tailor the communication of findings to each audience.

3 | CONCLUSIONS

In this commentary, we draw upon findings from workshops with six parents living with HIV who provided feedback on priorities and approaches for research on children born HIV-free. We have highlighted how parents and children affected by HIV have unique and important insights into research on children born HIV-free. It is vital that academics, clinicians, funders and other stakeholders centre their voices to increase relevancy and maximise the impact of research. In collaboration with parents living with HIV, we have identified a set of research priorities and recommendations for the research agenda that are based on selecting a broad range of outcomes; using and linking existing data; using stigma-free language; and employing a holistic, life-course approach that values involving parents and children. We propose an extension to existing frameworks to decolonise global health that foreground the need for equitable research partnerships [59], by including this often marginalised population of parents living with HIV, and their children, as research partners in setting the research agenda in this growing population of children. Identifying potential barriers for involving affected communities is a necessary component in achieving this, and exploration of these challenges can facilitate ongoing dialogue with communities on how to overcome them.

AUTHORS' AFFILIATIONS

[1]UCL Great Ormond Institute of Child Health, London, UK; [2]4M Network of Mentor Mothers, London, UK; [3]UCL Institute for Global Health, London, UK; [4]Mortimer Market Centre, Central and North West London NHS Foundation Trust, London, UK

ACKNOWLEDGEMENTS

We would like to thank 4M Net and all the women who participated and contributed to the project. We would also like to thank UCL Culture for funding the workshops.

COMPETING INTERESTS

CT has received funding from ViiV Healthcare via the PENTA Foundation for a pharmacovigilance study on drug use and safety in pregnancy. ST has previously received speaker honoraria and funding for the preparation of educational materials from Gilead Sciences.

AUTHORS' CONTRIBUTIONS

LLB and AN conceived concept of the project. LLB, AN, CT and ST designed workshop. AN, MN, PC, GL, MB and EN contributed to workshop content. LLB wrote the manuscript. AN, CT and ST reviewed the manuscript.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

REFERENCES

1. Vrazo AC, Sullivan D, Phelps BR. Eliminating mother-to-child transmission of HIV by 2030: 5 strategies to ensure continued progress. Glob Health: Sci Pract. 2018;6(2):249–56.
2. Slogrove AL, Powis KM, Johnson LF, Stover J, Mahy M. Estimates of the global population of children who are HIV-exposed and uninfected, 2000–18: a modelling study. Lancet Glob Health. 2020;8(1):e67–75.
3. Peters HF, Bukasa L, Sconza R, Smeaton L, Webb S, Thorne C. Preventing vertical HIV transmission in the UK: successes and emerging challenges. In Conference on Retroviruses and Opportunistic Infections (CROI). 2021.
4. Linnér A, Almgren M. Epigenetic programming—the important first 1000 days. Acta Paediatr. 2020;109(3):443–52.
5. Kapetanovic S, Dass-Brailsford P, Nora D, Talisman N. Mental health of HIV-seropositive women during pregnancy and postpartum period: a comprehensive literature review. AIDS Behav. 2014;18(6):1152–73.
6. Desmonde S, Goetghebuer T, Thorne C, Leroy V. Health and survival of HIV perinatally exposed but uninfected children born to HIV-infected mothers. Curr Opin HIV AIDS. 2016;11(5):465–76.
7. Arikawa S, Rollins N, Newell ML, Becquet R. Mortality risk and associated factors in HIV-exposed, uninfected children. Trop Med Int Health. 2016;21(6):720–34.
8. Thorne C, Idele P, Chamla D, Romano S, Luo C, Newell M-L. Morbidity and mortality in HIV-exposed uninfected children. Future Virol. 2015;10(9):1077–100.
9. Prendergast AJ, Evans C. Children who are HIV-exposed and uninfected: evidence for action. AIDS. 2023;37(2):205–15.
10. Jonsson Funk M, Belinson SE, Pimenta JM, Morsheimer M, Gibbons DC. Mitochondrial disorders among infants exposed to HIV and antiretroviral therapy. Drug Saf. 2007;30(10):845–59.
11. Viganò A, Cerini C, Pattarino G, Fasan S, Zuccotti GV. Metabolic complications associated with antiretroviral therapy in HIV-infected and HIV-exposed uninfected paediatric patients. Expert Opin Drug Saf. 2010;9(3):431–45.
12. Shinar S, Agrawal S, Ryu M, Walmsley S, Serghides L, Yudin MH, et al. Perinatal outcomes in women living with HIV-1 and receiving antiretroviral therapy—a systematic review and meta-analysis. Acta Obstet Gynecol Scand. 2022;101(2):168–82.
13. Bender JM, Li F, Martelly S, Byrt E, Rouzier V, Leo M, et al. Maternal HIV infection influences the microbiome of HIV-uninfected infants. Sci Transl Med. 2016;8(349):349ra100–349ra1.
14. Adler C, Haelterman E, Barlow P, Marchant A, Levy J, Goetghebuer T. Severe infections in HIV-exposed uninfected infants born in a European country. PLoS One. 2015;10(8):e0135375.
15. Slogrove AL, Powis KM. Widening the lens to ensure children who are HIV exposed are alive, HIV-free and thriving. Clin Infect Dis. 2021;72(4):595–597.
16. Mallampati D, Maclean RL, Shapiro R, Dabis F, Engelsmann B, Freedberg KA, et al. Optimal breastfeeding durations for HIV-exposed infants: the impact of maternal ART use, infant mortality and replacement feeding risk. J Int AIDS Soc. 2018;21(4):e25107.
17. Ntozini R, Chandna J, Evans C, Chasekwa B, Majo FD, Kandawasvika G, et al. Early child development in children who are HIV-exposed uninfected compared to children who are HIV-unexposed: observational sub-study of a cluster-randomized trial in rural Zimbabwe. J Int AIDS Soc. 2020;23(5):e25456.
18. Mebrahtu H, Simms V, Chingono R, Mupambireyi Z, Weiss HA, Ndlovu P, et al. Postpartum maternal mental health is associated with cognitive development of HIV-exposed infants in Zimbabwe: a cross-sectional study. AIDS Care. 2018;30(2):74–82.
19. Liu Y, Kaaya S, Chai J, Mccoy DC, Surkan PJ, Black MM, et al. Maternal depressive symptoms and early childhood cognitive development: a meta-analysis. Psychol Med. 2017;47(4):680–9.
20. Wedderburn CJ, Weldon E, Bertran-Cobo C, Rehman AM, Stein DJ, Gibb DM, et al. Early neurodevelopment of HIV-exposed uninfected children in the era of antiretroviral therapy: a systematic review and meta-analysis. Lancet Child Adolesc Health. 2022;6(6):393–408.
21. UNAIDS. *The Greater Involvement of People Living with HIV (GIPA)*. 2007.
22. Schroeder D, Chatfield K, Singh M, Chemmels R, Herrisone-Kelly P. Equitable research partnerships. A global code of conduct to counter ethics dumping. SpringerBriefs in Research and Innovation Governance. 2018: Springer. p. 134.
23. Kasadha B, Tariq S, Nyatsanza F, Freeman-Romilly N, Namiba A, Rai T. Stakeholder engagement is essential to maximise the impact of research on infant feeding in the context of HIV. Therap Adv Infect Dis. 2021;8:20499361211057970.
24. Namiba A, Orza L, Bewley S, Crone ET, Vazquez M, Welbourn A. Ethical, strategic and meaningful involvement of women living with HIV starts at the beginning. J Virus Erad. 2016;2(2):110–1.
25. Renaud F, Mofenson LM, Bakker C, Dolk H, Leroy V, Namiba A, et al. Surveillance of ARV safety in pregnancy and breastfeeding: towards a new framework. J Int AIDS Soc. 2022;25(S2):e25922.
26. Clayden P, Zech JM, Irvine C, Mahaka IC, Namiba A. Engaging the community of women living with HIV to tailor and accelerate ARV research for pregnant and breastfeeding women. J Int AIDS Soc. 2022;25(S2):e25920.
27. Shibemba M, Conway M, Kiganda C, Ahimbisibwe GM. Adolescents living with HIV from multiple countries being lead-partners in the co-production of research information and findings across global clinical trials. In AIDS 2022. 2022.
28. Thorne C, Tookey P. Strategies for monitoring outcomes in HIV-exposed uninfected children in the United Kingdom. Front Immunol. 2016;7:185.
29. Hankin C, Lyall H, Peckham C, Tookey P. Monitoring death and cancer in children born to HIV-infected women in England and Wales: use of HIV surveillance and national routine data. AIDS. 2007;21(7):867–9.
30. Peters HB, Francis K, Sconza R, Thorne C. Trends in maternal characteristics and pregnancy outcomes among women living with HIV in the UK: 2014–2019. HIV Med. 2022;23:3–15.
31. Nyatsanza F, Gubbin J, Gubbin T, Seery P, Farrugia P, Croucher A, et al. Over a third of childbearing women with HIV would like to breastfeed: a UK survey of women living with HIV. Int J STD AIDS. 2021;32(9):856–60.
32. BHIVA. *BHIVA* guidelines on the management of HIV in pregnancy and postpartum (2020 third interim update). British HIV Association; 2020.
33. Francis K, Sconza R, Peters H. Supported breastfeeding among women with diagnosed HIV in the UK - the current picture. J Int AIDS Soc. 2022;25(S6):18.
34. US Department of Heath and Human Services. Recommendations for use of antiretroviral drugs in transmission in the United States. 2021.
35. Labuda SM, Huo Y, Kacanek D, Patel K, Huybrechts K, Jao J, et al. Rates of hospitalization and infection-related hospitalization among HIV-exposed uninfected children compared to HIV-unexposed uninfected children in the United States, 2007–2016. Clin Infect Dis. 2019;72(2):332–339.
36. Slogrove AL, Goetghebuer T, Cotton MF, Singer J, Bettinger JA. Pattern of infectious morbidity in HIV-exposed uninfected infants and children. Front Immunol. 2016;7:164.
37. UK Administration. What is administrative data? Accessed 9 September 2022 Available from: https://www.adruk.org/our-mission/administrative-data/.
38. Toledo G, Côté HCF, Adler C, Thorne C, Goetghebuer T. Neurological development of children who are HIV-exposed and uninfected. Dev Med Child Neurol. 2021;63(10):1161–1170.
39. Hankin C, Lyall H, Willey B, Peckham C, Masters J, Tookey P. In utero exposure to antiretroviral therapy: feasibility of long-term follow-up. AIDS Care. 2009;21(7):809–16.
40. Watson S, Namiba A, Lynn V. The language of HIV: a guide for nurses. HIV Nurs. 2019;19(2):BP1–4.
41. People First Charter.People First Charter. 2022 [cited 2023] Accessed 7 January 2023. Available from: https://peoplefirstcharter.org/.
42. Waters L, Hodson M, Josh J. Language matters: the importance of person-first language and an introduction to the People First Charter. HIV Med. 2023;24(1):3–5.
43. Lampe FC. Increased risk of mental illness in people with HIV. Lancet HIV. 2022;9(3):e142–4.
44. Waldron EM, Burnett-Zeigler I, Wee V, Ng YW, Koenig LJ, Pederson AB, et al. Mental health in women living with HIV: the unique and unmet needs. J Int Assoc Provid AIDS Care. 2021;20:2325958220985.
45. Orza L, Bewley S, Logie CH, Crone ET, Moroz S, Strachan S, et al. How does living with HIV impact on women's mental health voices from a global survey. J Int AIDS Soc. 2015;18(6):20289.
46. Yao T-J, Malee K, Zhang J, Smith R, Redmond S, Rice ML, et al. In utero antiretroviral exposure and risk of neurodevelopmental problems in HIV-exposed uninfected 5-year-old children. AIDS Patient Care STDs. 2023;37(3):119–30.
47. Rutter M, Quinton D. Parental psychiatric disorder: effects on children. Psychol Med. 1984;14(4):853–80.
48. Haas AD, Ruffieux Y, Van Den Heuvel LL, Lund C, Boulle A, Euvrard J, et al. Excess mortality associated with mental illness in people living with HIV in Cape

Town, South Africa: a cohort study using linked electronic health records. Lancet Glob Health. 2020;8(10):e1326–34.
49. Cluver L, Orkin M, Boyes ME, Sherr L, Makasi D, Nikelo J. Pathways from parental AIDS to child psychological, educational and sexual risk: developing an empirically-based interactive theoretical model. Soc Sci Med. 2013;87:185–93.
50. Bauman LJ, Silver EJ, Draimin BH, Hudis J. Children of mothers with HIV/AIDS: unmet needs for mental health services. Pediatrics. 2007;120(5):e1141–7.
51. Qiao S, Li X, Stanton B. Disclosure of parental HIV infection to children: a systematic review of global literature. AIDS Behav. 2013;17(1):369–89.
52. Osingada CP, Okuga M, Nabirye RC, Sewankambo NK, Nakanjako D. Prevalence, barriers and factors associated with parental disclosure of their HIV positive status to children: a cross-sectional study in an urban clinic in Kampala, Uganda. BMC Public Health. 2016;16(1):547.
53. Goodrum NM, Masyn KE, Armistead LP, Avina I, Schulte M, Marelich W, et al. A mixed-methods longitudinal investigation of mothers' disclosure of HIV to their children. Child Dev. 2021;92(4):1403–20.
54. Judd A, Le Prevost M, Melvin D, Arenas-Pinto A, Parrott F, Winston A, et al. Cognitive function in young persons with and without perinatal HIV in the AALPHI cohort in England: role of non-HIV-related factors. Clin Infect Dis. 2016;63(10):1380–7.
55. Bunyasi EW, Coetzee DJ. Relationship between socioeconomic status and HIV infection: findings from a survey in the Free State and Western Cape Provinces of South Africa. BMJ Open. 2017;7(11):e016232.
56. Brown A, Kelly C, Nash S, Kall M, Enayat Q, Croxford S, et al. *Women and HIV in the UK*. PHE Publications: 2019.
57. Bird D, Culley L, Lakhanpaul M. Why collaborate with children in health research: an analysis of the risks and benefits of collaboration with children. Arch Dis Child Educ Pract Ed. 2013;98(2):42–48.
58. Paquette ET, Palac H, Bair E, Schultz B, Stenquist N, Joffe S, et al. The importance of engaging children in research decision-making: a preliminary mixed-methods study. Ethics Hum Res. 2020;42(3):12–20.
59. Khan M, Abimbola S, Aloudat T, Capobianco E, Hawkes S, Rahman-Shepherd A. Decolonising global health in 2021: a roadmap to move from rhetoric to reform. BMJ Glob Health. 2021;6(3):e005604.

Davtyan M et al. *Journal of the International AIDS Society* 2023, **26**(S4):e26167
http://onlinelibrary.wiley.com/doi/10.1002/jia2.26167/full | https://doi.org/10.1002/jia2.26167

JIAS JOURNAL OF THE INTERNATIONAL AIDS SOCIETY

RESEARCH ARTICLE

The role of internalised HIV stigma in disclosure of maternal HIV serostatus to children perinatally HIV-exposed but uninfected: a prospective study in the United States

Mariam Davtyan[1,§], Deborah Kacanek[2], Jessica Lee[2], Claire Berman[3], Ellen G. Chadwick[4], Renee Smith[5], Liz Salomon[3], Toinette Frederick[1] and for the Pediatric HIV/AIDS Cohort Study

[§]**Corresponding author**: Mariam Davtyan, Keck School of Medicine, Maternal, Child & Adolescent Center for Infectious Diseases and Virology, University of Southern California, 1640 Marengo Street, Suite #300, Los Angeles, CA 90033, USA. (mdavtyan@usc.edu)

Abstract

Introduction: Decisions to disclose HIV serostatus may be complicated by internalised HIV stigma. We evaluated the association of internalised HIV stigma in biological mothers living with HIV with disclosure of their serostatus to their children perinatally HIV-exposed but uninfected (CHEU).

Methods: Mothers and their CHEU were enrolled in the United States (U.S.)-based Surveillance Monitoring for Antiretroviral Therapy (ART) Toxicities (SMARTT) study of the Pediatric HIV/AIDS Cohort Study (PHACS), a longitudinal study of outcomes related to *in utero* exposure to HIV and ART among CHEU. Mothers completing at least one stigma and disclosure assessment starting at the child's age 11-, 13-, 15- and/or 17-year study visits between 16 August 2016 and 1 October 2020 were eligible. Stigma was measured with the 28-item Internalised HIV Stigma Scale (IHSS). Mean stigma scores were linearly transformed to a range of 0–100, with higher scores indicating greater levels of stigma. At each visit, mothers were asked if their child was aware of their HIV diagnosis and at what age the child became aware. The Kaplan-Meier estimator evaluated the cumulative probability of disclosure at each child age. Logistic regression models with generalised estimating equations to account for repeated measures were fit to examine the association between stigma and disclosure, controlling for relevant socio-demographic variables.

Results: Included were 438 mothers of 576 children (mean age 41.5 years, 60% U.S.-born, 60% Black/African American and 37% with household income ≤$10,000). The prevalence of disclosure across all visits was 29%. Mothers whose children were aware versus not aware of their serostatus reported lower mean IHSS scores (38.2 vs. 45.6, respectively). The cumulative proportion of disclosure by age 11 was 18.4% (95% CI: 15.5%, 21.8%) and 41% by age 17 (95% CI: 35.2%, 47.4%). At all child ages, disclosure was higher among children of U.S.-born versus non-U.S.-born mothers. After adjusting for age, marital status and years since HIV diagnosis, higher IHSS scores were associated with lower odds of disclosure (OR = 0.985, 95% CI: 0.975, 0.995).

Conclusions: Providing support to women as they make decisions about serostatus disclosure to their children may entail addressing internalised HIV stigma and consideration of community-level factors, particularly for non-U.S.-born mothers.

Keywords: internalised HIV stigma; PHACS; SMARTT; maternal HIV disclosure; parental HIV disclosure; perinatal HIV exposure

Received 27 January 2023; **Accepted** 23 August 2023

1 | INTRODUCTION

HIV-related stigma involves negative, judgemental or discriminatory attitudes that people and society have about persons living with HIV (PLWH) and it has been a long-established barrier to optimal HIV care and service uptake [1]. It has also been linked to decreased social support, adverse mental health conditions and marginalisation, resulting in PLWH being excluded from exerting influence on dynamic structures and systems (i.e. healthcare, political, economic and community) [1–5].

HIV stigma has also been linked to reduced HIV serostatus disclosure to others [6]. HIV serostatus disclosure entails informing others of one's HIV status and is a complex process by which personal information is communicated [7]. Disclosure occurs on a continuum, from non-disclosure to partial disclosure, to full disclosure, and involves multiple cognitive, emotional and behavioural reactions [8–10].

Disclosure of parental HIV serostatus to children has been documented as a significant challenge for parents [8, 11]. Parental serostatus disclosure to children has implications for parental and child health, parenting and guardianship plans, increased risk of unintended disclosures and discrimination against other family members, and family dynamics [8]. Children are typically disclosed to less often, compared to intimate partners, other family members and healthcare providers [11, 12]. Research shows that rates of parental (mothers and fathers) disclosure to children range from 20% to 97% in studies conducted within the United States (U.S.) and between 11% and 44% in studies conducted outside of the U.S [8]. Variations in disclosure proportions across different studies have been attributed in part to differences in sample characteristics and the lack of standardisation in how disclosure is measured [8].

Other studies have shown that the proportion of mothers disclosing their HIV serostatus to their children range from 30% to 66% [13, 14]. Noted reasons for maternal disclosure have included wanting to tell the child herself, the child's right to know, preparing the child for the future, a sense of parental obligation and the need to protect the child [11, 15]. Reasons mothers choose not to disclose may include HIV stigma and discrimination, not wanting to burden the child and perceived immaturity of the child [11, 15–17].

Maternal benefits of disclosure to children may include stress alleviation around the need to hide medical care, better compliance with clinical appointments, lower anxiety and depression, higher levels of social support, stronger relationships with children and greater family cohesion [12, 17, 18–24]. However, disclosure to children may also lead to fears about the quality of the relationship with their child declining and feeling overwhelmed and nervous post disclosure [20, 25].

Benefits of disclosure for children may include decreased problematic behaviours over time, reduction in negative mood and depression, increase in household responsibilities and higher self-concept [24, 26, 27]. Downsides of the disclosure may encompass lower emotional and social functioning, externalizing symptoms, higher levels of depression, unprotected sexual behaviours and substance use, and negative feelings about and poor performance in school [19, 28–31].

The contribution of HIV stigma to decisions about HIV serostatus disclosure to others has also been explored in the literature. Higher levels of internalised HIV stigma, defined as stigma (i.e. perceived, experienced, enacted and anticipated) that is incorporated into the self-definition, results in negative self-perception and self-injurious behaviours, and lower levels of disclosure [5, 32–36]. For parents living with HIV, fear of discrimination due to secondary disclosure by children, rejection and loss of respect from children, and internalised HIV stigma manifested as self-shaming and experienced guilt about having HIV, have all been implicated as barriers to disclosure [37–40]. The explicit role of maternal internalised HIV stigma in serostatus disclosure to their children, particularly children perinatally HIV-exposed but uninfected (CHEU) who may need long-term monitoring, is currently understudied. Understanding the role of internalised HIV stigma in disclosure among mothers and their CHEU may help women with their disclosure decisions [15–17, 21, 24, 27, 41].

In this study, we aimed to understand the role of internalised HIV stigma in the disclosure of maternal HIV serostatus to their CHEU (ages 0–17 years) enrolled in the Surveillance Monitoring for Antiretroviral Therapy (ART) Toxicities (SMARTT), a study of the Pediatric HIV/AIDS Cohort Study (PHACS). Specifically, we estimated the prevalence of disclosure to CHEU and determined the association between internalised HIV stigma and disclosure.

2 | METHODS

2.1 | Ethical considerations

The SMARTT study was reviewed and approved by Institutional Review Boards (IRBs) at all participating sites and Harvard T.H. Chan School of Public Health. Mothers provided informed consent for themselves and their children to participate in the PHACS SMARTT study. Children signed an age-appropriate (per site IRB guidelines) assent form to participate in a study about their general health and development. Children who turned 18 years during the study period were invited to participate in the SMARTT Young Adult Cohort only if they were aware of their mother's HIV serostatus and their own HIV and ART exposure.

2.2 | Study population

SMARTT evaluates the long-term safety of ART taken during pregnancy among women living with HIV and their CHEU and its methods have been described elsewhere [42]. The population for this study included biological mothers of CHEU enrolled in the Static and Dynamic cohorts of SMARTT as of 1 October 2020. Mothers were eligible if they had at least one study visit since 16 August 2016, when SMARTT began collecting interview data on internalised HIV stigma and maternal serostatus disclosure to children at the child's visit ages 11, 13, 15 and 17 years.

2.3 | Exposure measure

The primary exposure was internalised HIV stigma, measured with the 28-item validated Internalised HIV Stigma Scale (IHSS) [43]. The IHSS measures current internalised HIV stigma and consists of four subscales: stereotypes (12-items), disclosure concerns (5-items), social relationships (7-items) and self-acceptance (4-items), with each item response ranging from 0 to 4. To obtain an overall stigma score, mean scores of the IHSS subscales were averaged and linearly transformed to a range of 0–100, with higher scores indicating greater perceptions and experiences of internalised HIV stigma. Participants were allowed up to a 1-year window around the visit age to complete the corresponding stigma surveys to be included in the analysis. Stigma surveys with at least half of the items in each subscale answered were considered complete. The rationale for only including participants who responded to at least half of each subscale was that some of the IHSS subscales had very few items compared to the others. The IHSS score comprised the average of the completed subscale items.

2.4 | Outcome measure

The primary outcome was maternal HIV disclosure status. Disclosure status was assessed via interview at child visit ages 11, 13, 15 and 17 years and defined as a "yes" response to the question "Is [child's name] aware of your HIV diagnosis?" This disclosure could have been by the child's mother or by someone else. To estimate the probability of disclosure by each child age, the actual age (in years) at which the child was reported to have learned of the mother's HIV serostatus was used (assessed with the question "How old was [child's name] when he/she first learned you had HIV?"). In the event of a discrepancy in actual age across interviews for the same child, the age reported at the first interview in which the mother reported the child was aware of her diagnosis was used.

2.5 | Covariates

Child and maternal covariates were also considered. Child characteristics included cohort (Static/Dynamic), age, sex, race, ethnicity, educational level and primary language. Maternal characteristics included site/region, country of birth, age at time of stigma/disclosure assessment, race, ethnicity, language spoken at home, highest educational level, annual household income, employment status, living arrangement, marital status, health limitations (i.e. difficulties with mobility, physical activity, work, household chores, etc.) and years since HIV diagnosis. In the adjusted model of the association between internalised HIV stigma and maternal disclosure, maternal age, marital status and years since maternal HIV diagnosis were considered as potential confounders.

2.6 | Statistical analysis

The prevalence of disclosure in the study population and by child age at the time of assessment was estimated from all visits. The denominator included everyone with a visit at that child age, regardless of disclosure status, and the numerator was the number of children who were aware of their mother's HIV serostatus as of that age. The way the child learned of the mother's diagnosis and reasons for disclosing or not disclosing were also summarised from the first interview that each child was reported to have been aware of their mother's HIV serostatus. Among children who were never reported to be aware of their mothers' HIV serostatus, the distribution of maternal intention to disclose in the future as reported at the first visit when disclosure and stigma were assessed was summarised, and reasons for not disclosing were summarised by maternal intention to disclose. Distributions of child and maternal demographic, socio-economic and clinical characteristics were summarised and compared at visits at which the mother reported the child being aware of her diagnosis versus not aware. Distributions were also summarised by child visit age.

The Kaplan-Meier estimator was used to estimate the probability of disclosure by each child age, using the actual age at which the mother reported the child learned of her HIV diagnosis. Children were censored at the age at which disclosure was reported, or, if not disclosed to, at the age at time of the last visit when their mothers were interviewed. The estimated probability of disclosure by each child age was compared between mothers who were born in the U.S. and Puerto Rico and mothers born in other countries. A score test from Cox proportional hazards models with the robust sandwich estimator was used to evaluate whether the Kaplan-Meier curves were statistically different at any time point, accounting for correlation from repeated measures (multiple children per biological mother). The proportionality assumption of the Cox proportional hazards model was tested via the Kaplan-Meier curves graphically and the Schoenfeld residuals.

To evaluate the association between internalised HIV stigma and maternal HIV disclosure status, univariable and multivariable logistic regression models were fit with generalised estimating equations to account for repeated measures per mother and child. Both unadjusted and adjusted measures of association were evaluated with odds ratios (ORs) and 95% confidence intervals. All analyses were performed using SAS software, Version 9.4.

3 | RESULTS

3.1 | Study population

As of 1 October 2020, 915 biological mothers of 1216 children were eligible for the analysis. Of the 915 mothers, 454 (49.6%) submitted at least one IHSS survey, while 461(50.4%) mothers had no survey submitted. Of those who submitted their surveys, 446 mothers (48.7% of the 915 eligible) submitted a completed IHSS. Among the 446 mothers with a completed IHHS, eight did not complete the maternal disclosure interview, leaving a total of 438 mothers of 576 children across 739 visits included in the analysis (Figure 1).

3.2 | Prevalence of maternal HIV serostatus disclosure

Mothers indicated that the child was aware of their HIV serostatus at 28.1% (208/739) visits, representing 166 unique children and 132 unique mothers (28.8% of 576 children and 30.1% of 438 mothers in the final study population). Prevalence of disclosure was lowest at the child age 11 visit (11%) and increased to 28% at the age 13 visit, 42% at the age 15 visit and 47% by the age 17 visit. The estimated probability that a child was aware of their mother's serostatus by age 11 was 18.4% (95% CI: 15.5%, 21.8%), and this probability increased to 41% (95% CI: 35.2%, 47.4%) by age 17. Additionally, there was a higher probability of disclosing to the child among mothers born in the U.S. and Puerto Rico compared to mothers born in other countries, and this difference increased with older child age (Figure 2). Most children who were aware of their mother's serostatus (70% or 117/166) learned via a planned disclosure by the mother herself. The remainder of the children learned about their mothers' serostatus through others means, including from a family member, from a non-family member, by seeing maternal HIV medications and other unplanned disclosures.

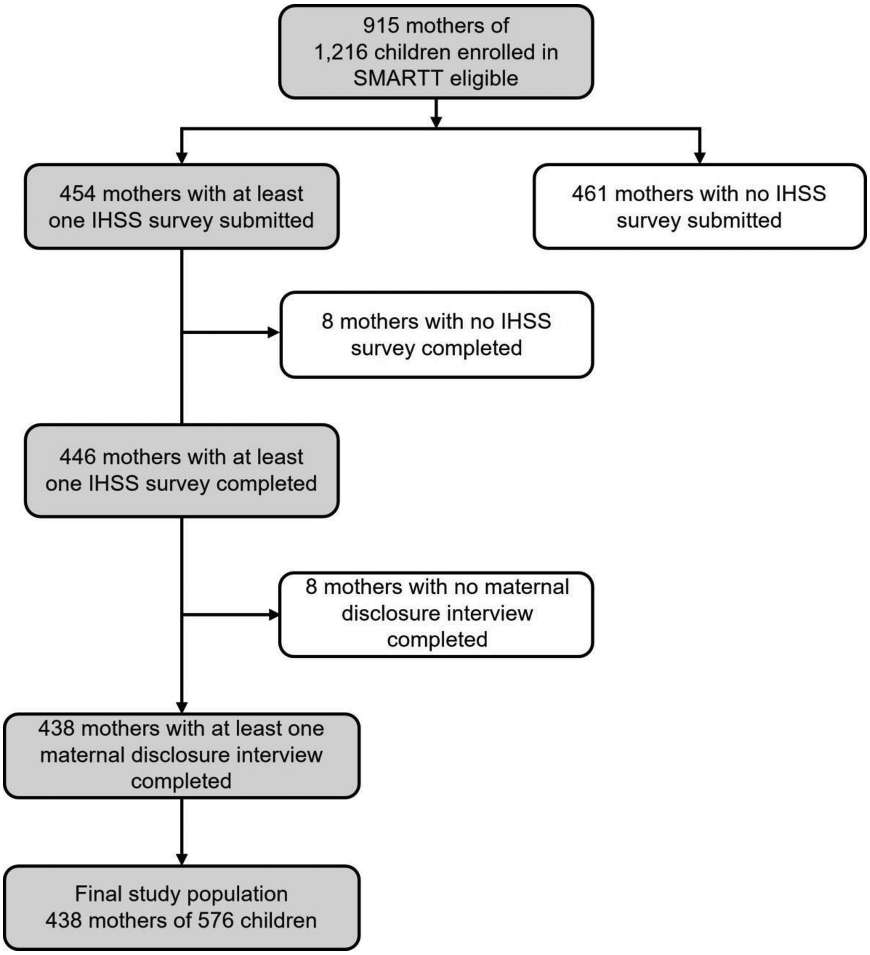

Figure 1. Study population selection. Abbreviations: SMARTT, Surveillance Monitoring for Antiretroviral Therapy Toxicities; IHSS, Internalised HIV Stigma Scale.

3.3 | Maternal and child characteristics by disclosure status

Table 1 summarises the characteristics of children and their mothers among children who were reported to be aware versus unaware of their mother's HIV serostatus. Compared to mothers whose children were aware of their HIV serostatus, mothers whose children were not aware were more likely to be born outside of the U.S. and Puerto Rico (31% vs. 17%). Mothers of children who were aware of their HIV serostatus were more frequently separated or divorced and had a longer mean number of years since their HIV diagnosis compared to mothers who did not disclose. Children who were aware of their mother's HIV serostatus were more frequently female and in high school versus middle school and elementary school.

3.4 | Reported reasons for disclosing and not disclosing maternal HIV serostatus

For each unique child aware of their mother's HIV serostatus (n = 166), the mother was asked about their reasons for disclosure. Reasons that were "very much a factor" in their decision to disclose included: wanting the child to hear it from the mother rather than from someone else (72% or 119/166), not wanting to keep the diagnosis a secret from the child (70% or 117/166), wanting to educate the child about HIV to help the child avoid acquiring HIV (70%) and wanting the child to understand the mother's health condition and/or treatment needs (67% or 111/166). For children who were unaware of their mother's HIV serostatus (n = 410), the most frequent reasons identified by mothers as "very much a factor" for not disclosing were not wanting to worry or burden the child with this information (80% or 326/410) and wanting to protect the child so others will not hurt them because of their mother's HIV serostatus (65% or 266/410) (data not shown in tables).

3.5 | Intention to disclose maternal HIV serostatus

Among the 410 children who were not aware of their mother's HIV serostatus, 16% had mothers who planned to never disclose their diagnosis, 27% who planned to disclose in the near future and 42% who planned to disclose in the future but "no time soon." For children whose mothers planned to disclose sometime in the future (n = 285), the most frequent reasons endorsed as "very much a factor"

Table 1. Characteristics of children and biological mothers by disclosure status to child at all visits

	Disclosed (*n*=208)	Did not disclose (*n*=531)	Total (*N*=739)
Cohort	*n* (%)	*n* (%)	*n* (%)
Dynamic	16 (8%)	103 (19%)	119 (16%)
Static	192 (92%)	428 (81%)	620 (84%)
Child sex			
Male	90 (43%)	284 (53%)	374 (51%)
Female	118 (57%)	247 (47%)	365 (49%)
Child visit age (in years)			
11	30 (14%)	235 (44%)	265 (36%)
13	57 (27%)	144 (27%)	201 (27%)
15	65 (31%)	88 (17%)	153 (21%)
17	56 (27%)	64 (12%)	120 (16%)
Child race			
Asian	0 (0%)	1 (0%)	1 (0%)
Black or African American	128 (62%)	322 (61%)	450 (61%)
White	66 (32%)	148 (28%)	214 (29%)
More than one race	5 (2%)	7 (1%)	12 (2%)
Unknown	9 (4%)	53 (10%)	62 (8%)
Child ethnicity			
Hispanic or Latino	63 (30%)	195 (37%)	258 (35%)
Not Hispanic or Latino	144 (69%)	334 (63%)	478 (65%)
Unknown	1 (0%)	2 (0%)	3 (0%)
Child education level			
Grade 6 and younger	45 (22%)	269 (51%)	314 (42%)
Grades 7 and 8	56 (27%)	124 (23%)	180 (24%)
Grades 9 to 12	105 (50%)	134 (25%)	239 (32%)
Other	2 (1%)	4 (1%)	6 (1%)
Child primary language			
English	167 (80%)	395 (74%)	562 (76%)
Spanish	24 (12%)	81 (15%)	105 (14%)
English and another language	16 (8%)	35 (7%)	51 (7%)
Other	1 (0%)	20 (4%)	21 (3%)
Mother's birthplace region			
US and Puerto Rico	170 (82%)	366 (69%)	536 (73%)
Other country	35 (17%)	163 (31%)	198 (27%)
Unknown	3 (1%)	2 (0%)	5 (1%)
Maternal age (in years)			
N	208	531	739
# missing	0	0	0
Mean (95% CI)	42.26 (41.38, 43.13)	41.60 (41.08, 42.12)	41.79 (41.34, 42.24)
Min, Max	27.07, 58.03	27.72, 57.13	27.07, 58.03
Median (Q1, Q3)	40.90 (37.72, 47.62)	41.23 (36.95, 46.13)	41.15 (37.22, 46.45)
Maternal race			
Asian	0 (0%)	1 (0%)	1 (0%)
Black or African American	124 (60%)	323 (61%)	447 (60%)
White	77 (37%)	145 (27%)	222 (30%)
American Indian	0 (0%)	1 (0%)	1 (0%)
More than one race	0 (0%)	2 (0%)	2 (0%)
Unknown	7 (3%)	59 (11%)	66 (9%)

(*Continued*)

Table 1. Continued

	Disclosed (*n*=208)	**Did not disclose (*n*=531)**	**Total (*N*=739)**
Maternal ethnicity			
Hispanic or Latino	66 (32%)	202 (38%)	268 (36%)
Not Hispanic or Latino	142 (68%)	329 (62%)	471 (64%)
Mother's education level			
Less than high school	62 (30%)	174 (33%)	236 (32%)
High school or GED	70 (34%)	152 (29%)	222 (30%)
More than high school	76 (37%)	205 (39%)	281 (38%)
Annual household income			
≤ $10,000	71 (34%)	183 (34%)	254 (34%)
$10,001–$20,000	62 (30%)	113 (21%)	175 (24%)
$20,001–$30,000	30 (14%)	95 (18%)	125 (17%)
≥ $30,001	41 (20%)	133 (25%)	174 (24%)
Unknown	4 (2%)	7 (1%)	11 (1%)
Mother's employment status			
Employed	76 (37%)	245 (46%)	321 (43%)
Not employed	132 (63%)	286 (54%)	418 (57%)
Mother's living arrangement			
Living with partner/spouse	84 (40%)	237 (45%)	321 (43%)
Not living with partner/spouse	122 (59%)	288 (54%)	410 (55%)
Other	2 (1%)	6 (1%)	8 (1%)
Mother's marital status			
Married	50 (24%)	157 (30%)	207 (28%)
Separated/divorced	43 (21%)	62 (12%)	105 (14%)
Widowed	10 (5%)	7 (1%)	17 (2%)
Single, never married	105 (50%)	305 (57%)	410 (55%)
Language spoken at home			
English	160 (77%)	350 (66%)	510 (69%)
Spanish	29 (14%)	100 (19%)	129 (17%)
English and another language	19 (9%)	49 (9%)	68 (9%)
Other	0 (0%)	32 (6%)	32 (4%)
Maternal health limitations			
No limitation	123 (59%)	339 (64%)	462 (63%)
At least one limitation	85 (41%)	190 (36%)	275 (37%)
Unknown	0 (0%)	2 (0%)	2 (0%)
Years since maternal HIV diagnosis			
N	172	439	611
# missing	36	92	128
Mean (95% CI)	19.38 (18.63, 20.12)	17.64 (17.19, 18.09)	18.13 (17.74, 18.52)
Min, Max	11.47, 35.08	11.18, 32.62	11.18, 35.08
Median (Q1, Q3)	18.38 (15.61, 22.46)	16.82 (13.66, 20.52)	17.53 (14.22, 21.04)

for wanting to disclose included wanting the child to hear it from them (92%) and wanting to educate the child about HIV (86%).

3.6 | Distribution of internalised HIV stigma by maternal HIV disclosure status

The overall mean IHSS score among visits where the mother reported that the child was aware of her HIV serostatus was 38.2 (SD = 17.5), compared to 45.6 (SD = 19.5) among visits where the mother reported that the child was not aware. This trend was seen in all subscales of the IHSS, except for the stereotypes subscale, where mean scores were similar in the two groups (Figure 3). Across all child visit ages, the overall mean IHSS score was lower by at least 5 points for visits where the child was aware of mother's diagnosis.

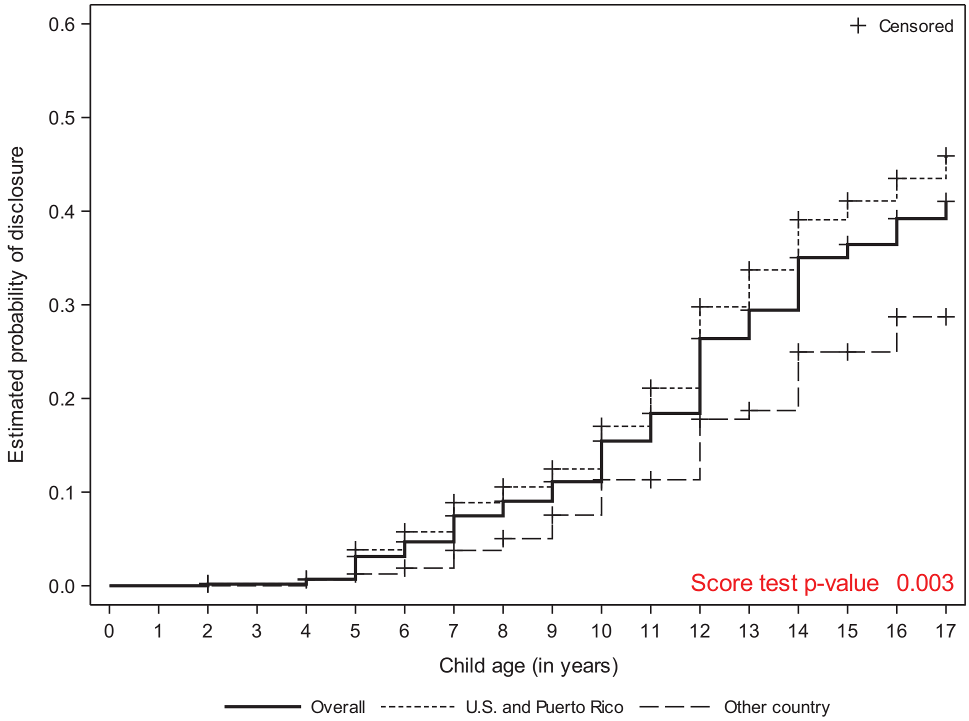

Figure 2. Estimated probability of disclosure by mother's birth region across child's age.

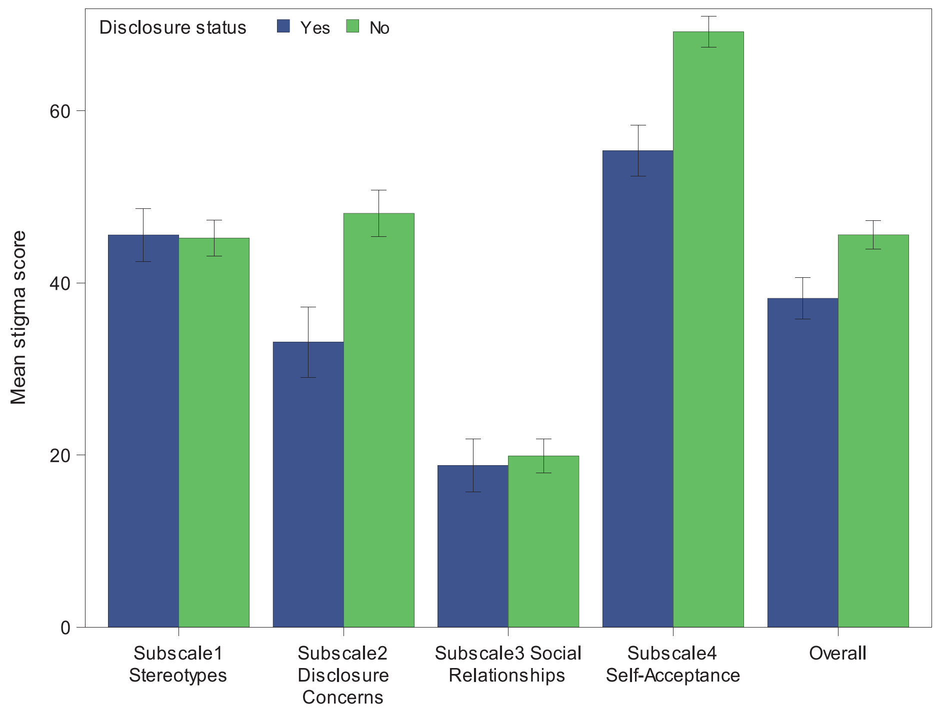

Figure 3. Mean stigma scores overall and for each subscale, by maternal HIV disclosure status. Error bars represent 95% confidence intervals.

3.7 | Associations of internalised HIV stigma with maternal HIV disclosure status

In the unadjusted model, for every 1-point increase in the overall IHSS score, there was a 2% decrease in the odds of disclosure (OR = 0.98, 95% CI: 0.98, 0.99). This association remained after adjusting for maternal age, marital status and years since maternal HIV diagnosis (adjusted OR [aOR] = 0.985; 95% CI: 0.975, 0.995).

4 | DISCUSSION

In this study, we found that 29% of CHEU enrolled in SMARTT and whose mothers completed the IHSS were aware of their mother's HIV serostatus. This number was lower than the disclosure proportion reported by Schrimshaw and Siegel, who found that 66% of mothers had disclosed their HIV serostatus to their children who were not living with HIV [14]. Similarly, Abdulrahman et al. reported that 36% of caregivers (both biological and non-biological parents) had disclosed their HIV status to children living with and without HIV [44]. The prevalence of disclosure in our study was similar to the 28% reported by Armistead et al. whose study population included biological mothers and their CHEU [13]. Differences in disclosure proportions may be due to concomitant stigmas related to mothers' race, gender, socio-economic status, immigration status and mental health conditions exacerbating internalised HIV stigma and complicating the disclosure process. In addition, there is no standardised way of measuring disclosure. In our study, we defined disclosure as the child being aware of their mother's HIV serostatus regardless of who informed the child. Other studies define disclosure as the parent or caregiver directly disclosing their HIV serostatus to their children [8, 17, 45, 46].

The reasons for disclosure and non-disclosure in this study were similar to other studies examining disclosure of maternal HIV serostatus to their children [14, 15, 47]. The primary reasons for mothers disclosing were to ensure that their children learned about their mother's diagnosis directly from them, not wanting to keep the diagnosis a secret and wanting to educate the child about HIV. The main reported reasons for not disclosing were not wanting to burden the child with diagnosis information and wanting to protect the child from being hurt by others.

Most of the mothers in our study had disclosed or planned to disclose their serostatus to their children. Only 16% of mothers reported that they never want to disclose their HIV serostatus to their children. Most reported that their diagnosis was personal. This is understandable given that parents living with HIV experience challenges in managing the disclosure process, discomfort discussing death and reasons for their diagnosis, fear of children's emotional reactions and perceived rejection from children [6]. Since some parents may not have the appropriate resources or skills to facilitate HIV disclosure, specialised intervention programmes, such as Teaching, Raising, and Communication with Kids (TRACK), developed by Murphy et al., may help prepare and support parents dealing with disclosure decisions [47].

In this study, we found a greater likelihood of maternal HIV serostatus disclosure with the child's increasing age. Increased disclosure to older children versus younger children may be attributed to the perceived maturity of the child, the perceived ability of the child to keep the mother's HIV serostatus a secret and needing assistance or support from that child [13, 26, 44, 48]. We also found lower proportions of maternal HIV serostatus disclosure among non-U.S.-born mothers compared to U.S.- and Puerto Rico-born, which may be related to community-level factors [44, 49, 50]. Mothers born in other countries may fear that disclosure to their children may lead to community disclosure and subsequent community shaming and judgements. Non-U.S.-born mothers may also be uncomfortable seeking help to disclose to their children from their HIV providers [6]. Additionally, due to traditional gender roles and unique cultural conditioning, some mothers may find it inappropriate or uncomfortable to discuss perceived taboo subjects, such as sex and sexuality [51].

We found that higher levels of internalised HIV stigma were associated with lower odds of disclosure to CHEU, which is consistent with other studies [37–39, 52–54]. This study adds to the existing literature on the relationship between internalised HIV stigma and maternal HIV serostatus disclosure to CHEU. It contextualises HIV stigma and maternal disclosure of HIV status from the position of a large, multisite, U.S.-based longitudinal cohort study of mothers and their adolescent CHEU, which is currently missing from the literature. Understanding maternal serostatus disclosure to CHEU and related factors may be helpful for healthcare providers in assisting parents with disclosure-related matters. For CHEU, knowledge of their mothers' HIV seropositivity and associated struggles (i.e. navigating complex healthcare systems, ART adherence, stigma and discrimination) and their own exposure to HIV and ART may help them avoid high-risk behaviours. Knowledge of their own exposure to HIV and ART may also be important for the management of health conditions that may not arise until an individual has advanced into adulthood [41].

There are several study limitations in need of acknowledgement. Due to the cross-sectional design of the study and that disclosure is a dynamic process, we were unable to explore how stigma leads to disclosure decisions. The IHSS, while validated both in women living with HIV in the U.S. and outside of the U.S., may not have captured the nuanced experiences of mothers living and parenting with HIV who were born in other countries. Those completing the stigma and disclosure assessments were older and living with their HIV diagnosis longer. Therefore, the findings of this study may not be generalizable to younger mothers and mothers with more recent HIV diagnoses, as these groups may experience stigma and disclosure decisions differently. Moreover, stigma assessments were implemented only after a certain time point, and only mothers with children who reached the age of at least 11 years were assessed, limiting the generalizability of study results to mothers with younger children. Additionally, we did not have appropriate maternal data on mental health conditions and intimate partner violence, which may have impacted the internalisation of HIV stigma and decisions around serostatus disclosure to their CHEU.

Importantly, this study found that most mothers (84%) intend to disclose their HIV serostatus to their CHEU. However, these mothers may not have the necessary tools or needed support to do so. Thus, the results of this study have implications for future research and programme development. First, interventions are needed to reduce internalised HIV stigma. Mobilizing and strengthening communities impacted by HIV with opportunities for peer leadership, support, education, outreach and advocacy may be valuable in reducing internalised HIV stigma and its harmful effects [4]. Incorporating disclosure practices that recognise and accommodate the cultural diversity and norms of families may be particularly advantageous for mothers born outside of the U.S [8]. Studies exploring the specific role of HIV stigma experienced in the community and the impact of non-HIV-related discrimination among mothers who immigrated to the U.S. on disclosure decisions to children may also provide rich experiential insight for shaping community-level interventions.

5 | CONCLUSIONS

The current study explored the prevalence of maternal HIV serostatus disclosure among CHEU and their biological mothers enrolled in the SMARTT study and evaluated the relationship between internalised HIV stigma and disclosure. We found that disclosure was prevalent in 29% of mother-child pairs and that higher internalised HIV stigma was associated with lower odds of disclosing to the child. An additional 54% of mothers planned to disclose to HIV serostatus in the future. Providing culturally sensitive and unbiased support to women as they make decisions about disclosure of their HIV serostatus to their children may entail addressing internalised HIV stigma and consideration of community-level factors, particularly for non-U.S.-born mothers.

AUTHORS' AFFILIATIONS

[1]Department of Pediatrics, Keck School of Medicine, University of Southern California, Los Angeles, California, USA; [2]Harvard T.H. Chan School of Public Health, Center for Biostatistics in AIDS Research, Boston, Massachusetts, USA; [3]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA; [4]Department of Pediatrics, Feinberg School of Medicine, Northwestern University, Chicago, Illinois, USA; [5]Department of Pediatrics, College of Medicine, University of Illinois, Chicago, Illinois, USA

COMPETING INTERESTS

The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

MD wrote the first draft of the manuscript. DK and JL completed the data analysis and contributed to the revisions of the manuscript. CB, EGC, RS, LS and TF contributed to the revisions of the manuscript. All authors have read and approved the final version of the manuscript.

ACKNOWLEDGEMENTS

We thank the participants and families for their participation in PHACS, and the individuals and institutions involved in the conduct of PHACS.

FUNDING

The study was supported by the Eunice Kennedy Shriver National Institute of Child Health & Human Development (NICHD), Office of the Director, National Institutes of Health (OD), National Institute of Dental & Craniofacial Research (NIDCR), National Institute of Allergy and Infectious Diseases (NIAID), National Institute of Neurological Disorders and Stroke (NINDS), National Institute on Deafness and Other Communication Disorders (NIDCD), National Institute of Mental Health (NIMH), National Institute of Drug Abuse (NIDA), National Cancer Institute (NCI), National Institute on Alcohol Abuse and Alcoholism (NIAAA), and National Heart, Lung, and Blood Institute (NHLBI) through cooperative agreements with the Harvard T.H. Chan School of Public Health (HD052102) (Principal Investigator: George R Seage III; Program Director: Liz Salomon) and the Tulane University School of Medicine (HD052104) (Principal Investigator: Russell Van Dyke; Co-Principal Investigator: Ellen Chadwick; Project Director: Patrick Davis) and through Harvard T.H. Chan School of Public Health for the Pediatric HIV/AIDS Cohort Study 2020 (P01HD103133) (Multiple Principal Investigators: Ellen Chadwick, Sonia Hernandez-Diaz, Jennifer Jao, Paige Williams; Program Director: Liz Salomon). Data management services were provided by Frontier Science (Data Management Center Director: Suzanne Siminski), and regulatory services and logistical support were provided by Westat, Inc (Project Directors: Julie Davidson, Tracy Wolbach).The following institutions, clinical site investigators and staff participated in conducting PHACS SMARTT in 2020, in alphabetical order: **Ann & Robert H. Lurie Children's Hospital of Chicago**: Ellen Chadwick, Margaret Ann Sanders, Kathleen Malee; **Baylor College of Medicine**: Mary Paul, Ruth Eser-Jose, Chivon McMullen-Jackson, Lynnette Harris; **Bronx-Care Health System**: Murli Purswani, Mahoobullah Mirza Baig, Alma Villegas, Marvin Alvarado; **Children's Diagnostic & Treatment Center**: Lisa-Gaye Robinson, Jawara Dia Cooley, James Blood, Patricia Garvie; **New York University School of Medicine**: William Borkowsky, Nagamah Sandra Deygoo, Jennifer Lewis; **Rutgers—New Jersey Medical School**: Arry Dieudonne, Linda Bettica, Juliette Johnson, Karen Surowiec; **St. Jude Children's Research Hospital**: Katherine Knapp, Jamie Russell-Bell, Megan Wilkins, Stephanie Love; **San Juan Hospital Research Unit/Department of Pediatrics, San Juan Puerto Rico**: Nicolas Rosario, Lourdes Angeli-Nieves, Vivian Olivera; **SUNY Downstate Medical Center**: Stephan Kohlhoff, Ava Dennie, Jean Kaye, Jenny Wallier; **Tulane University School of Medicine**: Karen Craig, Margarita Silio, Patricia Sirois; **University of Alabama, Birmingham**: Cecelia Hutto, Paige Hickman, Julie Huldtquist, Dan Marullo; **University of California, San Diego**: Stephen A. Spector, Veronica Figueroa, Megan Loughran, Sharon Nichols; **University of Colorado, Denver**: Elizabeth McFarland, Christine Kwon, Carrie Glenny, Jennifer Englund; **University of Florida, Center for HIV/AIDS Research, Education and Service**: Mobeen Rathore, Saniyyah Mahmoudi, Sarah El-Hassan, Jamilah Tejan; **University of Illinois, Chicago**: Karen Hayani, Lourdes Richardson, Renee Smith, Alina Miller; **University of Miami**: Gwendolyn Scott, Gustavo Gil Garcia, Gabriel Fernandez, Anai Cuadra; **Keck Medicine of the University of Southern California**: Toni Frederick, Mariam Davtyan, Guadalupe Morales-Avendano; **University of Puerto Rico School of Medicine, Medical Science Campus**: Zoe M. Rodriguez, Lizmarie Torres, Nydia Scalley.

The Pediatric HIV/AIDS Cohort Study (PHACS) network was supported by the *Eunice Kennedy Shriver* National Institute of Child Health & Human Development (NICHD), Office of The Director, National Institutes of Health (OD), National Institute of Dental & Craniofacial Research (NIDCR), National Institute of Allergy and Infectious Diseases (NIAID), National Institute of Neurological Disorders and Stroke (NINDS), National Institute on Deafness and Other Communication Disorders (NIDCD), National Institute of Mental Health (NIMH), National Institute on Drug Abuse (NIDA), National Cancer Institute (NCI), National Institute on Alcohol Abuse and Alcoholism (NIAAA), and the National Heart, Lung, and Blood Institute (NHLBI) through cooperative agreements with the Harvard T.H. Chan School of Public Health (HD052102), Tulane University School of Medicine (HD052104) and Harvard T.H. Chan School of Public Health for the Pediatric HIV/AIDS Cohort Study 2020 network (P01HD103133).

DISCLAIMER

The conclusions and opinions expressed in this article are those of the authors and do not necessarily reflect those of the National Institutes of Health or the U.S. Department of Health and Human Services.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study can be made available upon reasonable request.

REFERENCES

1. Armoon B, Fleury MJ, Bayat AH, Fakhri Y, Higgs P, Moghaddam LF, et al. HIV related stigma associated with social support, alcohol use disorders, depression, anxiety, and suicidal ideation among people living with HIV: a systematic review and meta-analysis. Int J Ment Health Syst. 2022;16(1):1–7.
2. Jones HS, Floyd S, Stangl A, Bond V, Hoddinott G, Pliakas T, et al. Association between HIV stigma and antiretroviral therapy adherence among adults living with HIV: baseline findings from the HPTN 071 (PopART) trial in Zambia and South Africa. Trop Med Int Health. 2020;25(10):1246–60.
3. Daniels I, Anthony T, Peavie J, Miesfeld N, Pyatt T, Robinson D, et al. Black men who have sex with men with HIV and providers in HIV care settings reflect on stigma reducing strategies to promote engagement in health care. AIDS Patient Care STDs. 2022;36(S1):S–28.
4. Brown G, Reeders D, Cogle A, Allan B, Howard C, Rule J, et al. Tackling structural stigma: a systems perspective. J Int AIDS Soc. 2022;25:e25924.
5. Ferguson L, Gruskin S, Bolshakova M, Yagyu S, Fu N, Cabrera N, et al. Frameworks and measures for HIV-related internalized stigma, stigma and discrimination in healthcare and in laws and policies: a systematic review. J Int AIDS Soc. 2022;25:e25915.
6. Adam A, Fusheini A, Ayanore MA, Amuna N, Agbozo F, Kugbey N, et al. HIV stigma and status disclosure in three municipalities in Ghana. Ann Glob Health. 2021;87(1):49.
7. Obermeyer CM, Baijal P, Pegurri E. Facilitating HIV disclosure across diverse settings: a review. Am J Public Health. 2011;101(6):1011–23.
8. Qiao S, Li X, Stanton B. Disclosure of parental HIV infection to children: a systematic review of global literature. AIDS Behav. 2013;17(1):369–89.
9. Wiener L, Mellins CA, Marhefka S, Battles HB. Disclosure of an HIV diagnosis to children: history, current research, and future directions. J Dev Behav Pediatr. 2007;28(2):155.
10. Greene K, Derlega VJ, Mathews A. Self-disclosure in personal relationships. In Vangelisti AL, Perlman D, editors. The Cambridge handbook of personal relationships. Cambridge University Press: 2006, p. 409–427.
11. Osingada CP, Okuga M, Nabirye RC, Sewankambo NK, Nakanjako D. Disclosure of parental HIV status to children: experiences of adults receiving antiretroviral treatment at an urban clinic in Kampala, Uganda. AIDS Res Treat. 2017;2017:1–11.
12. Armistead L, Morse E, Forehand R, Morse P, Clark L. African-American women and self-disclosure of HIV infection: rates, predictors, and relationship to depressive symptomatology. AIDS Behav. 1999;3(3):195–204.
13. Armistead L, Tannenbaum L, Forehand R, Morse E, Morse P. Disclosing HIV status: are mothers telling their children? J Pediatr Psychol. 2001;26(1):11–20.
14. Schrimshaw EW, Siegel K. HIV-infected mothers' disclosure to their uninfected children: rates, reasons, and reactions. J Soc Pers Relatsh. 2002;19(1):19–43.
15. Ostrom RA, Serovich JM, Lim JY, Mason TL. The role of stigma in reasons for HIV disclosure and non-disclosure to children. AIDS Care. 2006;18(1):60–5.
16. Ostrom Delaney R, Serovich JM, Lim JY. Reasons for and against maternal HIV disclosure to children and perceived child reaction. AIDS Care. 2008;20(7):876–80.
17. Osingada CP, Okuga M, Nabirye RC, Sewankambo NK, Nakanjako D. Prevalence, barriers and factors associated with parental disclosure of their HIV positive status to children: a cross-sectional study in an urban clinic in Kampala, Uganda. BMC Public Health. 2016;16(1):1–7.
18. Tompkins TL. Disclosure of maternal HIV status to children: to tell or not to tell… that is the question. J Child Fam Stud. 2007;16:773–88.
19. Mellins CA, Brackis-Cott E, Dolezal C, Leu CS, Valentin C, Meyer-Bahlburg HF. Mental health of early adolescents from high-risk neighborhoods: the role of maternal HIV and other contextual, self-regulation, and family factors. J Pediatr Psychol. 2008;33(10):1065–75.
20. Wiener LS, Battles HB, Heilman NE. Factors associated with parents' decision to disclose their HIV diagnosis to their children. Child Welfare. 1998;77(2):115
21. Murphy DA, Steers WN, Dello Stritto ME. Maternal disclosure of mothers' HIV serostatus to their young children. J Fam Psychol. 2001;15(3):441.
22. Dane B. The voices of Thai women living with HIV/AIDS. Int Soc Work. 2002;45(2):185–204.
23. Vallerand AH, Hough E, Pittiglio L, Marvicsin D. The process of disclosing HIV serostatus between HIV-positive mothers and their HIV-negative children. AIDS Patient Care STDs. 2005;19(2):100–9.
24. Murphy DA, Marelich WD, Amaro H. Maternal HIV/AIDS and adolescent depression: a covariance structure analysis of the 'Parents and Children Coping Together' (PACT) Model. Vulnerable Child Youth Stud. 2009;4(1):67–82.
25. Shaffer A, Jones DJ, Kotchick BA, Forehand R, Family Health Project Research Group. Telling the children: disclosure of maternal HIV infection and its effects on child psychosocial adjustment. J Child Fam Stud. 2001;10:301–13.
26. Lee MB, Rotheram-Borus MJ. Parents' disclosure of HIV to their children. AIDS. 2002;16(16):2201–7.
27. Murphy DA, Marelich WD, Hoffman D. A longitudinal study of the impact on young children of maternal HIV serostatus disclosure. Clin Child Psychol. 2002;7(1):55–70.
28. Xu T, Yan Z, Rou K, Wang C, Ye R, Duan S, et al. Disclosure of parental HIV/AIDS to children in rural China. Vulnerable Child Youth Stud. 2007;2(2):100–5.
29. Palin FL, Armistead L, Clayton A, Ketchen B, Lindner G, Kokot-Louw P, et al. Disclosure of maternal HIV-infection in South Africa: description and relationship to child functioning. AIDS Behav. 2009;13:1241–52.
30. Rotheram-Borus MJ, Draimin BH, Reid HM, Murphy DA. The impact of illness disclosure and custody plans on adolescents whose parents live with AIDS. AIDS. 1997;11(9):1159–64.
31. Woodring LA, Cancelli AA, Ponterotto JG, Keitel MA. A qualitative investigation of adolescents' experiences with parental HIV/AIDS. Am J Orthopsychiatry. 2005;75(4):658–75.
32. Nordberg B, Gabriel EE, Were E, Kaguiri E, Ekström AM, Kågesten A, et al. Social concerns related to HIV status disclosure and participation in the prevention of mother-to-child transmission of HIV care among pregnant women in Kenya. BMC Pregnancy Childbirth. 2020;20(1):1–9.
33. Chandra PS, Deepthivarma S, Manjula V. Disclosure of HIV infection in South India: patterns, reasons and reactions. AIDS Care. 2003;15(2):207–15.
34. Bogart LM, Cowgill BO, Kennedy D, Ryan G, Murphy DA, Elijah J, et al. HIV-related stigma among people with HIV and their families: a qualitative analysis. AIDS Behav. 2008;12(2):244–54.
35. Steward WT, Herek GM, Ramakrishna J, Bharat S, Chandy S, Wrubel J, et al. HIV-related stigma: adapting a theoretical framework for use in India. Soc Sci Med. 2008;67(8):1225–35.
36. Tsai AC, Bangsberg DR, Kegeles SM, Katz IT, Haberer JE, Muzoora C, et al. Internalized stigma, social distance, and disclosure of HIV seropositivity in rural Uganda. Ann Behav Med. 2013;46(3):285–94.
37. Madiba S, Mahloko J, Mokwena K. Prevalence and factors associated with disclosure of HIV diagnosis to infected children receiving antiretroviral treatment in public health care facilities in Gauteng, South Africa. J Clin Res HIV AIDS Prev. 2013;1(2):13–23.
38. Qiao S, Li X, Stanton B. Practice and perception of parental HIV disclosure to children in Beijing, China. Qual Health Res. 2014;24(9):1276–86.
39. Lee SJ, Li L, Iamsirithaworn S, Khumtong S. Disclosure challenges among people living with HIV in Thailand. Int J Nurs Pract. 2013;19(4):374–80.
40. Kyaddondo D, Wanyenze RK, Kinsman J, Hardon A. Disclosure of HIV status between parents and children in Uganda in the context of greater access to treatment. SAHARA-J. 2013;10:S37–45.
41. Jao J, Hazra R, Mellins CA, Remien RH, Abrams EJ. Disclosing in utero HIV/ARV exposure to the HIV-exposed uninfected adolescent: is it necessary? J Int AIDS Soc. 2016;19(1):21099.
42. Williams PL, Seage III GR, Van Dyke RB, Siberry GK, Griner R, Tassiopoulos K, et al. A trigger-based design for evaluating the safety of in utero antiretroviral exposure in uninfected children of human immunodeficiency virus-infected mothers. Am J Epidemiol. 2012;175(9):950–61.
43. Sayles JN, Wong MD, Kinsler JJ, Martins D, Cunningham WE. The association of stigma with self-reported access to medical care and antiretroviral therapy adherence in persons living with HIV/AIDS. J Gen Intern Med. 2009;24(10):1101–8.
44. Abdulrahman R, Stuard E, Vachon ME, Nicholas C, Neugebauer R, Hagmann SH, et al. Predictors of disclosure of maternal HIV status by caregivers to their children in an inner-city community in the United States. AIDS Behav. 2017;21(1):141–51.
45. Namasopo-Oleja SM, Bagenda D, Ekirapa-Kiracho E. Factors affecting disclosure of serostatus to children attending Jinja Hospital Paediatric HIV clinic, Uganda. Afr Health Sci. 2015;15(2):344–51.
46. Appiah SC, Kroidl I, Hoelscher M, Ivanova O, Dapaah JM. A phenomenological account of HIV disclosure experiences of children and adolescents from northern and southern Ghana. Int J Environ Res Public Health. 2019;16(4):595.
47. Murphy DA, Armistead L, Marelich WD, Payne DL, Herbeck DM. Pilot trial of a disclosure intervention for HIV+ mothers: the TRACK program. J Consult Clin Psychol. 2011;79(2):203.

48. Corona R, Beckett MK, Cowgill BO, Elliott MN, Murphy DA, Zhou AJ, et al. Do children know their parent's HIV status? Parental reports of child awareness in a nationally representative sample. Ambul Pediatr. 2006;6(3):138–44.
49. Körner H. Negotiating cultures: disclosure of HIV-positive status among people from minority ethnic communities in Sydney. Cult Health Sex. 2007;9(2):137–52.
50. Åsander AS, Björkman A, Belfrage E, Faxelid E. HIV-infected African parents living in Stockholm, Sweden: disclosure and planning for their children's future. Health Soc Work. 2009;34(2):107–15.
51. Mkwanazi NB, Rochat TJ, Imrie J, Bland RM. Disclosure of maternal HIV status to children: considerations for research and practice in sub-Saharan Africa. Future Virol. 2012;7(12):1159–82.
52. Qiao S, Li X, Zhou Y, Shen Z, Tang Z, Stanton B. The role of enacted stigma in parental HIV disclosure among HIV-infected parents in China. AIDS Care. 2015;27(sup1):28–35.
53. Clifford G, Craig GM, McCourt C, Barrow G. What are the benefits and barriers of communicating parental HIV status to seronegative children and the implications for Jamaica? A narrative review of the literature in low/middle income countries. West Indian Med J. 2013;62(4): 357–63.
54. Letteney S, Laporte HH. Deconstructing stigma: perceptions of HIV-seropositive mothers and their disclosure to children. Soc Work Health Care. 2004;38(3):105–23.

JIAS JOURNAL OF THE INTERNATIONAL AIDS SOCIETY

COMMENTARY

Strengthening the evidence to improve health outcomes of children with perinatal HIV exposure

Sonia Lee[1,§], Susannah Allison[2] and Pim Brouwers[2]

[§]**Corresponding author**: Sonia Lee, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, 6710B Rockledge Drive, Bethesda, MD 20817, USA. Tel: +(301) 594–4783. (Sonia.Lee@nih.gov)

Abstract

Introduction: The number of children exposed to HIV and possibly to antiretroviral therapy (ART) in utero and during breastfeeding and are uninfected (HEU) globally will continue to increase from the estimated 15.9 million in 2021.

Discussion: There are still significant gaps in our understanding of the impact of HIV and/or ART exposure in children who are HEU, in terms of prevalence/incidence and severity on health and wellbeing, and long after exposure has ended. While there have been substantial programmatic efforts to support the elimination of vertical transmission of HIV, additional rigorous research is needed to better understand the biological, (psycho)social and structural factors contributing to optimal health for populations who are HEU. Furthermore, the best approaches to address and study the gaps in understanding also need to be explored. Given the scope of the problem including the large numbers of affected people as well as the often limited and competing in-country resources for populations affected by HIV, novel methodologies, including multi-level approaches and advanced analytics, need to be considered.

Conclusions: A growing population of children who are HEU are maturing into adolescence and young adulthood. Research to advance understanding of the possible negative long-term effects of HIV and/or ART exposure in these youth is supported by the US National Institutes of Health. Both large epidemiological studies and smaller more comprehensive cohort studies may be required to address the complexity of the issue. Integrating both types of studies could allow the establishment of more reliable and validated predictions of which youth who are HEU are at the highest risk for specific negative health outcomes, such as mental health and neurocognitive disorders, and which interventional approaches may be most successful to address specific deficits both in terms of prevention and treatment. Finally, these goals can be more rapidly achieved with data science efforts, data harmonisation between studies and with sustainable data-sharing practices. It is important to expand the commitment to research to identify biological, social and structural drivers, to develop screening tools, and impactful and contextually appropriate interventions to address the health and wellbeing of children who are HEU from birth through adulthood.

Keywords: adolescents; children; epidemiology; HEU; HIV-exposed uninfected; perinatal

Received 26 January 2023; **Accepted** 21 August 2023

1 | INTRODUCTION

The number of children exposed to HIV and possibly to antiretroviral therapy (ART) in utero and during breastfeeding who are uninfected (HEU) will continue to increase from the estimated 15.9 million children in 2021 [1, 2]. Furthermore, an increasing number of these children are now growing into adolescence (13–18 years of age) and young adulthood (18–21 years of age) [3]. These biological exposures put this population at increased risk for negative health outcomes. A number of studies indicate that children who are HEU are at increased risk for complicated maternal pregnancy and delivery, increased rates of preterm delivery, mortality, infectious morbidity, immune abnormalities and impaired growth [4]. These complications may also act as mediators of the delays in cognitive, motor, language and neurodevelopment that have been reported in some studies [5], mainly focused on younger age groups. In addition to the more biologic factors, mental health and neurocognitive outcomes will also be moderated by psychosocial and behavioural factors in addition to social determinants of health [6]. There may also be a disproportionate impact of structural and health inequalities on the youth growing up in an environment affected by HIV.

A recent systematic review and meta-analysis highlighted the need for large high-quality longitudinal studies to assess the neurodevelopmental trajectories of children who are HEU [7]. Furthermore, psychosocial factors and social determinants of health also may play a significant and increasing role over time moderating the possible HIV and ART-related negative health outcomes of youth who are HEU. For example, inequitable access to healthcare services and education, low socio-economic status and HIV stigma continue to affect children who are HEU growing up in HIV-affected environments. Slogrove described a "package of risks," including potentially adverse factors beyond ART and HIV exposure, such as social and structural inequalities, exposures to other infectious diseases, and maternal morbidity and mortality, that also adversely affect the development of children who are HEU [8].

It is important to understand the underlying mechanisms and compounding risk factors for increased negative health outcomes to predict those at highest risk and inform appropriate targeted management and intervention strategies that optimise the overall wellness of the growing population of youth and young adults who are HEU. As most psychiatric disorders emerge in late childhood and adolescence, these disorders may not yet be apparent; therefore, it is important for older populations who are HEU to be assessed for mental health symptoms and disorders in order for them to be rapidly addressed [9]. Factors that extend beyond in-utero exposures also must be considered when evaluating the mechanisms or risk factors impacting health outcomes among older populations who are HEU. Given the breadth of both heterogeneous etiologic factors and health outcomes in populations who are HEU, the large affected populations of children, adolescents and young adults, as well as the often limited and competing in-country resources to address health and other inequities, research with a focus on adolescents and young adults that includes possible targeted interventions for mental and neurocognitive health need to be more highly prioritised.

This commentary focuses on research gaps related to the long-term effects of in-utero exposure to HIV and/or ART on mental health and neurocognitive development as populations who are HEU age into adolescence and young adulthood, highlights major US National Institutes of Health (NIH)-funded research programmes with populations who are HEU and proposes future research priorities and directions.

2 | DISCUSSION

2.1 | Selected NIH research programmes with paediatric populations who are HEU

The NIH has a mission to seek fundamental knowledge about the nature and behaviour of living systems and the application of that knowledge to enhance health, lengthen life, and reduce illness and disability. With respect to HIV research priorities, this includes funding a broad research agenda, in alignment with the NIH Strategic Plan for HIV and HIV-Related Research [10]. Specifically, Strategic Goal 1 to "Advance rigorous and innovative research to end the HIV pandemic and improve the health of people with, at risk for, and affected by HIV across the lifespan" addresses the need for additional research in understanding the impact of ART and HIV exposure and fostering the bridge from research findings to clinical and community policies and practice. Several NIH scientific programmes focus on research with populations who are HEU and provide opportunities to further the field. Innovative approaches, including novel and rigorous study designs, are needed to identify those with the highest need for evidence-based interventions that would be effective and implementable. Studies to link infant and child health outcomes with maternal health records during pre-pregnancy, pregnancy and breastfeeding are vital for this research.

Maintaining this information through the transition to adolescent and adult care is also critical but will be difficult. Study populations of individuals who are HEU will need to be large enough to allow for sufficient power to generate new insights around the impact of HIV and ART exposure on mental health and neurodevelopmental outcomes, because of possible complex interactions between individual, maternal, and environmental factors and low prevalence or small effect sises of associated abnormalities. Efforts to encourage and facilitate interactions among separate cohorts need to be strongly promoted to improve the sharing of approaches, methodologies, standardised assessments and data analyses, to develop harmonisation standards, and to establish sustainable data-sharing plans.

In response to these objectives, in 2020, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development and the National Institute of Mental Health supported a programme on HIV epidemiology research that establishes, monitors and evaluates large cohorts to understand the effects of in-utero HIV and/or ART exposure on mortality, morbidity and growth in the United States and/or international settings. Grants were issued to support cohorts of populations who are HEU in Botswana, Kenya, Malawi, South Africa and Zimbabwe [11]. Expected outcomes from the utilisation of innovative epidemiologic approaches to assess health in these cohorts include knowledge that can address care gaps in growth and nutrition, hearing, mental health, cognition, academic achievement and cardiovascular fitness.

Another NIH development that could further facilitate the progress in follow-up of populations who are HEU in Africa is the NIH Common Fund's Harnessing Data Science for Health Discovery and Innovation in Africa (DS-I Africa) [12]. This programme leverages data science technologies and prior NIH investments to develop solutions to the continent's most pressing public health problems through a robust ecosystem of new partners from academic, government and private sectors.

In the United States, the NIH has also provided long-standing research funding support for the Pediatric HIV/AIDS Cohort Study (PHACS), including the Surveillance and Monitoring for ART Toxicities (SMARTT) study to evaluate the long-term safety of antiretroviral (ARV) medications taken during pregnancy among women living with HIV (WLHIV) and their children born without HIV [13–15]. The PHACS SMARTT study is the largest comprehensive study of pregnant WLHIV in the United States, and one of the only large studies to follow children born to WLHIV beyond infancy into their adolescence. A major focus of the SMARTT study is the evaluation of effects of maternal exposures to ARVs, prescribed medications and substance use during pregnancy on health outcomes in their infants and children. These health outcomes cross a wide spectrum of domains, including growth, neurodevelopment, cardiometabolic, hearing and

Table 1. Future priorities and directions

- Larger longitudinal epidemiologic studies, including registries and/or cohorts of children, adolescents and young adults who are HEU, to efficiently identify clinically relevant mental health, behavioural and/or neurocognitive outcomes across the lifespan in ways that minimise participant burden
- Rigorous, innovative study designs and data science methodologies to identify and focus on early identification of those at highest risk of poor outcomes
- Focused measurement and assessment of smaller cohorts of populations who are HEU in greatest need of interventions
- Expanded data harmonisation and sharing efforts
- Increased ability to identify children, adolescents and young adults who are HEU in other longitudinal research to allow for comparative evaluations to those who are not HIV exposed

language, and neurologic functioning. While there are clearly many differences between this cohort and similar populations who are HEU in low- or middle-income countries (LMICs), these studies may also provide guidance for more targeted and efficient follow-up to identify sequelae in populations who are HEU in LMICs.

The NIH further supports additional important collaborative efforts with stakeholders of populations who are HEU to increase awareness and prioritise the dissemination of research findings, identify research gaps and encourage future opportunities. Notably, the 8th Workshop on Children and Adolescents with Perinatal HIV Exposure in 2022 presented up-to-date evidence of optimal methods to evaluate neurodevelopmental outcomes in HIV high prevalence settings, as well as child neurodevelopmental outcomes following perinatal HIV exposure [11]. The workshop included researchers, clinicians, programme implementers, policymakers, advocates and parents of youth who are HEU in order to be a catalyst for shaping research agendas and health policies to support this population of children and adolescents and young adults to reach their fullest human potential.

3 | CONCLUSIONS

3.1 | Future research directions

To achieve optimal healthcare for populations who are HEU, research priorities need to emphasise empirical investigations of the long-term effects of HIV and ART exposure in children, adolescents and young adults (see Table 1).

Longitudinal research with populations who are HEU may require large epidemiologic studies with innovative limited and possibly remote data collection methods and, importantly, the use of medical records with linkages between mother and child. Furthermore, mathematical predictive modelling using these biomedical cohort data, supplemented with structural and social determinants of health data, may also indicate which mental health and behavioural preventive and therapeutic interventions may be most successful to address the specific impacts of HIV and/or ART perinatal exposure. More comprehensive and neuroscientific approaches would include utilizing smaller cohorts to allow for limited but focused assessments. For example, magnetic resonance imaging technology or the use of biomarkers to assess brain development and functioning may be too costly to use in many settings or large-scale cohorts, but may be feasible in smaller cohorts [16].

Similarly, evidence-based screening approaches and protocols for developmental outcomes in children who are HEU that identify the need for further evaluation beyond the early life are a promising area for research and programmatic investments. Providing early opportunities for interventions during the early years of life when the children are still in active care and may support children as well as caregivers [17] may be critical as the likelihood for loss to follow-up when these children reach adolescence or young adulthood is great. For example, the World Health Organisation Nurturing Care Framework for Early Childhood Development highlights the provision of knowledge, skills, time and material resources to give appropriate childcare as essential for the healthy development of children [18]. The development of effective screening tools can lead to the delivery of differentiated services based on need. Differentiated care or differentiated service delivery is defined as client-centred approaches that simplify and adapt services, in ways that both better serve individuals and enhance efficiency of care delivery within the healthcare system. Differentiated care supports shifting resources to clients who are the most in need, innovating the way care is delivered through tailored services. There is a growing understanding of how to deliver differentiated care to adults living with HIV, but limited knowledge about how these approaches can be used to target the unique needs of the children of adults living with HIV.

There remain significant barriers to long-term follow-up studies of children who are HEU, particularly when they become more independent and age into adolescence and young adulthood, and have increasing autonomy to make medical decisions and actively participate in their healthcare. Disclosure of maternal status may not have occurred, limiting adolescent and young adults' knowledge of their HIV and/or ARV exposure and preventing their inclusion in studies on the long-term impact of these exposures. In addition, the lack of clinically relevant manifestations of exposures, as well as the desire to not be different from their HIV-unexposed peers, may decrease the interest in continuing to participate in such research. Other structural and economic factors may also lead to a loss to follow-up. A scientific concern here is that this loss may not be random and could bias the results.

Approaches to address these barriers or correct for them are needed.

Finally, impactful efforts to improve health outcomes for families with children and adolescents who are HEU will encompass the expertise, input, perspectives and voices of researchers, clinicians, programme implementers, policymakers, advocates and community, and of the children and their families themselves. As we expand efforts to achieve global elimination of vertical transmission, we should not allow optimal health for children and adolescents who are HEU to be far behind. The acknowledgement and integration of appropriate targets for health indicators and outcomes of children, adolescents and young adults who are HEU need to underlie global research partnerships and inform the global HIV agenda.

AUTHORS' AFFILIATIONS

[1]Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland, USA; [2]National Institute of Mental Health, National Institutes of Health, Bethesda, Maryland, USA

COMPETING INTERESTS

The authors have no competing interests to disclose.

AUTHORS' CONTRIBUTIONS

SL conceptualised, drafted and revised the manuscript. SA and PB conceptualised and revised the manuscript.

ACKNOWLEDGEMENTS

The authors would like to acknowledge the reviewers and editors for assistance in editing this manuscript. We also acknowledge the communities engaged in this work.

DISCLAIMER

The content is solely the responsibility of the authors and does not necessarily reflect the official views of the Department of Health and Human Services or the National Institutes of Health.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

REFERENCES

1. Joint United Nations Programme on HIV/AIDS (UNAIDS). 2021 UNAIDS Estimates. 2021. https://aidsinfo.unaids.org. Accessed 31 Jul 2023.

2. Edmonds A, Brazier E, Musick BS, Yotebieng M, Humphrey J, Abuogi LL, et al. Clinical and programmatic outcomes of HIV-exposed infants enrolled in care at geographically diverse clinics, 1997–2021: a cohort study. PLoS Med. 2022;19(9):e1004089.

3. Slogrove AL, Powis KM, Johnson LF, Stover J, Mahy M. Estimates of the global population of children who are HIV-exposed and uninfected, 2000–18: a modelling study. Lancet Glob Health. 2020;8:e67–75.

4. Slogrove AL, Goetghebuer T, Cotton MF, Singer J, Bettinger JA. Pattern of infectious morbidity in HIV-exposed uninfected infants and children. Front Immunol. 2016;7:164.

5. McHenry MS, Oyungu E, Yang Z, Ombitsa AR, Cherop C, Vreeman RC. Neurodevelopmental outcomes of young children born to HIV-infected mothers: a pilot study. Front Pediatr. 2021;9:697091.

6. Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. J Pers Soc Psychol. 1986;51:1173–82.

7. Wedderburn CJ, Weldon E, Bertran-Cobo C, Rehman AM, Stein DJ, Gibb DM, et al. Early neurodevelopment of HIV-exposed uninfected children in the era of antiretroviral therapy: a systematic review and meta-analysis. Lancet Child Adolesc Health. 2022;6:393–408.

8. Slogrove AL. It is a question of equity: time to talk about children who are HIV-exposed and "HIV-free". J Int AIDS Soc. 2021;24(11):e25850. https://doi.org/10.1002/jia2.25850

9. Ameri S, Moseholm E, Weis N. Psychiatric disorders in perinatally HIV-exposed, uninfected children: a systematic review. AIDS Care. 2022:1–10. https://doi.org/10.1080/09540121.2022.2141185. Epub ahead of print.

10. OAR. NIH strategic plan for HIV and HIV-related research. 2020 [cited 2022 Dec 23] https://www.oar.nih.gov/hiv-policy-and-research/strategic-plan.

11. 8th Workshop on Children and Adolescents with Perinatal HIV Exposure (Planning Committee and Presenter). 24th IAS AIDS Conference—July 2022, Montreal, Canada. https://programme.aids2022.org/Programme/Session/73. Accessed 31 Jul 2023.

12. Harnessing data science for health discovery and innovation in Africa. [Cited 2023 Jan 24] https://commonfund.nih.gov/AfricaData.

13. Van Dyke RB, Chadwick EG, Hazra R, Williams PL, Seage GR 3rd. The PHACS SMARTT Study: assessment of the safety of in utero exposure to antiretroviral drugs. Front Immunol. 2016;7:199.

14. Jao J, Kacanek D, Yu W, Williams PL, Patel K, Burchett S, et al. Neurodevelopment of HIV-exposed uninfected infants born to women with perinatally acquired HIV in the United States. J Acquir Immune Defic Syndr. 2020;84(2):213–9.

15. [Cited 2023 Jul 10] https://phacsstudy.org/.

16. Wedderburn CJ, Yeung S, Groenewold NA, Rehman AM, Subramoney S, Fouche J-P, et al. Subcortical brain volumes of children who are HIV-exposed and uninfected in the first three years of life: a South African birth cohort study. AIDS. July 29–August 2, Montreal, 2022.

17. World Health Organization. Policy brief: comprehensive package of care for infants and young children exposed to HIV. 2021. https://www.who.int/publications/i/item/9789240040236. Accessed 31 Jul 2023.

18. World Health Organization, United Nations Children's Fund, World Bank Group. Nurturing care for early childhood development: a framework for helping children survive and thrive to transform health and human potential. Geneva: World Health Organization; 2018.

Evans C and Prendergast AJ *Journal of the International AIDS Society* 2023, **26**(S4):e26157
http://onlinelibrary.wiley.com/doi/10.1002/jia2.26157/full | https://doi.org/10.1002/jia2.26157

JIAS JOURNAL OF THE INTERNATIONAL AIDS SOCIETY

VIEWPOINT

When and how to intervene to improve the health of children born HIV-free

Ceri Evans[1,2] and Andrew J. Prendergast[1,3,§]

[§]**Corresponding author**: Andrew J. Prendergast, Blizard Institute, Queen Mary University of London, 4 Newark Street, London E1 2AT, UK. Tel: +44 (0) 207 882 2269. (a.prendergast@qmul.ac.uk)

Received 27 July 2023; **Accepted** 21 August 2023

Children born to mothers with HIV, who themselves remain HIV-free, are at risk for poorer health outcomes compared to children born to mothers without HIV, including increased morbidity and mortality, and impaired growth and neurodevelopment [1]. However, there is limited evidence to inform interventions for this population (termed children born HIV-free).

Here, we highlight intervention options targeting either HIV-specific or universal risk factors, which may be impactful when delivered to the mother or infant (Figure 1).

Since advanced maternal HIV is associated with poor outcomes among children born HIV-free [1], maternal HIV-specific interventions should be started as soon as possible. Women of childbearing age should be able to access preconception HIV testing. Those without HIV in high-burden settings, and those in low-burden settings with a high risk of HIV acquisition, should be offered pre-exposure prophylaxis and other primary HIV prevention strategies, including repeat HIV testing, while ensuring that women living with HIV are retained in care and accessing antiretroviral therapy (ART). Where viral load testing is available during pregnancy, detectable viraemia should prompt urgent interventions to rapidly reduce HIV to undetectable levels. This is essential to prevent vertical HIV transmission, but may also be important for children born HIV-free, since antenatal HIV viraemia has been correlated with higher risk of child mortality [2] and suboptimal neurodevelopment [3]. Newer antiretrovirals, including injectable long-acting agents, may optimise adherence, but these agents need to be evaluated for use during pregnancy [4], with nested evaluation of short- and long-term child health outcomes.

Maternal systemic inflammation during pregnancy has been associated with infant mortality in a pathway independent of HIV viraemia [5], suggesting that interventions beyond ART might reduce infant mortality. Two approaches could be considered: evaluating anti-inflammatory agents, or addressing the underlying drivers of inflammation, including subclinical co-infections. Maternal co-infections may themselves drive adverse outcomes in children born HIV-free. For example, cytomegalovirus (CMV) viraemia during pregnancy has been associated with infant mortality, and with earlier CMV acquisition and immune activation among surviving infants [5]. Antenatal valacyclovir is, therefore, a logical strategy, but did not delay infant cytomegalovirus acquisition in HIV-affected mother-infant pairs in Kenya [6]. Newer, less toxic agents, such as letermovir, warrant evaluation during pregnancy, with infant mortality as the primary outcome, and infant CMV acquisition and immune activation as secondary outcomes.

First-trimester registration for antenatal care, a minimum of eight antenatal contacts and institutional delivery by a skilled attendant are recommended to reduce maternal deaths, newborn mortality and stillbirths [7], but priority interventions have low coverage across low- and middle-income countries (LMICs) [8]. For example, the median coverage of at least four antenatal visits in LMICs is below 80% [8]. Other evidence-based interventions [7] should focus on reducing the proportion of infants born preterm and small-for-gestational age, since these outcomes are more common among women living with HIV and are associated with increased infant morbidity, mortality and neurodevelopmental delays [1].

Current interventions for infants include postnatal antiretroviral prophylaxis to reduce HIV transmission, and co-trimoxazole (trimethoprim-sulfamethoxazole), which reduces mortality in children who acquire HIV; however, neither intervention has specific benefits for children born HIV-free. Two trials from non-malarial areas in sub-Saharan Africa show that co-trimoxazole did not reduce mortality among children born HIV-free [9], and some countries with effective programmes for the prevention of vertical transmission and early infant diagnosis may, therefore, stop providing universal co-trimoxazole. However, there are emerging data that excess mortality among children born HIV-free occurs in the neonatal period [10], so future trials could explore starting co-trimoxazole from birth. The safety concern regarding sulfamethoxazole-induced kernicterus is theoretical [11], and co-trimoxazole was safe when given to children from 2 weeks of age in Botswana [9]. Azithromycin is an alternative broad-spectrum antibiotic, although a large multi-country randomised-controlled trial of providing single-dose azithromycin to women in labour did not reduce neonatal

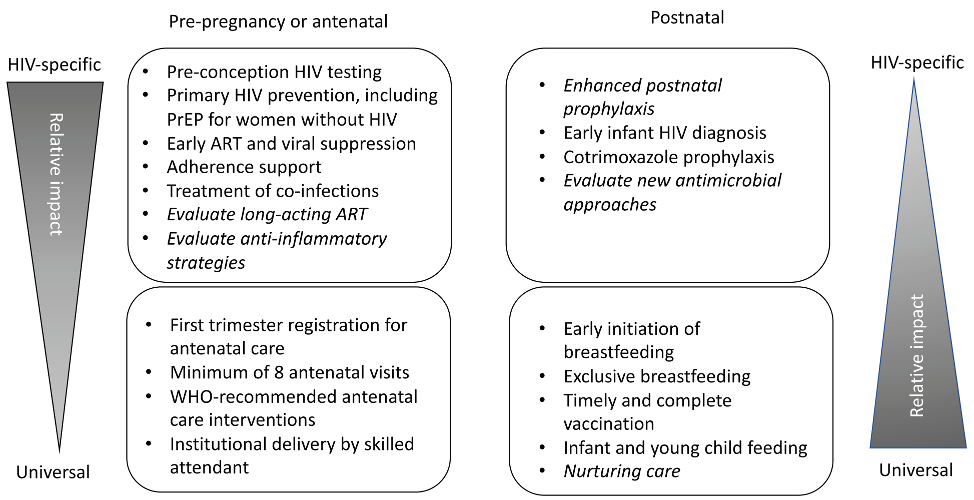

Figure 1. When and how to intervene.
HIV-specific and universal approaches to improve the clinical outcomes of children born HIV-free are shown according to the timing of intervention in the life cycle. The interventions shown in italics are plausible approaches to improve outcomes but require further evaluation. The thickness of the wedge shows the likely relative impact of each intervention. Abbreviations: ART, antiretroviral therapy; PrEP, pre-exposure prophylaxis.

sepsis [12]; however, women living with HIV were not specifically evaluated and infants did not receive azithromycin. In the MORDOR trial, azithromycin reduced infant deaths in high-mortality settings [13]. Clearly, antimicrobial stewardship concerns would need to be considered to avoid the emergence of resistance, especially in countries where a substantial proportion of children are born to women living with HIV.

Overcoming the additional risks and vulnerabilities among families affected by HIV is critical to ensure that children born HIV-free reach their full potential. Nurturing care comprises five inter-related elements to protect children from adversity and ensure they can thrive: good health, adequate nutrition, safety and security, responsive caregiving and early learning. Optimal breastfeeding helps all children survive and thrive, including children born to women living with HIV in sub-Saharan Africa. A South African study demonstrated reduced hospitalisation among children born HIV-free whose mothers initiated early and exclusive breastfeeding [14]; in the same study, timely and complete childhood immunisation was also associated with fewer hospitalisations [14]. However, in surveys across 36 LMICs, the median coverage of exclusive breastfeeding from birth through 5 months was below 50%, and coverage of complete vaccination series for diphtheria, tetanus, pertussis, measles and polio was below 80% [12]. Children born HIV-free have a high risk of stunting [1], which can be reduced with improved infant and young child feeding, including small-quantity lipid-based nutrient supplements [15]. These supplements may improve child survival, stunting, wasting and neurodevelopment, so it is particularly important that the global impetus to scale-up their use includes areas with high antenatal HIV prevalence, as children born HIV-free may particularly benefit [15]. Additional universal interventions include addressing parental mental health, family planning, prevention and cessation of smoking, alcohol and other substance use; and child deworming, healthy hygiene practices, neurodevelopmental screening and play.

Improving the outcomes of children born HIV-free requires identifying those most at risk and providing a comprehensive package of HIV-specific and universal interventions. Current HIV-specific interventions appear most effective when delivered during pregnancy, while available postnatal strategies principally address universal risk factors (Figure 1). New strategies addressing the underlying HIV-specific and universal risks are needed, which can be integrated with existing interventions to create a wraparound nurturing care package delivered through existing contacts with health services to help children born HIV-free to reach their full potential.

AUTHORS' AFFILIATIONS

[1]Zvitambo Institute for Maternal and Child Health Research, Harare, Zimbabwe; [2]Institute of Infection, Veterinary and Ecological Sciences, University of Liverpool, Liverpool, UK; [3]Blizard Institute, Queen Mary University of London, London, UK

COMPETING INTERESTS

The authors have no competing interests to declare.

AUTHORS' CONTRIBUTIONS

AJP wrote the first draft of the manuscript. CE designed the figure and critically revised the manuscript. Both authors have read and approved the final manuscript.

ACKNOWLEDGEMENTS

We thank colleagues at the Zvitambo Institute for Maternal and Child Health Research for valuable discussions about the issues in this Viewpoint.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

REFERENCES

1. Evans C, Jones CE, Prendergast AJ. HIV-exposed, uninfected infants: new global challenges in the era of paediatric HIV elimination. Lancet Infect Dis. 2016;16(6):e92–107.
2. Arikawa S, Rollins N, Newell M-L, Becquet R. Mortality risk and associated factors in HIV-exposed, uninfected children. Trop Med Int Health. 2016;21(6):720–34.
3. le Roux SM, Donald KA, Kroon M, Phillips TK, Lesosky M, Esterhuyse L, et al. HIV viremia during pregnancy and neurodevelopment of HIV-exposed uninfected children in the context of universal antiretroviral therapy and breastfeeding: a prospective study. Pediatr Infect Dis J. 2018;38(1):70–75.
4. Patel P, Ford SL, Baker M, Meyer C, Garside L, D'Amico R, et al. Pregnancy outcomes and pharmacokinetics in pregnant women living with HIV exposed to long-acting cabotegravir and rilpivirine in clinical trials. HIV Med. 2023;24(5):568–79.
5. Evans C, Mutasa K, Rukobo S, Govha M, Mushayanembwa P, Chasekwa B, et al. Inflammation and CMV viremia during pregnancy drive mortality and shape immune development in HIV-exposed infants. Nat Commun. In revision.
6. Roxby AC, Atkinson C, Asbjörnsdóttir K, Farquhar C, Kiarie JN, Drake AL, et al. Maternal valacyclovir and infant cytomegalovirus acquisition: a randomized controlled trial among HIV-infected women. PLoS One. 2014;9(2):e87855.
7. Hofmeyr GJ, Black RE, Rogozińska E, Heuer A, Walker N, Ashorn P, et al. Evidence-based antenatal interventions to reduce the incidence of small vulnerable newborns and their associated poor outcomes. Lancet. 2023;401(10389):1733–44.
8. Leventhal DGP, Crochemore-Silva I, Vidaletti LP, Armenta-Paulino N, Barros AJD, Victora CG. Delivery channels and socioeconomic inequalities in coverage of reproductive, maternal, newborn, and child health interventions: analysis of 36 cross-sectional surveys in low-income and middle-income countries. Lancet Glob Health. 2021;9(8):e1101–9.
9. Wedderburn CJ, Evans C, Slogrove AL, Rehman AM, Gibb DM, Prendergast AJ, et al. Co-trimoxazole prophylaxis for children who are HIV-exposed and uninfected: a systematic review. J Int AIDS Soc. 2023;26(6):e26079.
10. Evans C, Chasekwa B, Ntozini R, Majo FD, Mutasa K, Tavengwa N, et al. Mortality, HIV transmission and growth in children exposed to HIV in rural Zimbabwe. Clin Infect Dis. 2020;72(4):586–594.
11. Thyagarajan B, Deshpande SS. Cotrimoxazole and neonatal kernicterus: a review. Drug Chem Toxicol. 2014;37(2):121–9.
12. Tita ATN, Carlo WA, McClure EM, Mwenechanya M, Chomba E, Hemingway-Foday JJ, et al. Azithromycin to prevent sepsis or death in women planning a vaginal birth. N Engl J Med. 2023;388(13):1161–70.
13. Keenan JD, Bailey RL, West SK, Arzika AM, Hart J, Weaver J, et al. Azithromycin to reduce childhood mortality in sub-Saharan Africa. N Engl J Med. 2018;378(17):1583–92.
14. le Roux SM, Abrams EJ, Donald KA, Brittain K, Phillips TK, Zerbe A, 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;4(3):220–31.
15. Prendergast AJ, Chasekwa B, Evans C, Mutasa K, Mbuya MNN, Stoltzfus RJ, et al. 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(2):77–90.

AUTHOR INDEX

Journal Information

About the journal

The *Journal of the International AIDS Society*, the official journal of the Society, provides a peer-reviewed, open access forum for essential and innovative HIV research, across all disciplines. All articles published by the *Journal of the International AIDS Society* are freely accessible online. The editorial decisions are made independently by the journal's Editors-in-Chief.

Website: www.jiasociety.org

eISSN: 1758-2652

Contact details

Editorial office:
Avenue de France, 23
CH-1202 Geneva
Switzerland

Email: editorial@jiasociety.org

Tel: +41 (0) 22 710 0800

Publisher

The *Journal of the International AIDS Society* is published by John Wiley & Sons Ltd on behalf of the IAS - International AIDS Society

John Wiley & Sons Ltd
9600 Garsington Road
Oxford, OX4 2DQ UK

Telephone: +44 1865 776868

Email: customer@wiley.com

Production Editor

Geethu RS (rgeethu@wiley.com)

Abstracting and Indexing Services

The *Journal of the International AIDS Society* is indexed in a variety of databases including PubMed, PubMed Central, MEDLINE, Science Citation Index Expanded and Google Scholar. The 2022 Journal Impact Factor is 6.0, Journal Citation Reports (Clarivate Analytics, 2023).

Advertising, sponsorship and donations

Please contact the editorial office if you are interested in advertising on our journal's website. We also gladly receive inquiries on sponsorship and donations to support open access publications from authors in low- and middle-income countries.

Supplements

The *Journal of the International AIDS Society* publishes supplements and thematic series on its own initiative or based on proposals by external organisations or authors. Inquiries can be sent to the editorial office at editorial@jiasociety.org.

All articles submitted for publication in supplements are subject to peer review. Published supplements are freely accessible online and can also be produced in print.

Disclaimer

The Publisher, IAS - the International AIDS Society and Editors cannot be held responsible for errors or any consequences arising from the use of information contained in this journal; the views and opinions expressed do not necessarily reflect those of the Publisher, IAS and Editors, neither does the publication of advertisements constitute any endorsement by the Publisher, IAS and Editors of the products advertised.

Copyright and Copying

Wiley's Corporate Citizenship Initiative

Wiley's Corporate Citizenship Initiative seeks to address the environmental, social, economic, and ethical challenges faced in our business and which are important to our diverse stakeholder groups. Since launching the initiative, we have focused on sharing our content with those in need, enhancing community philanthropy, reducing our carbon impact, creating global guidelines and best practices for paper use, establishing a vendor code of ethics, and engaging our colleagues and other stakeholders in our efforts. Follow our progress at www.wiley.com/go/citizenship.

Research4Life

Wiley is a founding member of the UN-backed HINARI, AGORA, and OARE initiatives. They are now collectively known as Research4Life, making online scientific content available free or at nominal cost to researchers in developing countries.

Please visit Wiley's Content Access – Corporate Citizenship site:
www.wiley.com/WileyCDA/Section/id-390082.html

Editorial Board